EXPERT WORKSHOP

Promoting standards for the quality and safety assurance of pharmacy-prepared medicinal products for the needs of patients

PROCEEDINGS

24 September 2009
European Directorate for the Quality of Medicines & HealthCare (EDQM)
7 allée Kastner, CS 30026
F-67081 Strasbourg
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Dr Ged LEE

Group Manager – Laboratories and Pharmacopoeia

Session theme: Common language – the basis for understanding and cooperation

“What terminology can be used for medicinal products prepared in pharmacies: considerations”

Mr V’lain FENTON-MAY

Session theme: Aspects of the reconstitution of medicinal products

“Aspects of the reconstitution of medicinal products”

Dr Lars NIELSEN

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RESOLUTION CM/RESAP(2011)1 ON QUALITY AND SAFETY ASSURANCE REQUIREMENTS FOR MEDICINAL PRODUCTS PREPARED IN PHARMACIES FOR THE SPECIAL NEEDS OF PATIENTS
Today, as always, medicinal products prepared in community and hospital pharmacies are important elements of pharmaceutical care in most countries of Europe. Patients have special needs as regards the medication they need caused by age, pathologies, genetic and environmental factors. Not always can these needs be covered by medicinal products made available by the pharmaceutical industry but require individualised pharmacotherapy.

The primary objective of all healthcare professionals is to serve patients’ needs. Patients rightfully expect medicinal products that are of a guaranteed quality, and therapeutically effective, that are the same irrespective of where they are dispensed or whether they are prepared in pharmacies or manufactured by industry.

By providing policies and model approaches for the safe use of medicines in Europe, the Committee of Experts on quality and safety standards in pharmaceutical practices and pharmaceutical care (CD-P-PH/PC) contributes to the mission of the European Directorate for the Quality of Medicines & Healthcare (EDQM) which is to ensure the basic human right of access to good quality medicines and healthcare, and to promote and protect human and animal health.

The Committee of Experts CD-P-PH/PC has been entrusted with a comprehensive work programme contributing to public healthcare and practices involving pharmaceuticals in community, hospital and institutional care in Europe. It carries out this task through specific programmes and policies, with priority focused on the needs of patients and having in mind the social and ethical context of healthcare. In 2008, the Committee CD-P-PH/PC carried out a survey on “Quality and safety standards for pharmacy preparations” and the conclusions made mention of:

- the wide range of quality and safety assurance standards for pharmacy preparations in Europe;
- the variety of terminology used for medicinal products prepared in Europe;
- the quality and safety gaps between medicinal products prepared in pharmacies and those prepared on an industrial level;
- the quality and safety gaps between medicinal products prepared in pharmacies and those prepared in hospital wards.

These differences concern, in particular, the requirements for testing ingredients, the evaluation of therapeutic benefits, the requirements for pharmacovigilance, and the surveillance of the quality and safety of medicinal products prepared in pharmacies.

The observations of the survey were in line with the statements made at the June 2007 International Symposium on European cooperation and synergy in quality standards beyond the European Pharmacopoeia, which indicated that there was a need for harmonising patient safety issues and quality levels of medicinal products prepared in pharmacies.

The Committee of Experts CD-P-PH/PC is therefore organising this expert workshop with the support from experts in the field in order to identify in cooperation with the workshop participants criteria and key elements of standards for the quality and safety assurance of medicinal products prepared in pharmacies in Europe.

Health authorities have a duty to ensure that all medicinal products dispensed are of appropriate quality, reproducible as regards composition and effective.
Aim of the expert workshop

The expert workshop is aimed at identifying criteria and key elements of standards for the quality and safety assurance of medicinal products prepared in pharmacies in Europe, taking into account

- existing quality guidelines,
- new trends and possible issues in the fields of preparation and distribution which are not covered by current legal provisions and guidance documents.

Target audience

The target audience will comprise of

- nominees from the states parties to the Convention on the Elaboration of a European Pharmacopoeia and other Council of Europe member states with expertise and professional experience in the fields of quality assessment of pharmacy preparations, clinical safety, market surveillance, and pharmacovigilance matters related to pharmacy preparations. This will include officials from the health authorities, namely from the Ministries of Health and Drug Regulatory Authorities, such as officials in charge of pharmacy policies, officials reviewing information related to medicinal products prepared in pharmacies, and pharmacy inspectors,
- experts in the field from relevant professional associations in Europe,
- delegations of the European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH), the steering body, of its Committee of Experts on quality and safety standards in pharmaceutical practices and pharmaceutical care (CD-P-PH/PC), and of the European Pharmacopoeia Commission including relevant working groups.

The number of workshop participants is limited to 45 participants in total. Participation is upon personal invitation only. As the expert workshop will be held in English, participants need to be fluent in the language.

Speakers

The speakers, panellists, break-out session moderators and rapporteurs have relevant expertise and profound working experience dealing with quality and safety assurance of medicinal products prepared in pharmacies. They come from national regulatory or surveillance authorities or are health professionals. The speakers, break-out session moderators and rapporteurs are listed in the appendix of the programme.
Welcome address and opening

9.00 a.m. Dr Susanne KEITEL, Director, EDQM

Keynote address

9.10 a.m. Pharmacy preparations in changing times – new needs and new trends
Speaker: Dr Josee HANSEN, Dutch Health Care Inspectorate

Introduction and overview

9.30 a.m. Activities of the European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH) and its subordinate Committee of Experts CD-P-PH/PC dealing with quality and safety standards in pharmaceutical practices and pharmaceutical care
Speaker: Mr Nico KIJLSTRA, Dutch Health Care Inspectorate, Committee CD-P-PH Chairman; Committee of Experts CD-P-PH/PC Vice-Chairman

Session theme: “EUROPEAN STANDARDS FOR THE QUALITY AND SAFETY ASSURANCE OF MEDICINAL PRODUCTS PREPARED IN PHARMACIES”

Chair: Dr Gudrun BUSCH, Federal Health Office, Switzerland (tbc)

9.40 a.m. Is there a gap in quality and safety assurance between medicinal products prepared in pharmacies and those manufactured on an industrial level?
Speaker: Dr Henk SCHEEPERS, Dutch Healthcare Inspectorate, leader of the Committee of Experts CD-P-PH/PC project “Quality and safety assurance of pharmacy preparations”

10.10-10.40 a.m. Coffee break

10.40 a.m. Best practices for the preparation of medicinal products in pharmacies and healthcare establishments: overview of available guidance and aspects of practical implementation
Speaker: Dr Tobias GOSDSCHAN, Swiss Agency for Therapeutic Products (Swissmedic), Switzerland
11.10 a.m. Challenges posed by the therapeutic relevance assessment and vigilance of medicinal products prepared in pharmacies: viewpoints of regulators
Speaker: Mag. Helga LACINA, Austrian Agency for Health and Food Safety (AGES PHARM MED)

11.40 a.m. How to ensure quality and safety of medicinal products prepared in pharmacies for distribution to other pharmacies
Speakers: Dr Eva SJÖKVIST SAERS, Apoteket Produktion & Laboratorier AB, Sweden & Dr Paul P. H. LE-BRUN, Central Hospital Den Haag, Hospital Pharmacy, the Netherlands

Session theme: “COMMON LANGUAGE – THE BASIS FOR UNDERSTANDING AND COOPERATION”

Chair: Dr Jorgen HUSE, Medicines Agency, Norway (tbc)

12.20 a.m. What terminology can be used for medicinal products prepared in pharmacies: considerations
Speaker: Mr V'Iain FENTON-MAY, FRPharmS, United Kingdom

Panel session (PS)

Room: Salle 500
12.40 a.m. – 1.15 p.m.

Panellists: Ms Maria CARVALHO, School of Pharmacy, University London, Mr V'Iain FENTON-MAY, Dr Tobias GOSDSCHAN

The panellists will facilitate consensus building on the terminology to be used in the break-out sessions.

1.15 – 2.00 p.m. Lunch
CRITERIA AND EUROPEAN STANDARDS FOR QUALITY AND SAFETY ASSURANCE OF MEDICINAL PRODUCTS PREPARED IN PHARMACIES

Groups of participants selected according their expertise and preference will break out in parallel sessions (1-5) which will discuss the criteria and options for European standards on the basis of practice situations taking account of possible issues not covered by current provisions and guidance documents. All break-out sessions will be attended by moderators and rapporteurs.

BS 1: Criteria for product dossiers

Moderator: Dr Thomas ZAPF, BfArm, Germany
Rapporteur: Dr Henk SCHLEEPERS, Dutch Health Care Inspectorate

Room: Salle 500

BS 2: Criteria for pharmacy preparations, if authorised therapeutic equivalents are on the national market

Moderator: Mag. Thomas LANGEBNER MBA aHPh, Hospital Barmherzige Schwestern Linz, Hospital Pharmacy, Austria
Rapporteur: Ms Dace KIKUTE, State Agency of Medicines of Latvia

Room: Salle 200

BS 3: Criteria for production quality

Moderator: Dr Paul P. H. LE-BRUN
Rapporteur: Dr Blaženka JURISIC

Room: Salle 300

BS 4: Criteria for licensing the preparation of medicinal products in pharmacies

Moderator: Dr Gerard LEE, MHRA, United Kingdom
Rapporteur: Dr Jorgen HUSE, Medicines Agency, Norway

Room: Salle 550a

BS 5: Criteria for the distribution of medicinal products prepared in pharmacies

Moderator: Professor Vagn NEERUP HANDLOS, European Association of Hospital Pharmacists (EAHP)
Rapporteur: Dr Yvonne BOUWMAN-BOER, Dutch Pharmacists’ Association

Room: Salle 550b

3.00-3.45 p.m. Coffee break
Session theme: “ASPECTS OF THE RECONSTITUTION OF MEDICINAL PRODUCTS”

Room: Salle 500

Chair: Professor Vagn NEERUP HANDLOS, EAHP

3.45 p.m. Reconstituting medicinal products: considerations
Speaker: Dr Lars NIELSEN, Copenhagen University Hospital Pharmacy, Denmark

Panel session (PS)

Room: Salle 500

4.00 – 4.30 p.m.
Panellists: Ms Ann-Kristin BJERGA BJAEN, Sykehusapotekene HF, Norway, Mr Frits BOOM Zaans Medisch Centrum, the Netherlands, Professor Vagn NEERUP HANDLOS, EAHP, Dr Lars NIELSEN

The panellists will set the scene for discussion of criteria for distinguishing between the reconstitution and the preparation of ready-to-use drugs for individual patients in a hospital pharmacy and the usefulness of risk-based approaches.

Plenary session (PS)

Room: Salle 500

Session theme: “CONCLUSIONS - THE WAY FORWARD”

4.30 - 5.15 p.m.

Chair: Dr Henk SCHEEPERS, Dutch Healthcare Inspectorate, leader of the Committee of Experts CD-P-PH/PC project “Quality and safety assurance of pharmacy preparations”

Break-out session
Moderators
Dr Thomas ZAPF, Mag. Thomas LANGEBNER, Dr Paul P. H. LE-BRUN, Dr Gerald LEE, Professor Vagn NEERUP HANDLOS

The break-out session moderators will present the conclusions and moderate a discussion in the plenary session on the conclusions and on steps for the future. A summary of the BS conclusions will be adopted by the plenary.

Closing address

5.15 p.m. Speaker: Mr Jean-Marc SPIESER, Head DBO, EDQM
II - KEYNOTE ADDRESS
Patients’ needs for medicinal products to manage their diseases have to be met, either by an industrial manufactured product or – as EU legislation describes – a magisterial or officinal preparation.

Patients expect to receive a safe and effective medicinal product, disregarding the production site or legal requirements.

The regulatory systems for industrial products differ in approach, requirements, assessment for safety and efficacy, from the context and the regulation in which a medicinal product by a pharmacist is compounded. One could argue that the regulatory systems clash, that there is a mismatch of expectations (from the part of the patient and prescriber) and the ability of the health care system to fulfill these expectations.

Trends indicate a growth of products which challenge the current system: on the one hand the large scale industrial manufacturing, on the other hand the need for personalised medicine, customised therapy, advanced therapy medicinal products and borderline products in the grey area between medicinal product, foodstuff and medical device.

Pharmacists take their responsibility by drafting norms and guidelines to close that gap. However, the differences between countries are obvious. From the perspective of the European citizen a European approach is needed.
Pharmacy preparations in changing times: new needs and new trends

- Current situation
- Trends
- The way forward
Proceedings of “Promoting standards for the quality and safety assurance of pharmacy-prepared medicinal products for the needs of patients” Expert Workshop, 24 September, Strasbourg

- Assessment by CA
- Responsibility of pharmacist

- Standardized unalterable product
- Custom made

- QA+++
- QA???

- Interested parties
  - Patient
  - Prescriber
  - Health insurance company

- Pharmacist - balancing interests
  - Prescriber availability
  - Patient safety availability information
  - Insurance company cost

- Essential requirements for pharmacy preparations
  - Added therapeutic value
  - Assured quality
  - Informing the patient
  - Monitoring effects and side-effects
Trends and technologies - process
- More standardisation
- More bedside preparations needed
- Concentration of production
- Increasing European context

Trends and technologies - products
- advanced therapy medicinal products
- borderline products
- personalised medicine

What would pharmacists want?
- meet individual needs - all levels
- comply with quality standards
- take professional responsibility

What would regulators want?
- international standards for terminology
- international standards for products or product categories
- international standards for processes

clash?
- licensed and industrially manufactured
- pharmacy prepared

clash?
- licensed and industrially manufactured
- pharmacy prepared

harmony in the interest of the patient
III - PRESENTATIONS
Session theme: European Standards for the Quality and Safety Assurance of Medical Products prepared in Pharmacies
Session Chair

Ms Gudrun BUSCH
Federal Health Office, Switzerland

Speakers:

Dr Henk SCHEEPERS
Dutch Healthcare Inspectorate, Leader of the Committee of Experts CD-P-PH/PC project “Quality and safety assurance of pharmacy preparations”

Dr Tobias GOSDSCHAN
Swiss Agency for Therapeutic Products (Swissmedic), Switzerland

Mag. Helga LACINA
Austrian Agency for Health and Food Safety (AGES PHARM MED)

Dr Eva SJÖKVIST SAERS
Apoteket Produktion & Laboratorier AB, Sweden
&
Dr Paul P. H. LE-BRUN
Central Hospital Den Haag, Hospital Pharmacy, The Netherlands
1.1. Quality and safety assurance of pharmacy preparations

Dr Henk SCHEEPERS
Dutch Healthcare Inspectorate, The Netherlands

Quality and safety of pharmacy preparations in Europe

Henk Scheepers, PharmD, Senior-Inspector
Public Health Surveillance Service
Health Care Inspectorate
The Netherlands

Quality and safety of pharmacy preparations in Europe

1. Project
2. Survey of questionnaire results and conclusions
3. Introduction to the workshop

Quality and safety of pharmacy preparations in Europe; the project

- EDEM Committee of Experts on quality and safety standards in pharmaceutical practices and pharmaceutical care (CO-P-PHPC)
- Working Party
  - Comprising the delegations of the Netherlands, Austria, Norway, Switzerland.
  - Collaboration with SAIHP (European Association of Hospital Pharmacists).

Quality and safety of pharmacy preparations in Europe; objectives of the project

- to ensure safe and effective medicinal products for the patients independent of production site.
- improved and harmonised quality standards for pharmacy preparations.
- to make recommendations.

Quality and safety of pharmacy preparations in Europe; Survey of questionnaire results, conclusions

- Wide variety in quality assurance and standards for pharmacy preparations.
- Gap in quality assurance between pharmacy preparations and manufacturers at industry level.
- Terminology used for pharmacy preparations shows a wide variety.
- Quality and safety gap between preparations/reconstitutions of medicinal products in pharmacies and hospital wards.

Quality and safety of pharmacy preparations in Europe; Survey of questionnaire results

Requirements for preparation
- Only general requirements in most countries
- Additional requirements in some countries (e.g., sterile products)
- Regulations for preparation in other healthcare establishments (e.g., hospital wards) in very few countries.
- Differences in definition (reconstitution / preparation)
Proceedings of “Promoting standards for the quality and safety assurance of pharmacy-prepared medicinal products for the needs of patients” Expert Workshop, 24 September, Strasbourg

<table>
<thead>
<tr>
<th>Quality and safety of pharmacy preparations in Europe; Survey of questionnaire results</th>
<th>Quality and safety of pharmacy preparations in Europe; Survey of questionnaire results</th>
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<tbody>
<tr>
<td>Restrictions for pharmacy preparations</td>
<td>Definitions for pharmacy preparations</td>
</tr>
<tr>
<td>• No restrictions</td>
<td>• Wide variation</td>
</tr>
<tr>
<td>• Restrictions</td>
<td>• Majestral, extemporaneous and official</td>
</tr>
<tr>
<td>• Only individual patients or stock preparations</td>
<td>• Might be defined per country but no general definition across Europe.</td>
</tr>
<tr>
<td>• Other</td>
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<tr>
<th>Quality and safety of pharmacy preparations in Europe; Survey of questionnaire results</th>
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<tbody>
<tr>
<td>Delivery to other pharmacies</td>
<td>Authorisation of pharmacies</td>
</tr>
<tr>
<td>• Hospital pharmacies more often involved than community pharmacies</td>
<td>• 'Normal' authorisation includes permission to prepare medicinal products</td>
</tr>
<tr>
<td>• In some countries companies are involved in pharmacy preparations</td>
<td>• Licences</td>
</tr>
<tr>
<td></td>
<td>- For pharmaceutical dosage forms</td>
</tr>
<tr>
<td></td>
<td>- Dependent on production scale</td>
</tr>
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<td></td>
<td>- Enterprises not being pharmacies</td>
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<tr>
<th>Quality and safety of pharmacy preparations in Europe; Survey of questionnaire results</th>
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<tbody>
<tr>
<td>Quality standards</td>
<td>Additional standards for preparations carrying a higher risk</td>
</tr>
<tr>
<td>• Typical GMP chapters are covered but to a varying extent</td>
<td>• In a minority of the respondent countries</td>
</tr>
<tr>
<td>• Missing in some countries: QC, recall.</td>
<td>• Definition of a larger batch varies widely</td>
</tr>
<tr>
<td></td>
<td>• Delivery to other pharmacies; wide variation in regulation</td>
</tr>
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Quality and safety of pharmacy preparations in Europe; Survey of questionnaire results

Clinical relevance / risk benefit ratio
- Pharmacy preparation not allowed if there is a therapeutic alternative on the market or
- Obligation to deliver all medicines prescribed in some countries or
- Sound and documented proof for therapeutic rationale

Quality and safety of pharmacy preparations in Europe; Survey of questionnaire results

Testing of raw materials
- Identity testing in most of the countries
- Other tests required in less than half of the respondent countries
- Approval system for suppliers/manufacturers is in place in some countries

Quality and safety of pharmacy preparations in Europe; Survey of questionnaire results

Pharmacovigilance
- Required for pharmacy preparations in about half of the countries
- National registers for adverse events not always adequate for pharmacy preparations

Quality and safety of pharmacy preparations in Europe; Survey of questionnaire results

Marketing authorisation
- Not required in most countries
- Required in some countries when maximum allowed quantities for pharmacy preparations are exceeded
- Number of registrations varies from 0 to >100, depending on the country

Quality and safety of pharmacy preparations in Europe; Survey of questionnaire results

Trade in pharmacy preparations regulated in most of the countries
- Not allowed unless specific conditions are met
- License required in some countries
- Only allowed when no registered equivalent/alternative is marketed
- Only allowed when site specific chemical, pharmaceutical and microbiological data are available

Quality and safety of pharmacy preparations in Europe; Survey of questionnaire results

Centralisation / decentralisation trends
- So-called ‘chains’ do not want to have production in all of their pharmacies
- Centralisation trend?
Quality and safety of pharmacy preparations in Europe; introduction to the workshop

Objectives of the project
- To ensure safe and effective medicinal products for the patient independent of production site.
- Improved and harmonised quality standards for pharmacy preparations.
- To make recommendations.

Quality and safety of pharmacy preparations in Europe; introduction to the workshop

1. Introduction
   - Definitions, terminology and areas in focus for the workshop.
   - Understanding the basics of the discussions behind creating the workshop.
   - Guide for discussion in the group.
2. Free flow of ideas
   - Keep focus but free flow of ideas.

Quality and safety of pharmacy preparations in Europe; introduction to the workshop

Variables to be considered (risk approach) for all break-out sessions
1. Scale of the pharmacy preparation
2. Type of products prepared in the pharmacy
3. Other?

Quality and safety of pharmacy preparations in Europe; introduction to the workshop

Ad 1: Scale of the pharmacy preparation
- Magisterial preparations for direct supply to patients (a)
- Stock preparations for direct supply to patients (b)
- Export to other pharmacies (c)
- Export to other European countries (d)

Quality and safety of pharmacy preparations in Europe; introduction to the workshop

Ad 2: The types of products prepared in the pharmacy
- Products solely for dermal application, such as creams, ointments (1).
- All products except sterile and aseptic products (2).
- All products, including sterile and aseptic products (3).

Quality and safety of pharmacy preparations in Europe; introduction to the workshop

- Definitions, terminology and areas in focus for the Workshop.
Quality and safety of pharmacy preparations in Europe; introduction to the workshop

1. Product dossier (quality by design)
2. Therapeutic equivalent registered and available on the national market
3. Production quality

Quality and safety of pharmacy preparations in Europe; introduction to the workshop

4. License or alternatives (legal framework)
5. Distribution
6. Therapeutic relevance or risk benefit ratio
7. Reconstitution of registered products

Quality and safety of pharmacy preparations in Europe; introduction to the workshop

- Workshop with a European perspective
- Be ready to present the outcome of the session
- Results of workshop will be used for further steps in the project

Quality and safety of pharmacy preparations in Europe; introduction to the workshop

Have a good and creative workshop!!

Proceedings of “Promoting standards for the quality and safety assurance of pharmacy-prepared medicinal products for the needs of patients” Expert Workshop, 24 September, Strasbourg
1.2. “Best practices for the preparation of medicinal products in pharmacies and healthcare establishments”

Dr Tobias GOSDSCHAN
Swiss Agency for Therapeutic Products (Swissmedic), Switzerland

Before being able to supply a medicinal product to a patient, various activities have to be undertaken, such as designing/developing (prototyping), manufacturing (reproducing the prototype) and transporting (possibly including storage and distribution) a medicinal product. All these activities involve a series of different risks.

The risks related to the manufacture of medicinal products are well known. A key element in handling these risks is the manufacture within a quality assurance system. The concrete quality assurance measures that should be taken within such a system are described in existing international guidance documents. They may differ for different types of medicinal products: Whereas the manufacture of commercially distributed products should be performed according to the principles of the “Good Manufacturing Practices” (cf. PIC/S Document PE 009 or EudraLex Volume 4, i.e. the “GMP Guide”), the manufacture of medicinal products, that are prepared by pharmacies or other authorised healthcare establishments for direct supply to their own patients, should follow the principles of the “Good Preparation Practices” (cf. PIC/S Document PE 010: PIC/S Guide to good practices for the preparation of medicinal products in healthcare establishments, i.e. the “GPP Guide”).

Even though the PIC/S Document PE 010 (“GPP Guide”) represents the internationally agreed state of the art for the for the preparation of medicinal products in healthcare establishments, the extent to which the content of the Guide is binding, needs to be determined by national legislations. In this context, a recommendation by the Council of Europe/EDQM to implement the content of this Guide on a national level seems useful.

Further standards that might be developed by the Council of Europe/EDQM in the context of quality and safety aspects are recommended to focus on areas where currently less guidance is available. A concrete need for guidance exists for the following topics:

- Guidance for the scientific background documentation for medicinal products with no Marketing Authorisation (e.g. recommendations for a compilation of a product dossier, including the rationale behind the choice of the composition, the preparation process and the specifications of a specific formula)
- Compilation of a list of active ingredients that may be considered as generally well established and suitable for the use in “local niche products” (i.e. medicinal products prepared in pharmacies or other authorised healthcare establishments for direct supply to their own patients).
Best practices for the preparation of medicinal products in pharmacies and healthcare establishments

Overview of available guidance and aspects of practical implementation

The way of a medicinal product to the patient involves a series of activities

- Design & development of medicinal product
- Manufacture of medicinal product
- Registration of medicinal product
- Maintenance of the produced quality
- Transport of medicinal product (preparing, storing and destruction)
- Destabilization of the medicinal product

Risks

- All activities that are linked to a medicinal product bear certain risks
- The concrete product related risks depend on the characteristics of the concerned medicinal product
- Huge range of medicinal products
  - Products prepared according to a magistral formula for an individual patient
  - Individually manufactured and internationally distributed products that include new chemical entities as active ingredients

Handling of risks

- It is recommendable to group medicinal products with comparable characteristics into types, so that strategies how to handle risks may be developed type-specific
- The necessary measures to implement the developed strategies can then be laid down in type-specific guidance documents

A simple model with just two types of medicinal products

- "Distributed products"
- "Local niche products"

Remark: This is only one of many possible classifications, but it is simple and easy to handle.

<table>
<thead>
<tr>
<th>&quot;Distributed products&quot;</th>
<th>&quot;Local niche products&quot;</th>
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<tbody>
<tr>
<td>Classically, these are medicinal products with a marketing authorisation</td>
<td></td>
</tr>
<tr>
<td>Commercialised and distributed to authorised establishments or persons (nationally or internationally)</td>
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</tr>
<tr>
<td>Prepared by healthcare establishments (retail or hospital pharmacies, other authorised establishments) for their own patients</td>
<td></td>
</tr>
<tr>
<td>Higher risk (boxed distribution, over long distances, only patients)</td>
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<tr>
<td>Lower risk (internal delivery, no distribution, flow patients, directly supervised by the preparing establishment)</td>
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Strategies for handling of risks
- "Distributed products"
  - Assessment and approval of a comprehensive demonstration on effectiveness, safety and quality by the regulatory authority
- "Local niche products"
  - No prior approval by an authority
  - High degree of self-responsibility is assigned to healthcare professionals
  - Acting according to the best medicinal and pharmaceutical practice is of central importance

Available guidance to handle risks
- "Distributed products"
  - Well established legal and technical regulations
  - International guidance available (e.g. GMP, ICH)
- "Local niche products"
  - Variety of national regulations
  - Full quality aspects, international guidance is available since April 2008:
    PIC/S Guide PE 010

Some general words on PIC/S
- Pharmaceutical Inspection Co-operation Scheme
  - Co-operation agreement between competent authorities, created in 1995
  - Based on the Pharmaceutical Inspection Convention (treaty between states in 1979)
  - 37 participating authorities, mainly from Europe, but also from Africa, Americas (Canada, Argentina), Asia (Singapore, Malaysia) and Africa (South Africa)
- Website: http://www.picscheme.org

PIC/S Guide PE 010
- PIC/S Guide to good practices for the preparation of medicinal products in healthcare establishments (Good Preparation Practices, GPP)
- Established by PIC/S Expert Circle on Hospital Pharmacy between 1999 and 2006 (10 years)
- National consultation amongst the 37 PIC/S member agencies
- External consultation amongst national and international associations (approximately 450 specific and 40 general comments were considered)
- Adoption by PIC/S Committee at its Singapore meeting on 17 November 2007
- In force since 1 April 2008

PIC/S Guide PE 010
- First guidance document reflecting the internationally agreed state of the art for the preparation of medicinal products by healthcare establishments for direct supply to patients (Local niche products)
- Was developed, because the "classical" GMP Guide (PIC/S Document PE 009) identical with the EU GMP Guide, i.e. EudraLex Volume 4), existed, but was laid out for industrial manufacture and could not be easily applied to the small scale manufacture of medicinal products, which are prepared in healthcare establishments, such as hospital or retail pharmacies
- In order to distinguish these small scale activities from industrial large scale manufacture, the term preparation was used (instead of manufacture)

Format
- PIC/S Guide PE 010 (GPP Guide) follows the formal structure of the GMP Guide (PIC/S PE 009 respectively EudraLex Volume 4)
- Main Part
  - General rules
- Annexes
  - Supplementary guidance for specific types of preparations
Annexes
- Annex 1: Guidelines on the standards required for the sterile preparation of medicinal products
- Annex 2: Guidelines on the standards required for the preparation of non-sterile liquids, creams and ointments
- Work on Annex 3 (Preparation of radiopharmaceuticals) started in June 2009

The approach taken
- It is recognized that preparation activities are normally performed by or at least under direct supervision of pharmacists
- Therefore, only minimal and risk based requirements are described
- This gives on one side more flexibility, but imposes at the same time an increased self responsibility on the pharmacists

Examples for risk based requirements
- Minimal documentation requirements for extemporaneous preparations for single patients (Chapter 4.3)
- Possibility of a risk based demonstration of suitability of equipment and processes (Chapter 5.4)
- Adapted environmental monitoring for sterile preparations (Section 6 of Annex 1)

Implementation of the Guide
- The Guide reflects the internationally agreed state of the art
- National legislation needs to define to which extent the content of the Guide is binding
- Various solutions possible, e.g.:
  - Direct implementation of the Guide as binding rule
  - Implementation of the Guide as recommendation
  - Implementation of an own national rule or guidance, following the “philosophy” of the Guide, possibly with adaptations to the local situation for detail aspects

Conclusion
- Quality assurance measures to reduce risks related to the preparation/make manufacture of medicinal products are well defined on an international level (GMP and GPP Guides)
- In order to promote the harmonized implementation of quality assurance measures related to preparation activities (local niche products), a recommendation by Council of Europe/EDQM to implement the content of PIC/S Guide PE 010 (GPP Guide) on a national level seems useful

Future standards/guidances
- Further activities by the Council of Europe/EDQM that are dedicated to enhance the quality and safety assurance of pharmacy prepared medicinal products for the need of patients are recommened to focus on less regulated areas with a shown need for standardisation or guidance
- Main focus in this context: Activities related to design/development
Common questions showing the need for guidance

Final recommendation

- It is recommended that the Council of Europe/EDQM establishes standards or guidance documents for the following topics:
  - Guidance for the scientific background documentation for medicinal products with no Marketing Authorisation (e.g., recommendations for the completion of a product dossier for "local niche products")
  - A list of active ingredients that may be considered as generally well established and suitable for the use in medicinal products with no Marketing Authorisation (e.g., for the preparation of "local niche products")

Thank you very much for your attention!
1.3. “Challenges posed by therapeutic relevance assessment and vigilance of medicinal products prepared in pharmacies: viewpoints of regulators

Regulation of medicinal products prepared in pharmacies according to the Austrian Medicinal Products Act”

Mag Helga LACINA
Austrian Agency for Health and Food Safety (AGES PHARM MED)

The focus of the presentation will be on medicinal products prepared in pharmacies which are subject to registration (pharmacy medicinal products) according to the Austrian Medicinal Products Act. Provisions related to quality are briefly addressed, provisions related to the therapeutic relevance will be presented in more detail.

Entitled to apply for a registration is the operator of a community pharmacy. Amongst the documents that have to be submitted for the registration of a pharmacy medicinal product are a draft labelling and package leaflet that conform with the Quality Review of Documents (QRD) template, a description of the pharmacovigilance system and – if necessary – of the risk management system, and abstracts commenting and evaluating the pharmaceutical data included in the registration documents, the non-clinical, pharmacological-toxicological data as well as the clinical data obtained from the literature and required for an evaluation of the product. The application for registration of a pharmacy medicinal product can be compared with the application for marketing authorisation of a medicinal product with active substances which have a well-established use according to the EU Directive (bibliographic application) or with the application for registration of a traditional herbal medicinal product. The expert assessment of pharmacy medicinal products corresponds to the evaluation of these medicinal products, being based on a detailed bibliography for Module 4 and 5.

Actually, there are 1950 pharmacy medicinal products registered in Austria, the great majority of the registrations dates from 1992 to 1994. 21% of the community pharmacies are holders of registrations. According to their composition and dosage form, registered medicinal pharmacy products can be classified as 1) herbal tea preparations (59 %), 2) other herbal medicinal products (16 %), and 3) preparations containing as active ingredients other substances, e.g. chemical active ingredients (25 %).

From the regulatory point of view, the effective Austrian Medicinal Products Act provides regulations that shall ensure the safety and efficacy of registered pharmacy medicinal products. However, the figures point out that the great majority of the registrations dates from more than 10 years ago. Among these registrations are medicinal products which are currently under scientific revision, whereby some of them certainly will be judged as obsolete; for which registered therapeutic therapies are available on the market; or which currently have to update their quality documents, whereby for some of them certainly a quality gap between pharmacy preparation and manufacture at industry level will come up.
In the course of the adaption of the information provided to the patient to the European standard, the package leaflets of the registered pharmacy medicinal products are being revised according to the latest scientific findings. Holders of registrations of pharmacy medicinal products for which registered therapeutic alternatives are available are encouraged to apply for the revocation of these registrations, since they face extensive package leaflets (e.g. for combinations of paracetamol and caffeine) and quality charges. Registered herbal tea preparations and medicinal products for which no registered therapeutic alternatives are available (e.g. certain syrups for the treatment of cough) are seen as a well established and integral component of the Austrian market (see Appendix, “Labelling” and “Package leaflet”).

Appendix

<table>
<thead>
<tr>
<th>LABELLING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of the Medicinal Product</td>
</tr>
<tr>
<td>Name and address of the registration holder</td>
</tr>
<tr>
<td>Statement of ingredients</td>
</tr>
<tr>
<td>Contents</td>
</tr>
<tr>
<td>Batch Number</td>
</tr>
<tr>
<td>Expiry Date</td>
</tr>
<tr>
<td>Statement of supply</td>
</tr>
<tr>
<td>Information in Braille</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PACKAGE LEAFLET</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACKAGE LEAFLET: INFORMATION TO THE USER</td>
</tr>
<tr>
<td>Read all of this leaflet carefully because it contains important information for you. This medicine is available without prescription. However, you still need to take &lt;herbal tea&gt; carefully to get the best results from it.</td>
</tr>
<tr>
<td>– Ask your pharmacist if you need more information or advice.</td>
</tr>
<tr>
<td>– You must contact a doctor if your symptoms worsen or do not improve after 7 days.</td>
</tr>
</tbody>
</table>
WHAT IS <HERBAL TEA> AND WHAT IS IT USED FOR?

BEFORE YOU TAKE <HERBAL TEA>?

Do not take < Herbal Tea>,
   − if….

Take special care with <Herbal Tea>:
   if applicable

Taking other medicines

Pregnancy and breast-feeding

HOW TO TAKE <HERBAL TEA>?

If you have further questions on the use of <Herbal Tea>, ask your doctor or pharmacist.

POSSIBLE SIDE EFFECTS

If any of the side effects gets serious, or if you notice any side effect not listed in this leaflet, please tell your doctor or pharmacist.

HOW TO STORE <HERBAL TEA>

FURTHER INFORMATION

What <Herbal Tea> contains:
   expressed qualitatively and quantitatively for active substances and excipients

Registration Number

This leaflet was last approved in MM/YYYY
Introduction

The preparation of medicinal products has an ageing tradition in community pharmacies as well as in hospital pharmacies in Austria. In brief, these products can be categorized as medicinal products prepared on the basis of a prescription of a physician or dentist, and medicinal products prepared autonomously by the pharmacist (pharmacy medicinal products). Only since the effective date of the Austrian Federal Law on the production and putting into circulation of medicinal products (Medicinal Products Act) in 1984, the latter preparations are subject to registration.

This presentation will give an overview of the regulations concerning medicinal products prepared in pharmacies. The focus will be on preparations which are subject to registration according to the Medicinal Products Act.

Provisions related to quality are briefly addressed, provisions related to the therapeutic relevance will be presented in more detail.

The Medicinal Products Act defines the following types of medicinal products prepared in pharmacies:

- Medicinal products not subject to registration:
  - "Official preparations"
  - "Magistral preparations"

- Medicinal products subject to registration:
  - Pharmacy medicinal products

'Official preparations'

Medicinal products that comply with a monograph of the Pharmacopeia within the scope of § 1 of the Pharmacopeia Act, intended to be sold directly to the consumer in the pharmacy in which these have been produced.

These products shall be labeled and provided with a package leaflet as defined by the Medicinal Products Act.
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Pharmacy medicinal products
Pharmacy medicinal products are medicinal products that are...are comprised solely of the products listed in the Austrian Official List of Medicinal Product Prices and that...not subject to prescription and are dispensed only in the pharmacy in which they are produced either wholly or for the most part.

The Austrian Official List of Medicinal Product Prices contains a list of substances which may be kept in community pharmacies.
This list serves as a guidance for the pharmacist which substances may be used as ingredients of a pharmacy medicinal product.
The composition of the medicinal product applied for is then subject to an expert assessment in every single case. Concerning e.g. the check that the product is not subject to patents and to the combination of the compounds, the indications applied for.

- Pharmacy medicinal products are subject to registration since the effective date of the Medicinal Products Act in 1964.
- Entitled to apply for a registration is the operator of a community pharmacy.
- For those pharmacy medicinal products put into circulation before the effective date of the Medicinal Products Act registration expired, unless an application for registration in accordance with the Medicinal Products Act was filed before 31 March 1992.

Regulations concerning the registration of pharmacy medicinal products
Independent of the type of application for a marketing authorization or registration the following regulations of the Medicinal Products Act are applicable:

§ 3
Medicinal products shall not be put into circulation unless it has been ensured according to the latest scientific findings and to the extent of practical experience, that if used as directed they have no harmful effect in excess of what is acceptable in the light of medical science.

§ 4
No medicinal product may be produced or brought into circulation whose quality does not conform with the latest scientific findings.

Registration documents
MODULE 1
- Name and address of the applicant together with the evidence of entitlement to submit the application
- Name of the pharmacy medicinal product
- Qualitative and quantitative composition of the pharmacy medicinal product
- Assessment of potential environmental risks of the pharmacy medicinal product
- Usually not applicable to pharmacy medicinal products due to the kind, number and amount of these products.
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- Draft labelling in accordance with the Medicinal Products Act
- Draft package leaflet in accordance with the Medicinal Products Act
- Sample of the intended product packaging upon the authorities request

- A description of the pharmacovigilance system and – if necessary – of the risk management system, the applicant plans to imply.
- Generally, the same regulations concerning pharmacovigilance apply to pharmacy medicinal products than to any other marketing authorisation in Austria. The proposed pharmacovigilance system must comply with the EU Directive and the Medicinal Products Act, respectively.
- A risk management plan is usually not applicable to pharmacy medicinal products due to the kind of these products.

MODULE 3
- Particulars on the manufacturing process
- Reasons for potential precautions for storage, administration to patients and disposal of waste products
- Particulars on the planned controls in the framework of manufacture
- Particulars on the quality criteria for the ingredients used in the pharmacy medicinal product
- A declaration that the substance samples necessary for conducting technical tests will be made available upon the authorities request

- Particulars on scientific findings or data from practical experience relating to the safety of the ingredients used in the pharmacy medicinal product
- Particulars on the quality characteristics and properties of the packaging materials that come into contact with the pharmacy medicinal product and a list of the test procedures for these packaging materials (applicable; not applicable for medicinal products for external use)
- Reports on the shelf life in the proposed retail package (not applicable if shelf life applied for does not exceed 1 year)

In contrast to an application for a marketing authorisation of a medicinal product, the following documents don’t have to be submitted with the application for a registration of a pharmacy medicinal product:

- Draft summary of the product characteristics in accordance with the Medicinal Products Act
- Fully developed, reproducible analytical and standardisation procedures for starting products, intermediates and the finished product
- Particulars on the practicality of the pharmaceutical form
- Non-clinical data (Module 4)
- Clinical data (Module 5)
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But an application for registration for a pharmacy medicinal product shall be accompanied by:

- information concerning the specification of the finished product, and
- one abstract commenting and one abstract evaluating:
  a) the pharmaceutical data included in the registration documents,
  b) the non-clinical, pharmacological-toxicological data obtained from the literature and required for an evaluation of the product
  c) the clinical data obtained from the literature and required for the evaluation of the product.

Including:

- Details of therapeutic indications, contraindications, undesirable effects, dosage, posology and method of administration, unless this information is included in the labelling and package leaflet.
- Usually not applicable to pharmacy medicinal products due to the risk of these products. This information is usually included in the package leaflet.
- In the case of pharmacy medicinal products containing several components that influence effectiveness or tolerance, information about the suitability of the combination of such components.

The application for registration of a pharmacy medicinal product can be completed with:

- the application for marketing authorisation of a medicinal product with active substances which have a well-established use according to the EU Directive (bibliographic application) or
- the application for registration of a traditional herbal medicinal product.

The expert assessment of pharmacy medicinal products corresponds to the evaluation of the listed medicinal products, being based on a detailed bibliography for Module 4 and 5.

Labelling and packaging leaflet:

In accordance with the Medicinal Products Act the labelling and package leaflet of pharmacy medicinal products have to conform with the GDP-templates before 1 January 2011.

The GDP(2nd) Annotated GDP-templates provides guidance on how to present the labelling and package leaflet for an application in the Mutual Recognition and the Decentralised Procedure.

http://www.europa.eu.int/comm/health/pharmacovigilance/gdpurencepharma/gdptemplate.html
http://www.europa.eu.int/comm/health/pharmacovigilance/gdpurencepharma/gdptemplate.htm

Renewal

The registration of a pharmacy medicinal product is valid for 5 years.

The registration may be renewed after 5 years on the basis of a re-evaluation of risk-benefit balance by the authorities.

For this purpose, the holder of the registration of a pharmacy medicinal product shall provide a consolidated version of the registration documents.
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**Periodic Safety Update Report (PSUR)**

For pharmacy medicinal products a PSUR shall be submitted to the authorities immediately according to the EU Directive.

The holder of the registration may request the amendment of the periods.

Such a request is approved if justified — which is usually the case for pharmacy medicinal products — and the period is amended to a three-yearly interval after authorisation.

**Additional regulations of the Medicinal Products Act applying to registered pharmacy medicinal products:**
- Listing in the registry of medicinal products
- Information about the actual bringing into circulation
- Changes
- Revocation and suspension of the registration
- Inspections
- Safety precautions

**Figures and facts about pharmacy medicinal products**

The actual total number of registered pharmacy medicinal products in Austria in 1959.

**Number of registrations of pharmacy medicinal products per year since the effective date of the Medicinal Products Act**

**Classification of registered pharmacy medicinal products according to their composition and dosage form**

**Contribution of community pharmacies that are leaders of registrations of pharmacy medicinal products to total number of community pharmacies**

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Strategies and perspectives

- From the regulatory point of view, the Austrian Medicinal Products Act provides regulations that shall ensure the safety and efficacy of registered pharmacy medicinal products:
  - The name on which a registered pharmacy medicinal product is available to the user is limited to one community pharmacy – namely the pharmacy that is the holder of this registration.
  - The package leaflet complying with the QRD-template provides relevant information to the patient concerning efficacy, tolerability and safety of the medicinal product.
  - Adverse drug events are documented.

- The great number of registered pharmacy medicinal products suggests that:
  - There is a demand for such products, and
  - There is a long experience in pharmacy preparation of medicinal products for which not always registered therapeutic alternatives are available on the market.

- The figures also point out that the great majority of the registrations date from more than 10 years ago.
  - Among these registrations are medicinal products:
    - Which are currently under scientific revision, whereby some of them certainly will be judged as obsolete,
    - For which registered therapeutic alternatives are available on the market (e.g. herbal medicinal products, traditionally herbal medicinal products, medicinal products with active ingredients like paracetamole or acetaminophen).
    - Which currently have to update their quality documents, whereby some of them certainly a quality gap between pharmacy preparation and manufacture at industry level will emerge.

- In the course of the adoption of the information provided to the patient by the European standard, the package leaflets of the registered pharmacy medicinal products are being revised according to the latest scientific findings:
  - Holders of registrations of pharmacy medicinal products for which registered therapeutic alternatives are available (e.g. certain syrups for the treatment of cough) are seen as a well established and integral component of the Austrian market.

- Registered herbal tea preparations and medicinal products for which no registered therapeutic alternatives are available (e.g. certain syrups for the treatment of cough) are seen as a well established and integral component of the Austrian market.
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- Most registered herbal tea preparation are based on a mixture defined in a national pharmacopeia.
- For registered herbal tea preparations a specific format of the information provided to the patient was developed that meets the requirements of the European standard and is practicable for the pharmacies.
- Herbal Tea Preparations.doc

Thank you for your attention!
1.4. “How to ensure quality and safety of medicinal products prepared in pharmacies for distribution to other pharmacies”

Dr Eva SJÖKVIST SAERS
Apoteket Produktion & Laboratorier AB, Sweden

A specific licence for pharmacies to prepare/manufacture pharmaceutical products, should most likely improve the quality. Reviews should be made periodically with written reports to identify processes and areas for further improvement. By centralising the manufacturing of pharmacy-prepared medicinal products to certain pharmacies or companies offering this service, the quality of the produced products can be improved. Experienced personnel work according to standardised and quality controlled processes. By the standardisation of the range of products and by defining composition and master batch documentation in a National Formulary (or equivalent) a more clinically relevant range of products can be obtained.

It is suggested that an agreement, including a quality agreement, is written between the supplying pharmacy (or company offering this service) and the receiving pharmacy that has the contacts with the patients/customers. Periodical reviews, with written reports, identify areas for further improvements regarding e.g. ordering process, process at the supplying pharmacy (or company) and distribution process.

The patient/customer should be presented with written information about all medicinal products he/she receives.

The pharmacovigilance systems for medicinal products should also be used for pharmacy prepared products. The reporting for pharmacy-prepared products should be simplified in order to find trends regarding certain products or certain producing pharmacies.

In Sweden the state-owned, limited liability company Apoteket AB has had the exclusive right to sell pharmaceuticals in Sweden. Under its agreement with the state, Apoteket AB has had responsibility to manufacture and supply extemporaneous preparations and stock preparations (common name “special products”). The manufacturing has been centralised to four production units organised within the subsidiary Apoteket Produktion & Laboratorier AB (APL).

The Swedish pharmacy market is being reregulated and the pharmacy market will open up for other players than Apoteket AB. APL will have the obligation to (and wants to!) deliver special products to all pharmacy players, but without exclusivity. All new pharmacy players want, at least initially, to have special products delivered by APL and agreements are developed.

As in all transitions from one system to another, the experience from going from a fairly simple system with few players in the supply chain, to a more complex system with many players on different levels in the supply chain, will be interesting to study and evaluate over time. It is important that no one in the new process looses the obvious focus – the safety of the patient!
How to ensure quality and safety of medicinal products prepared in pharmacies for distribution to other pharmacies

Eva Sjöqvist Sahra
Apoteket Production & Laboratoriet AB (APL)
Sweden

Content
- Experience from Sweden - the transformation of the
  Swedish model to a regulated open pharmacy market
- Important aspects for consideration
  - General concept of preparations
  - Clinical relevance of the prescribed pharmaceutical
    product
  - Availability of registered product
  - National formularies or equivalents
  - Simplification of manufacturing
  - Quality of distribution
  - Medication for patient
  - Quality of information to the patient
  - Pharmaceutical compliance
- Agreement between supplying pharmacy and receiving pharmacy

The Swedish pharmacy market until July 1, 2009

APL is a state-owned limited liability company which has,

- Since 2003, been operating as a separate company within the
  Aurore Group, and
- Since 2006, has been operating independently.

It is responsible for adequate supply of all drugs that have been approved for use in Sweden or are imported, and

- Must provide for adequate supply of drugs for the treatment of
  health and welfare services.
- Must ensure that there is a control over the supply of
  medicinal preparations, and
- Must ensure that the supply of medicinal preparations is
  provided by the pharmaceutical industry or the
  establishment designated by the Ministry of Social Affairs.

Reregulation of the pharmacy market in Sweden

- September 2008
  - The pharmacy model will change from a "fixed" to a "flexible"
    model, and
  - The pharmacy market will open up to new players, such as APLAB.

- APLAB will be able to prepare and sell medicinal preparations
  to pharmacies, and
  - New pharmacies will be established.

- The company was acquired in May 2009.

Special Products

- A Special Product is a product that is not prescribed by a
  doctor and is not covered by the pharmaceutical industry, and
  - Can be purchased and sold in all pharmacies.

- The preparation of a medicinal product in small quantities
  - Will be allowed.
- The preparation of a medicinal product in small quantities
  - Can be done by the pharmacist, and
  - Can be sold in all pharmacies.
Definitions according to legislation

- Non-prescription preparation
  A non-prescription drug manufactured at Apoteket AB/SPA (current text) – a pharmacy-compounded drug for a certain
  - patient
  - care unit
  - site of use
  - batch or serial

- Stock preparation
  A standardised preparation or non-prescription drug manufactured by Apoteket AB/SPA which is intended to be sold without registration (market authorisation) or national licence

- National Licence
  A licence that gives the Swedish patent (or standardised preparation or non-prescription drug) the right to be sold without registration (market authorisation) and that has been manufactured by Apoteket AB/SPA (current text) – a pharmacy-compounded drug

Special Products for individualised drug therapy

- Approx. 1-2% of the drugs prescribed in Sweden are individualised products which meet patients’ special requirements

- A Special Product can be a product
  - with an unusual strength or composition, e.g. preservative free
  - for which the desired dosage form is not available
  - with a very short shelf-life

- That needs to be dose adjusted in conjunction with administration
  - with composition adjusted for children

- Which has been deregistered by a pharmaceutical company

- Unregistered product temporarily unavailable

APL’s range of products

- > 2000 products
- Approx. 2000 products batch manufactured
- 1200 (or shelf life)
- Main product groups
  - Paediatrics
  - Neonatal management
  - Skin disorders
  - Oral/rectal products
  - Cardiovascular
  - Other paediatrics
  - Paediatric products for dermatology and thermoactive
  - 60% of the products are for children’s and dermatological
  - 40% via hospital pharmacies

Range of products

- The range of products is developed in close collaboration between APL, prescribers, MPA, and others
- Monographs of the products are written together with specialists
  - The monographs are collected in booklets called APL-booklets – also available at Apoteket AB/SPA
  - APL = Apoteket AB/SPA
  - "Pharmacy Manufacturing Medicinal Products"
  - Each booklet presents the products for a certain product group e.g. pain management, skin products, paediatric products etc.
  - Master Batch Records (MBR) for all stock preparations and commonly used self-preparations
  - APL product monograph = MBR = National Formular

APL’s licensed manufacturing units

- Central laboratory for the development and aseptic preparation of self-preparations and stock preparations
- Central manufacturing according to national and international standards
- Central manufacturing of self-preparations in hospital pharmacies

Manufacturing

- Central laboratory for the development and stock preparation of self-preparations and stock preparations
- Central manufacturing according to national and international standards
  - Central manufacturing of self-preparations in hospital pharmacies
- Central manufacturing of commercial products

Production

- Stock
  - Stocks and aseptic manufacturing of self-preparations in
  - hospitals (doses, oral, aseptic, aseptic syringes, aseptic production)

- Blackberry
  - Doses, sterile injection

- Sera
  - Sterile, injectable solutions
- Dosage forms
  - Injections, ointments, gels, lotions, liquids, suspensions, solutions
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Quality Assurance
- A Quality Assurance system covering all activities of the manufacturing process
- A responsible Quality Assurance Director reporting to the CEO of APL
- Each manufacturing unit has a Qualified Person (QP)
- The manufacturing lines are inspected by the Swedish Medical Products Agency (MPA)
- Manufacturing licence from MPA required

All manufacturing at APL is according to GMP standards
- Regulations according to the Swedish Initial Marketing authorization
- Within the manufacturing of extensions of marketing authorizations and stock preparations
- Published by the Swedish Pharmacopoeia Committee: the Swedish Medical Products Agency (MPA)
- Compliance with national and international standards
- The products are released by a Qualified Person (QP)

How to ensure quality and safety of medicinal products prepared in pharmacies for distribution to other pharmacies
- Important aspects to consider:
  - Reconstitution of drugs: the reconstituted product may differ from the original pharmaceutical product
  - Availability of regulated products
  - National formulas or equivalent
  - Quality assurance of manufacturing
  - Quality of the ingredients
  - Quality of the packaging
  - Quality of information for the patient
  - Quality of pharmacy
- Agreement between supplying pharmacy and receiving pharmacy

Clinical relevance
- Are pharmacy-prepared medicinal products a complement or a competitor to registered products?
- What clinical documentation/data shall be available?
- Is there a mix-up of “one size fits all”?
- What incentives to pharmacy-prepared? Or not?
- Responsibility – doctor, supplying pharmacy or the pharmacy that delivers the product to the patient?
- Preparing (local, regional, national) or European?
- Are products not available across all European countries? Brought in by licence or pharmacy-prepared?

National Formula or equivalent
- Standardisation!
- Ensure that product X is identical irrespective if manufactured at Pharmacy A or Pharmacy B
- Composition
- Manufacturing method
- Quality Control
- Indication, dosage, interactions, adverse events

Quality assurance of manufacturing
- Special licence to manufacture – should increase the standard
- How to follow up – internal inspections or inspections by the authorities
- Raw materials and packaging materials
- Processes, equipment and environment
- Training
Quality of distribution –
time to patient
• Traceability
• Unbroken cold chain
• Patient data – in safe hands?
• Lead time for patient/customer – “see your process through the eyes of your customer”
• Ordinary vs prioritised vs emergency
• Who pays?

Quality of information to the patient
• Is there any written information with the patient/customer as intended receiver?
• Who is responsible for the availability of validated written information?
• Dosing, interactions, ADR etc

Pharmacovigilance
vs reporting adverse reactions
• Standardise naming of pharmacy prepared products
• Use the same system as for registered products
• Develop reporting system with easy access for all pharmacies and doctors

Agreement
• Written agreement, including quality agreement, that states roles and responsibilities between supplying and receiving pharmacy
• Periodical reviews with written reports about process and areas for further improvements
• Patient safety and benefit – always in focus!

Thank you for your attention!

Eva Sjökvist Saers
eva.sjoqvistsaers@srf.se
1.5. “How to ensure quality and safety of pharmacy prepared products for distribution to other pharmacies”

Dr Paul P. H. LE BRUN
Central Hospital Den Haag, Hospital Pharmacy,
The Netherlands

Patients expect optimal care. Pharmacotherapy is part of the daily treatment of patients and pharmacy prepared medicinal products are essential in patient care since not all therapeutical needs are covered by products with a marketing authorisation. The focus of the pharmacist is patient care by preparing unique medicinal products in contrast to commercial trade with authorized drugs.

In some cases, medicinal products have to be prepared for immediate use. A preparation record is designed by an authorised pharmacist for a non-standardised formula to be prepared extemporaneously. The formulation and preparation cannot be validated, shelf life cannot be investigated, analysis is not feasible. In other words, GMP (Good Manufacturing Practices) is not applicable. A risk based approach is necessary in order to analyse the benefits of the preparation for the treatment of the patient. Professional standards based on GMP principles are in place to ensure safety and quality of the product.

Whenever the product is needed more often, the formulation and preparation can and will be standardised. The design of the formulation can be well founded and shelf life data can be investigated. As a next step, stock preparation may be considered. Quality and safety of the products are again ensured by professional standards.

Budgets are not unlimited and it seems not efficient for all pharmacies to invest in facilities for small scale preparation. Cooperation would be more cost effective and, therefore, would save public money. The necessity and the applicability of GMP principles will be discussed for several situations.

On a small scale (eg. one pharmacy with production facilities for several surrounding pharmacies within a region) professional standards based GMP are sufficient to ensure quality.

Delivery on a larger scale may also be efficient for products that are used in a larger region or nationwide. However, it is not allowed to trade drugs without a market authorisation. Therefore, clear conditions are necessary. As an example the experience with the situation in the Netherlands will be discussed. To date, delivery between pharmacies in The Netherlands is allowed for products when an evidence based therapeutic relevance is available, no comparable authorised medicines in the European market is available and production is in accordance with GMP.

This situation can be a starting point for further discussion.
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Daily practise: case 1

- May 2008: bone metastases, which are very painful. Treatment: paclitaxel.
- July 2008: Trametinib is added because of increasing pain.
- August 2008: Pain medication is changed to Duramethan.
- September 2008: Patient is terminally ill and hospitalised.

Patient is treated with intravenous morphine, a branded generic.

(continues)

Daily practise: case 1 (contd)

- October 2008: The patient wishes to spend her last days at home. Her daughter takes care but is not able to administer IV drugs.
- The oncologist prepares a combination of morphine and midazolam to be administered subcutaneously from a 100 ml infusion container to be exchanged every 3 days. Not available as an authorised product.
- The hospital pharmacist prepares a combination of 1 g morphine and 100 mg midazolam in 100 ml.

Two scenarios: adherence to GMP or to professional standards.

Case 1: Scenario 1 GMP

- Literature search for therapeutic evidence.
- Search for a GMP licensed supplier for the raw materials.
- Formulation experiments (e.g., pH dependency).
- Process validation (e.g., the mixing process and the removal of O2 from the solution).
- A test solution is sent to the laboratory. The analysis is validated. Criteria for release are defined. Shelf life is started.
- Degradation products are identified.
- The product is completed.

September 2009: First batch is prepared and released; relatively fast and efficient!

Unfortunately the patient already died in pain Nov. 2008.

Case 1: Scenario 2 professional standards

Day 1:
- Literature: Morphine and midazolam in a mixture is stable for at least 7 days at a low pH.
- Design of a preparation record and review by a second pharmacist.
- The mixture is prepared by a trained technician and kept overnight for observation.

Day 2:
- Visual inspection: A clear and colourless solution.
- Aseptic preparation of the mixture and filling into an infusion container, class A LAF hood class D environment. Expiry date: 1 week after preparation.
- The patient is discharged at the end of the morning with a subcutaneous infusion and dies, free of pain, four days later at home.

Scenario 1 or 2?

- Strict adherence to GMP?
- Or adherence to professional standards?

- Added value of GMP?
- Yes, but GMP needs interpretation.
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Daily practice: case 2
- Common practice during operations: bupivacain 0.1% + sufentanil 1 mg/ml by diluting Sufentanil® and mixing with Marcain® by the anesthesiologist.
- Every day 6 of these mixtures are used in the hospital.
- One day the sufentanil was accidentally not diluted and two patients died of an overdose.
- The accident is discussed, the hospital pharmacists propose to prepare this mixture under controlled conditions in the pharmacy.
- The mixture is prepared aseptically with a shelf life of 24 hours.
- The pharmacist starts stock production of the mixture.

Daily practice: case 2: developments
- Design of the formulation and preparation is started; raw materials are available.
- Methods for analysis from literature are used.
- Test solutions are prepared; a loss of 10% sufentanil is found, probably due to absorption by the filter; a 10% excess is used.
- Shelf life is started; the dosser is prepared and after 6 months, production produces a product with proven quality is started.
- Every 3 weeks a batch of 500 ampoules is produced; complying to professional standards, which differ from industry GMP.

Daily practice: case 2: developments (cont'd)
- Nearby hospital with no production facilities is interested in buying the product on base of a formal cooperation which already exists between both pharmacies.
- The batch is increased to 750 units per 3 months and the nearby hospital receives part of it.
- The production complies to professional standards, one pharmacist responsible for production, another for QC; no QA department and no qualified person.
- More hospitals all over the country, are interested to buy the product; batch size is increased to 2000 units.

Scenario 1 or 2?
- Strict adherence to GMP?
- Or
- Adherence to professional standards?
- GMP (interpretation)?
- Consider care (pharmacy) and trade (industry)
- Risk based approach

Preparations for patient care!
- Focus: availability, service and quality
- Policy in manufacturing?
  - Not commercially available products
    - Therapeutically relevant
    - Not available in required administration form
  - Not for Profit! Added value!

Legislation
- No drugs on the market without a market authorisation
- Exemption:
  - Preparation in a pharmacy prescribed by a physician is allowed
- Efficient? Investments!
- Deliveries between pharmacies?
- Yes: for a limited number of drugs it is appropriate and efficient
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Delivery between hospitals: How are quality and safety ensured in The Netherlands
- Delivery is allowed by Dutch authorities (IGZ, circular 2007-02)
- However, under clear conditions:
  - 1. no authorized drugs available in Europe
  - 2. product file (including therapeutic relevance?)
  - 3. production under GMP

Cooperation in practice condition 1: no authorized drugs available in Europe
- Information available?
- Import company necessary?
- Pharmacovigilance?
- Patient information?
- Cooperation in Europe?

Cooperation in practice condition 2: product file
- Items to be described:
  - Therapeutic relevance
  - Product and process design and validation
  - Specifications (raw materials and finished products)
  - Validated analysis, shelf life

Cooperation in practice condition 2: product file
- Therapeutic relevance is the foundation:
  - Added value!
  - Evidence-based!
  - Systematic approach: A, B, C, D
  - D4 = pharmacotherapy is countrywide accepted

Cooperation in practice condition 3: process quality GMP
- Easy to describe with clear goals
- Evaluation by inspectorate?
- Evidence-based interpretations!
- Education!

Summary
- A patient expects good care
- Patient care requires pharmacy prepared drugs
- Pharmacy prepared drugs: Focus on care and not on trade
- Pharmacy prepared drugs for own patients: professional standards based on GMP
- Delivery between pharmacies: under strict well-defined conditions, e.g., GMP and therapeutic relevance
1.6. “The criteria for the licensing of the preparation of medicinal products in pharmacies”

Dr Ged LEE  
Group Manager – Laboratories and Pharmacopoeia  
Medicines and Healthcare products Regulatory Agency

In the United Kingdom there are two mechanisms for the regulatory control of the preparation of unlicensed medicines. Firstly, manufacturers may obtain a Manufacturing (Specials) Licence (ML Specials) after demonstrating that their facilities and procedures comply with EU GMP requirements. Secondly, the monographs of the British Pharmacopoeia create legally enforceable standards for individual finished product formulations of unlicensed medicines.

The paper will describe the United Kingdom experience with the operation of these regulations. It will also describe the proposals to change the UK regulation of unlicensed medicines following a review of the current legislation.
Break-out session 4
Criteria for Licensing the Preparation of Medicinal Products

Licensing of Preparation
- The value of a licence needs to be considered; it can be withdrawn; it can define conditions; it can define activity, obligations to produce to meet needs
- It should not increase itself requirements but be part of pharmacist’s responsibility
- It can provide false confidence unless appropriate external review is in place.

- Companies who perform commercial pharmacy preparation activities should be licensed
- Pharmacies who are licensed or registered with the National Authority do not need a separate license for preparation. They are required to notify the authority if they are performing pharmacy preparation and will be subject to inspection. The authority must have the power to suspend activity

Restrictions on Preparation Activity
- Not when an authorised pharmaceutically/therapeutically equivalent product is available
- Notification defines the volume of activity
Session theme: Common language – the basis for understanding and cooperation
Session Chair

Dr Jorgen HUSE
Medicines Agency, Norway

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Mr V’lain FENTON-MAY
FRPharmS, United Kingdom

Panellists:

Ms Maria CARVALHO
School of Pharmacy, University London

Mr V’lain FENTON-MAY
FRPharmS, United Kingdom,
Dr Tobias GOSDSCHAN, Swiss Agency for Therapeutic Products
“What terminology can be used for medicinal products prepared in pharmacies: considerations”

Mr V’lain FENTON-MAY
FRPharmS, United Kingdom

This presentation will cover the history and derivation of many of the words used in the preparation of medicines for patients among the words discussed will be

Extemporaneous preparation: A product, which is dispensed immediately after preparation and not kept in stock

Intermediate product: A partly processed material, which should undergo further preparation steps.

Preparation: All operations including the purchase of materials and products, production, quality control, release, storage, delivery of medicinal products and the related controls.

Note: The simple provisioning of medicinal products according to authorized instructions and without necessitating pharmaceutical technical knowledge, where medicinal products are made ready for immediate application (e.g. dissolution of a powder for immediate application according to the instructions in the package leaflet of an authorised product), is normally not normally considered as preparation.

Processing: That part of the preparation of a medicinal product involving the dosage form.

Production: Part of preparation. It involves all processes and operations in the preparation of a medicinal product, from receipt of materials, through processing and packaging, to its completion as a finished product.

Products for immediate use: Products to be administered immediately after preparation, which do not undergo holding or storage.

Starting material: A substance, used for the preparation of a medicinal product, excluding packaging material.

Stock preparation: A product, which is prepared for stock and is available for dispensing

Magistral Formula Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the).

Officinal 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).

Compounding A term that reflects the art implied in the Latin phrase Secundum Artem, whereby a pharmacist uses his/her professional knowledge, experience and skill to produce a medicine
for an individual patient. In the US the term extends to the preparation of chemicals for research, teaching or analysis.

Dispensing To label from stock and supply a clinically appropriate medicine to a patient/client/career, usually against a written prescription, for self-administration or administration by another professional, and to advise on safe and effective use.

Formulation Devising a suitable recipe which will ensure that the patient receives the required medicament in an appropriate form which will be stable for a suitable length of time.

Manufacturing In order to make a clear distinction between industrial manufacture of marketed products and the smaller size manufacture of non-marketed products in pharmacies, the new Guide uses the term preparation instead of manufacture.

Production Production is part of preparation. It involves all processes and operations in the preparation of a medicinal product, from receipt of materials, through processing and packaging, to its completion as a finished product.

CIVA Central intravenous additive service Patient Ready Products Medicinal products which can be administered without any further preparation.
Terminology in Medicine preparation

V. Fenton-May

How important is terminology and how is it derived

- Essential to convey a concept
- But
  - New concepts require new terms
  - Local circumstances differ
  - Perceived variations require different terms
- Legal terminology is derived after word usage has become common, but different.
- Multi Country/Language increase complexity

How important is terminology(2)

- The Committee of Experts CD-PH/PC of EDOM
  - and
- The Pharmaceutical Preparations Working Party of the EP
  - Are both discussing the activities of pharmacists and need a common language

History of preparative service

- In the beginning
  - The apotheker prepared a medicine for an individual patient by compounding a number of starting materials according to his formula and dispensed it to the individual
- Then
  - Society/professions agreed on standard formulations giving rise to Official Preparations

Industrial Revolution to 1980

- The effectiveness of medicines and the ability to manufacture them in a factory created an alternative to the individual compounding
- In parallel, large institutions realised that they too could manufacture in house, efficiently, economically and with improved quality by preparing in anticipation of need
- When the economic advantage declined they turned their facilities to more pressing needs

Administration errors

- The deluge of medicines not ready to administer from industry has lead to an increase in errors arising from preparation/administration at the bedside
- The institutions have turned their facilities to centralised intravenous additive services (CIVAS), which are also known as aseptic compounding
- Such services now rely on manufactured intermediate stocks
- Neither the intermediates nor the final mixture have marketing authorisations.
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Miscellaneous activities

- Instability of many products requires preparation in anticipation of need
  - Radiopharmaceuticals
  - Gene therapy products etc.
- These are often prepared within the terms of the Marketing Authorisation
  - But are prepared before a prescription is issued.
Session theme: Aspects of the reconstitution of medicinal products
Session Chair

Professor Vagn NEERUP HANDLOS
EAHP

Speakers

Dr Lars NIELSEN
Copenhagen University Hospital Pharmacy, Denmark

Panellists:

Ms Ann-Kristin BJERGA BJAEN
Sykehusapotekene HF, Norway

Mr Frits BOOM
Zaans Medisch Centrum, the Netherlands

Professor Vagn NEERUP HANDLOS
EAHP

Dr Lars NIELSEN
Copenhagen University Hospital Pharmacy, Denmark
“Aspects of the reconstitution of medicinal products”

Dr Lars NIELSEN
Copenhagen University Hospital Pharmacy, Denmark

Reconstitution of medicinal products is sometimes required before the product can be administered to patients. As far as possible, reconstitution will be carried out by a hospital pharmacy especially when the product concerned with risk or when the process of reconstitution itself contains risks (e.g. of contamination). Sometimes the nurses on the wards have to reconstitute a medicinal product before its administration to the patient.

There is a quality and safety gap between preparations of medicinal products prepared in hospitals pharmacies and on hospital wards, respectively. There seems to be a discrepancy between the regulations in pharmacies and in other healthcare establishments, respectively.

- Topics covered:
  o Reconstitution of antibiotics and cytotoxics on hospital wards
  o The risks associated with the reconstitution on hospital ward (wrong medicine, wrong solvent, mistakes in calculation, dissolution and labelling; no check by an independent second person; insufficient hygiene, operator exposure).
  o Applicability of risk based approaches (personnel; facilities, such as laminar airflow cabinet) in order to define which activities must be performed in the pharmacy.
  o Obstacles for the hospital pharmacy to take over the process.
  o How the Capital Regional Pharmacy in Copenhagen prepares cytotoxics and antibiotics ready for administration today and in the future (manual process for the individual patient, dose banding and batch process, automation).
  o Quality systems for reconstitution/preparation of medicinal products in the hospital pharmacy (describes process and relevant steps including double check by second person; training and qualification of personnel etc.).
  o Criteria for distinguishing between reconstitution and preparation (administration to patient within 24 hours; prepared for administration to just one patient; no delivery to other hospitals).
  o Different quality and safety standards for pharmacy preparations in Europe.
  o Shelf life for cytotoxics ready for administration in countries in Europe.

- messages conveyed
  o Recommendations for defining activities which must be performed in the hospital pharmacy and not on the wards.
  o Remember, that if it becomes to expensive for the hospitals to perform the activities in the hospital pharmacy, the reconstitution of medicinal products will take place in the hospital wards.
  o Recommendations for the set-up of quality systems for reconstitution of parenterals including the importance of defining responsibilities and authorities for the different professionals.
  o The need for generally accepted guidelines for reconstitution in hospital pharmacies in Europe.
  o The need for a European harmonisation of shelf life’s for cytotoxics.
Aspects of the reconstitution of medicinal products

Reconstituting medicinal products: Considerations

<table>
<thead>
<tr>
<th>Aspects of the reconstitution of medicinal products</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reconstituting medicinal products</td>
<td>Considerations</td>
</tr>
</tbody>
</table>

How many reconstituted units do the hospitals in the Capital Region need and who perform the reconstitution?

<table>
<thead>
<tr>
<th>Consumption in 2009</th>
<th>Reconstitution performed in the pharmacy</th>
<th>Reconstitution performed on the wards</th>
<th>Supply from Bath</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytostatics</td>
<td>100,000</td>
<td>74,000</td>
<td>8,000</td>
<td>130,000</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>260,000</td>
<td>180,000</td>
<td>25,000</td>
<td>465,000</td>
</tr>
<tr>
<td>Other medicinal products that need reconstitution</td>
<td>?</td>
<td>&lt;10%</td>
<td>&gt;50%</td>
<td>0</td>
</tr>
</tbody>
</table>

Reconstitution of Cytostatics in a Danish hospital pharmacy is a safe process!

- Safety Cabinets in dedicated Grade B or C rooms with double enclosure
- Qualified and trained staff and cleaning staff, ensuring programmes
- Production, storage and QC areas is only accessible for authorized staff
- Microbiological monitoring of air, working areas and staff
- Monitoring pressure differences
- All prescriptions is controlled by a pharmacist
- Always check records and recording materials by an independent second person
- Medication errors and deviations from standard procedure are recorded and evaluated

Obstacles for the pharmacy to take over reconstitution of medicinal products from the hospital wards

- The hospital wards and the hospital management don’t understand the requirements to the pharmacy from the Danish Medicine Agency
- The requirements are often very expensive to fulfill, e.g. continuous monitoring of air contamination
- When the hospital pharmacy uses money for fulfilling demands from the Danish Medicine Agency, the money is taken from the wards with consequences for their ability to improve patient safety and quality of treatment
- The wards wish the majority of the finished products delivered from the pharmacy between 8 a.m. and 10 a.m.
- The demand from the wards for cytostatics grows 10-15% per
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Solutions:

- Automation
- Dose branding - Shelf life periods longer than 24 hours
- Stock rationalization
- Work is contracted out to private companies in UK

DiviBoxX – a new closed system for reconstitution of dry substances immediately before use

- With a six-armed robot the hospital pharmacy connects the Divibox transfer needs, the infusion container and the vial.
- Capacity 500-600 units yearly.
- No contamination of the medicinal product.
- No contamination of the surroundings.
- No contact between the dry substance and the infusion fluid before activation.

Shelf life periods for selected cytotoxics ready for administration in UK and Denmark

<table>
<thead>
<tr>
<th></th>
<th>Capital Regional pharmacy</th>
<th>English Hospital pharmacy</th>
<th>Bath ASU UK</th>
<th>Hospita UKE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>14 days</td>
<td>25 days</td>
<td>54 days</td>
<td>35 days</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>14 days</td>
<td>21 days</td>
<td>51 days</td>
<td>84 days</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>14 days</td>
<td>26 days</td>
<td>54 days</td>
<td>84 days</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>14 days</td>
<td>21 days</td>
<td>42 days</td>
<td>84 days</td>
</tr>
</tbody>
</table>

USP chapter 797: Up to 14 days (2-8°C)
DHSGM7 for hospital pharmacy: Up to 30 days (2-8°C)

What we know:
- There is a gap within European countries in quality assurance and standards for reconstitution of medicinal products.
- There is a quality and safety gap between reconstitution of medicinal products performed in hospital pharmacies and hospital wards.
- There is also validity in shelf life periods for cytoxics ready for administration in the European countries.

What we need in 2 documents:
- “Quality and safety standards for reconstitution of medicinal products in European hospitals and European hospital pharmacies.”
- “Quality and safety standards for small scale preparations in European hospitals pharmacies” (could be the PICs guide PE 019.5)

And a list:
- “Shelf life periods for reconstituted Cytotoxics ready for administration”
IV – BREAK-OUT SESSIONS
Note: The views of the Expert Workshop participants indicated during the break-out sessions were taken into account by the Committee of Experts on Quality and Safety Standards in Pharmaceutical Practices and Pharmaceutical Care (CD-P-PH/PC) when it drafted resolution CM/ResAP(2011)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients
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APPENDIX 2 - SPEAKERS’ CURRICULA VITAE

Mr Frits A. BOOM

Mr A. Boom is a hospital pharmacist aged 61 years old. He is Director of Pharmacy in the Central Sterilisation Unit Zaans Medical Centre (ZMC) Zaandam, the Netherlands. He pays special attention to the preparation and quality assurance of medicines in the hospital pharmacy. He is one of the authors of the GMP (Good Manufacturing Practices)-Hospital pharmacy guidelines in the Netherlands, member of the GMP-committee of the organisation of the Dutch hospital pharmacists (NVZA) and also member of the expert panel for medicines’ dispensing on the wards. He is the author of many articles on the topic of small scale drug preparation.

Dr Yvonne BOUWMAN-BOER

Dr Yvonne Bouwan-Boer is a senior pharmacist, working more than 35 years at the Laboratory of the Dutch Pharmacists (LNA), belonging to the Royal Dutch Association of Pharmacists. The LNA supports Dutch local and hospital pharmacists as regards the preparation of medicines. This support takes place through publications, courses and individual consultation. The LNA cooperates with the German NRF. Among the projects in which she is involved are:
- quality system on preparation in local pharmacies,
- quality system on preparation in hospital pharmacies,
- textbook on preparation and drug design,
- set of about 150 SOP’s (Standard Operating Procedures) for preparation.
- Formulary of Dutch Pharmacists containing about 200 formulations for pharmacy prepared medicines.

Ms Ann-Kristin BJERGA BJÅEN, B.Sc

Education:
1987 – 1990: Cand. Pharm. (M.Sc. Pharmacy), Pharmaceutical Institute, University of Oslo
1983 – 1985 B.Sc. Pharmacy, Statens reseptarhøgskole, Oslo
1980 – 1983 St. Svithun videregående skole, Stavanger

Employment History:
2008 - Quality Assurance Director, Sykehusapotekene HF
2007 - 2008 Director, Quality Assurance and Regulatory Affairs, North Europe, Linde Gas Therapeutics
2005 - 2007 QA Manager, Qualified Person (QP), Documentation and Batch Release, GE Healthcare, Oslo Plant
2002 - 2005 Global QA Manager GMP, QP, Quality Assurance R&D, GE Healthcare (Earlier Amersham Health AS), Oslo
2001 - 2002 Department Manager/Chief Pharmaceutical Inspector, The Inspection Function, Norwegian Medicines Agency
1999 - 2001 Pharmaceutical Inspector GMP, Norwegian Medicines Agency, Oslo
1998 - 1999 Manager, Department of Pharmaceutical Development R&D, Weifa AS, Oslo
1991 - 1992 Pharmaceutical Adviser (Analytical development), Norsk Medisinaldepot, Oslo
1990 - 1991 QA/QC Manager, T.Skretting AS, Stavanger
1987 - 1989 Pharmacist, different Pharmacies
1986 Pharmacist, Storhaug Pharmacy, Stavanger

Other Experience:
2007 - Assessed and approved by the University of Oslo to be External Examiner in Production of Sterile Pharmaceutical Products, FRM 3010
2004 - Given lessons in general Quality Assurance aspects and in Qualification and Validation of processes and equipments, Pharmaceutical Institute, University of Oslo
1992 – 2003 Examiner in Galenic Pharmacy, PGG 162, Pharmaceutical Institute, University in Oslo

Ms Maria Joao Reis DE CARVALHO

Qualifications and professional experience: 1998 – 2004 MPharm in Pharmaceutical Sciences. First-class Honours Faculty of Pharmacy, University of Porto, Portugal 2004 – 2006 Compounding Pharmacist at the Community Pharmacy Farmácia Lodelo Vila Real, Portugal 2006 – present PhD in Pharmaceutical Sciences School of Pharmacy, University of London, UK 2007 – present Teaching Assistant at the Master of Pharmacy Course B: Scientific Basis of Pharmacy (Year One, February to June) Course C: Pharmaceutical & Pharmacological Approaches to Therapeutics (Year Two, October to January) School of Pharmacy, University of London, UK.

Honours and grants: 1996 Expedition to the Legendary Potosí. Ruta Quetzal BBVA Complutense University of Madrid, Spain and Bolivia Nominated for top academic achievements 1998 National Youth Leadership Forum on Medicine University of Georgetown, Washington DC, USA Nominated for academic excellence and leadership potential 2006 – 2009 School of Pharmacy Studentship for a 3-year PhD research project School of Pharmacy, University of London, UK Nominated as one of the two best European candidates 2008 Best Poster Presentation. PhD Research Day School of Pharmacy, University of London, UK 2009 Best Lecture Presentation. PhD Research Day School of Pharmacy, University of London, UK.

International experience: 2001 Holland Student Exchange Programme (IPSF-SEP) Zaandam Zaans Medisch Centrum 2002 USA Professional Compounding Centers of America (PCCA). Introductory Boot Camp Houston Internship at Compounding Pharmacies 2004 Brazil Internship at the Compounding Pharmacy Artpharma São Paulo Compounding course at Racine. Quality Control on Compounding Pharmacies Compounding courses at Anfarmag 2009 Denmark European University Consortium for Pharmaceutical Students (ULLA) Copenhagen Summer School at the Faculty of Pharmaceutical Sciences, Univ. of Copenhagen.

for Therapeutic Products (Swissmedic) 2008 Poland Academic Meeting at the Medical University of Gdańsk 2008 Brazil Professional Meeting at the National Institute of Cancer (INCA), Rio de Janeiro 2008 Brazil 31st Catarinense Meeting of Hospitals and Providers of Health Services Florianópolis Association of Hospitals from the State of Santa Catarina (AHESC-FEHOESC) 2009 UK Conference by EuPFI and APS: Formulating Better Medicines for Children London Royal Pharmaceutical Society of Great Britain (RPSGB) 2009 Portugal Symposium: New Compounded Medicines and New Therapeutic Systems Porto Faculty of Health Sciences, University Fernando Pessoa (UFP) 2009 Denmark Symposium: Crossing-Borders Copenhagen Faculty of Pharmaceutical Sciences, University of Copenhagen.


Ms V'Lain FENTON-MAY, BPharm., M.I. Pharm. M.

Qualifications:
B Pharm., M.I Pharm.M. - Bradford 1971
M P.S. - Edinburgh Royal Infirmary 1972
Registered as a Qualified Person under EEC Directive on the Pharmaceutical Industry
Elected Fellow of Royal Pharmaceutical Society in 1992 for activities in the Profession and Practice of Pharmacy.

Current activities:
Member of the British Pharmacopoeia Commission 1998 –
- Chairman BP Working Party on Unlicensed Preparations
- Chairman BP Expert Advisory Group on Medicinal Chemistry
Vice Chairman British Pharmacopoeia Commission 2006-
- UK Delegate to the European Pharmacopoeia Commission 2006-
- UK representative on EP Expert Group on Microbiology
- Chairman EP Working Party on Pharmaceutical Preparations
- Secretary of State nomination on the Advisory Committee on Borderline Substances 1995-
- External assessor to Strathclyde M.Sc. Course in Pharmaceutical Manufacturing
- Lecturer to Brighton University Associate of Lowden International (Consultancy to the Pharma Industry and the NHS)
- Member Investigating Committee of the RPSGB Qualified Person (IMPs) Cardiff & Vale NHS Trust.

Pre-retirement activities:
Quality Control Pharmacist to the Welsh Hospitals 1979-2007
Chairman of Welsh Drugs Contracting Committee 1996- 2005
Member of the Welsh Pharmaceutical Committee 1975- 2005
Member of the DOH Risk Assessment group on Manufacture in the NHS 2000
Chairman Welsh Quality Control Sub-Committee of the Welsh Pharmaceutical Committee 1975-2007
Chairman of the NHS Regional Quality Assurance Working Party on Extemporaneous Preparations
Member of the Welsh NHS Industry forum 2000-
Lead pharmacist in Wales responsible for organising and co-ordinating management training for Principal Pharmacists (Inter Regional Undisciplinary Training) PM(80)19.
Member of the inter-regional training consortia responsible for the management training of Principal Pharmacists. (Wales, East Anglia, Wessex, S.E. Thames)

Extra Curricular:
President UK Guild of Hospital Pharmacists 1988/90
Recipient of the Evans Gold Medal 1992 for merit in hospital pharmacy
Member of the Editorial Board of Hospital Pharmacy Practice 1989-2001
Member of Editorial Board of Pharmacy Management 1987-2004
Chief Science Editor of European Journal of Hospital Pharmacy 1994-
Qualified Person to a Pharmaceutical Company
Founder member of PDIG
Recipient of the David Samways Award for Pharmaceutical Procurement 2009.

Dr Tobias GOSDSCHAN

Dr Tobias Gosdschan is graduated in Pharmacy at the University of Basel, Switzerland, in 1989. After a practical year in a public pharmacy, he returned to university as an assistant for practical studies in pharmaceutical technology and finished his PhD thesis (subject: physico-chemical characterization of oils and surfactants) under the lead of Prof. Dr Hans Leuenberger in 1994.

The following four and a half years, he worked in pharmaceutical industry, being responsible for qualifications, process and cleaning validations at an international solid dosage form manufacturing site.

Since October 1998 he worked as an inspector and establishment license reviewer at the Swiss regulatory authority (Swissmedic, Swiss Agency for Therapeutic Products, formerly IOCM/IKS). From 2000 to 2007, he was member of the Expert Group ‘Galenics’ of the Swiss Pharmacopoeia.

Besides the conduct of inspections, he was involved in various special projects. These included the elaboration of technical documents (e.g. Good Manufacturing Practice rules on a national and international level, Guidance documents for the Swiss inspection system and texts for the Swiss Pharmacopoeia) as well as the elaboration of legal texts (e.g. ordinances related to the Swiss Law on Therapeutic Products).

From 2003 to 2006 he represented Switzerland in several European and world wide bodies and working groups developing strategies to fight counterfeit medicines and pharmaceutical crime.

From 2005 to 2007 he chaired the ‘Expert Circle on Hospital Pharmacy’ of the Pharmaceutical Inspection Convention and the Pharmaceutical Inspection Cooperation Scheme (PIC/S), an expert group elaborating for the first time on an international basis a guide for the preparation of medicinal products by healthcare establishments for direct supply to patients (PIC/S document PE 010: ‘PIC/S Guide to good practices for the preparation of medicinal products in healthcare establishments’).
He became Head of the Pharmacopoeia Division at Swissmedic (National Pharmacopoeia Authority of Switzerland) on 15 December 2007 and acts in this function as Head of the Swiss delegation at the European Pharmacopoeia Commission. Furthermore, he is member of the EDQM Working Party Pharmaceutical Preparations (PHP).

Dr Josee Maria HANSEN

Dr Josee Maria Hansen holds the position of Chief inspector for Pharmaceutical Affairs and Medical Technology at the Dutch Health care inspectorate. Trained as a pharmacist she started her career in the eighties in public and hospital pharmacy. After working in a generic industry in Nicaragua she worked for eleven years in a public pharmacy, owned by a social security insurance company in The Netherlands. In that capacity she was responsible for the production of pharmaceutical products for 65,000 patients. In the early nineties she joined the Dutch Health care inspectorate as a senior inspector, with responsibilities for coordinating norms and standards for inspecting pharmacies and medical devices in hospitals. In 1999 she became chief inspector. Currently she is also project leader of a WHO project on Priority medical devices, in Geneva, Switzerland. The project aims to identify the gaps between the availability of medical devices and public health needs on a global level. One of the objectives of the project is to propose a research agenda to close those gaps.

Mr Jorgen HUSE

Education:
1998 One year post-graduate studies in pharmacy (including management)
1975 – 1980 Cand. Pharm. (M.Sc. Pharmacy), Pharmaceutical Institute, University of Oslo
1972 – 1975 Teisen Gymnas

Employment History:
2001 - Pharmaceutical inspector, Norwegian Medicines Agency
1999 – 2000 Pharmaceutical inspector, Norwegian Board of Health
1997 – 1998 Pharmaceutical advisor, Norwegian Board of Health
1995 – 1997 Marketing manager, ADA as (wholesaler medicinal products)
1986 – 1995 Manager, Nordstrand pharmacy (Oslo)
1983 – 1986 Pharmacist, Lambertseter pharmacy (Oslo)
1981 – 1983 Advisor, Norwegian Poison Information Center
1981 Pharmacist, Sankp /BrigN (military duty)

Other Experience:
1999 - Given lessons in law for pharmacists at Pharmaceutical Institute, University of Oslo

Several honorary functions in pharmaceutical societies, local politics, housing cooperative, environmental protection societies etc.
Dr Blaženka JURIŠIĆ

Education: Dr Blaženca Jurišič is a Doctor of Philosophy at the University of Zagreb, Croatia since February 1996, with a Master of Science in Chemistry, University of Zagreb, Croatia, August 1987, Faculty of Pharmacy and Biochemistry, University of Zagreb, Croatia, Bachelor of Science in Pharmacy, January 1982.

Professional Experience:

2005 - present Head of Microbiological Methods Unit, Agency for Medicinal Products and Medical Devices, Republic of Croatia
2003 - 2005 Consultant of Director of Agency for Medicinal Products and Medical Devices, Republic of Croatia
1999 - 2003 Director of the Croatian Institute for the Control of Drugs, Zagreb
1989 -1999 Associate Research Scientist, Department of Pharmaceutics, Toxicological Chemistry, Faculty of Pharmacy and Biochemistry, University of Zagreb
1984 - 1989 Research Associate, Institute for the Control of Drugs, Zagreb, Croatia
1982 - 1984 Assistant Research Scientist, Department of Physical Chemistry, Faculty of Pharmacy and Biochemistry, University of Zagreb, Croatia

Scientific specialisations:

January 1991-April 1992 Research Associate, Institute of Molecular Biophysics, Florida State University, Tallahassee, FL., USA
September 1987 Institute fur Biochemie, Deutsche Sporthochshule, Köln, Germany
August -September 1986 Drug Control and Teaching Center, King's College, London, UK

Professional requirements:
1994 State exam, professional licence for pharmacists
2002 Specialisation in quality control of drugs (Ministry of Health)

Academic activities:
Teaching in theoretical and practical courses in Toxicological Chemistry (ungraduate study) and in Clinical Toxicological Chemistry Zagreb (post-graduate study), Faculty of Pharmacy and Biochemistry, University of Zagreb

Scientific Activities/Publications:

7 full papers (cited in CC)
Chapters in 2 international books and 3 croatian books
Invited lecturer in 1 international and 6 croatian conferences
Participation in 10 international and 12 croatian conferences
International Activities:

EMEA IPA-EudraGMP expert subgroup
Council of Europe (EDQM) Committee of Experts on quality and safety standards in pharmaceutical practices and pharmaceutical care (CD-P-PH/PC)

Professional Affiliations:
Croatian Pharmaceutical Society
Chromatographic Section of Croatian Society of Chemical Engineers
Croatian Toxicological Society

Ms DACE KIKUTE

Ms Dace Kikute is an expert in the Committee of Experts on quality and safety standards in pharmaceutical practices and pharmaceutical care (CD-P-PH/PC)

Work Experience:

2006
State Agency of Medicines of Latvia
Pharmaceutical Issues Director
Chairperson of the Licensing Committee of pharmaceutical activities

1985 – 2006
Keguma pharmacy Ltd.

Common pharmacy
Director and responsible pharmacy manager
Responsible pharmacist

Education and training

1975 - 1980
Riga Medical Institute
Faculty of Pharmacy
Received Degree of Pharmacist

1998 – 2001
Europharm Forum, WHO
Twinning project "Questions about Medicines"
Project manager
Additional information:

Member of the European Committee on Pharmaceuticals and Pharmaceutical care (CD-P-PH) from Latvia.

Mr Nico KIJLSTRA

Mr Nico Kijlstra studied pharmacy and public administration. He has working experience in a public and hospital pharmacy and was part-time assessor of applications for marketing authorisations for the Medicines Evaluation Board. In 1996 he joined the Healthcare Inspectorate, a public supervisory service and enforcement agency in the Netherlands. There he had several assignments, such as head of the section for pharmaceutical care (2002).

At present his main responsibilities are the coordination of supervisory activities regarding the use of medicines and the quality of pharmaceutical care, chairing the monthly meetings of the inspectors involved. He is responsible for several projects in the field of medication safety and performance measurement in healthcare, all related to the safe and effective use of medicines. He has been involved in the subject of medicines and Internet since 2002, e.g. as a member of the Ad hoc working group on mail-order of medicines of de Council of Europe. He regularly inspects e-pharmacies. Currently he is Vice-chair of the European Committee on Pharmaceuticals and Pharmaceutical Care, and Chair of the Committee of Experts on quality and safety standards in pharmaceutical practices and pharmaceutical care, under the aegis of the European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe, Strasbourg.

Mag Pharm. Helga LACINA

1971 – 1976 Studies of Pharmacy at the University of Vienna
1977 Approbation as a Pharmacist
1977 – 1990 Assessor at the Federal Institute for chemical and pharmaceutical analyses
1990 – 2005 Expert for Regulatory Affairs medicinal products at the Ministry of Health, Vienna, Austria
2006 – Head of Department Regulatory Affairs – national Procedures; Marketing Authorisation of med. Products & Lifecycle Management at AGES/ PharmMed, Vienna, Austria
Austrian Delegate Committee of Experts of the classification of medicines as regards their supply (CD-P-PH/PHO)

Dr Thomas LANGEBNER

Education at University/Medical School Level:

<table>
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<td>Mag. pharm.</td>
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<td>Post graduate course in hospital pharmacy</td>
<td>2002</td>
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<td>AHPH</td>
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</tbody>
</table>
Dr Paul P.H. LE BRUN

Dr Paul Lebrun obtained his degree in pharmacy from the Groningen University in 1982. He started his career in the Dutch Laboratory of Pharmacists (LNA), belonging to the Royal Dutch Association of Pharmacists. The LNA supports Dutch local and hospital pharmacists on the preparation of medicines. From 1985 to 1988 he trained and worked as a hospital pharmacist in the Central Hospital Pharmacy of The Hague. He joined Merck Sharp & Dohme from 1989 to 1992 as production pharmacist. GMP implementation, troubleshooting, training of personnel and product and process validation were the main responsibilities. In 1992 he was appointed as head of production of the Central Hospital Pharmacy of The Hague (AHZ), where he is still working. The AHZ is the largest hospital pharmacy in the Netherlands. The pharmacy supplies 6000 beds in 6 hospitals and 22 nursing homes. It has a centralised production department and laboratory. He is responsible for all production activities, including management, product development, product and process validation and the renovation of premises. He obtained his Ph.D in 2001 on the improvement and development of antibiotic inhalation in CF patients; the title of his thesis was: “Optimization of antibiotic inhalation therapy in Cystic Fibrosis. Studies on nebulised tobramycin. Development of colistin dry powder inhaler system”. In 2001 he received the innovation award of the Royal Dutch Society of Pharmacists for his research. He further specialized as clinical pharmacologist in 2002. To date he is a member of the board of the Dutch Society of Hospital Pharmacists (NVZA); his area of attention is production, QC and QA policy regarding hospital pharmacy in the Netherlands. He is also member of the board of the Dutch section of the International Society of Pharmaceutical Engineering (ISPE).
Dr Gerard LEE: B Pharm, PhD, F R Pharm S, MRSC, C Chem. Group Manager, Laboratories and Pharmacopoeias, Medicines and Healthcare products Regulatory Agency.

Dr Gerard Lee graduated in pharmacy from the School of Pharmacy, University of London in 1971. His pre-registration training was followed by doctoral studies back at the School of Pharmacy. He obtained his PhD in 1975 and carried out post-doctoral studies in the chemistry department at University College, Cardiff. His research field was analytical chemistry, specialising particularly in gc, hplc, ms and gs-ms. He managed the All Wales QC laboratory in Cardiff between 1977-85. In 1985 Dr Lee was appointed Regional Quality Controller for Mersey Regional Health Authority, and in 1996, he moved as Director of Quality Control to newly commissioned analytical laboratories in the Liverpool Pharmacy Practice Unit. From 1996 to 1999 he was President of the European Association of Hospital Pharmacists.

Dr Lee took up his current post as Group Manager, in the Inspection, Enforcement and Standards Division of the Medicines Control Agency (MCA) in February 1999 (now Medicines and Healthcare products Regulatory Agency (MHRA)).

In his current role Dr Lee is responsible for the UK Medicines Testing Scheme of MHRA, the MHRA laboratory services, and the British Pharmacopoeia. Dr Lee is the Secretary and Scientific Director of the British Pharmacopoeia Commission and has a team dedicated for the publication of the British Pharmacopoeia, the British Pharmacopoeia (Veterinary) and British Approved Names. He was elected vice-chair of the European Pharmacopoeia Commission in June 2007.

Professor Vagn NEERUP HANDLOS

Education
June 1969   Cand. Pharm. From the Royal Danish School of Pharmacy
November 1974 Ph.d. in pharmacy. Theses: Radiation cross linking of polyethylene
September 1986 Dr pharm. Theses. Technical aspects of gas sterilisation of medical devices

Appointments
69-70 Private in the Danish army
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 and Capital Region Pharmacy

Others
81-92 Chairman of the national Danish autoclave standardization 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
89-96 Member of the Danish Pharmacopoeia Commission
95-99 Chairman of the Assoc. of Danish hospital pharmacy directors.
2008- Chairman of work group 16, European Pharmacopeia Commission, Strasbourg (Plastic materials and Containers)
Member of the Committee of experts on quality and safety standards in pharmaceutical care. European Directorate for the Quality of Medicines and Health Care (EDQM), Strasbourg

Present work research areas

Research areas:
Cytotoxic drugs in the work place of Scandinavian hospital pharmacies.
Liposomes for gene therapy
The Safe Chemo project. (www.safechemo.eu)
Pulmonary drug delivery for IC-patients.

Dr Lars NIELSEN

Mc in Pharmacy from the Royal Danish School of Pharmacy (1985).

Appointments:

1985-1991: Working with GMP and Quality control on Copenhagen County Hospital Pharmacy
1992-1997: Deputy Head on the Copenhagen County Hospital Pharmacy
1997-2004: Director of the Copenhagen County Hospital Pharmacy
2005-2006: Director of the Hospital Pharmacy in the Copenhagen Hospital Corporation
2007- : Director of the Capital Regional Pharmacy

Board memberships
1993-1995: Chairman of the Hospital Pharmacy section in the Association of Professionals in Pharmaceutical Sciences
1997-2003: Member of the committee for the Danish Pharmaceutical Society
2004-2007: Chairman of the Association of Danish Hospital Pharmacy directors

Dr Henk SCHEEPERS

The Dutch Health Care Inspectorate is an autonomous part of the Ministry of Health, Welfare and Sports and involves professionals of medical, psychiatric and pharmaceutical backgrounds. The pharmacist inspectors mainly supervise the quality and distribution of medicines and medical devices. Mr. Scheepers is working in the Product Safety Programme and in the Hospital Programme. His present activities include inspections of hospital pharmacies and small scale preparations in pharmacies. He is also a specialist in medicinal gases. Mr. Scheepers attended the PIC/S Expert Circle on Hospital Pharmacy. Within the Inspectorate Mr. Scheepers has several special assignments:
- Small scale preparations in pharmacies.
- Large scale preparations in pharmacies, that are specialised in manufacturing.
- Automated distribution through pharmacies (Baxter etc.).
- Hospital pharmacies.

Before he joined the inspectorate, Mr. Scheepers worked in the Pharmaceutical Industry from 1984 to 1998.

Dr Eva SJÖKVIST SAERS

Dr Eva Sjökvist Saers holds a PhD (Pharm) from University of Uppsala, Sweden. Her thesis treated the subject of drug formulation of drugs with extremely low solubility and parts of the research were performed at School of Pharmacy, University of London, UK. She has made numerous publications and presentations over the years.

Eva Sjökvist Saers has held different management positions within the pharmaceutical industry. Eva Sjökvist Saers worked for Astra/AstraZeneca 1992-2003 within Research & Development, where she held global positions. Her field of expertise is formulation development, quality assurance and manufacturing of pharmaceuticals.

Since 2003 Eva Sjökvist Saers is head of Apoteket Produktion & Laboratorier AB, APL, a subsidiary to Apoteket AB. APL develops and manufactures special products that are delivered to patients through retail pharmacies and hospital pharmacies. The service is offered to all operators on the pharmacy market, which is under change in Sweden since the market is deregulated from July 1, 2009. APL offers more approx. 2000 products and also performs other related services to the pharmacies. APL has approx. 450 members of staff, the majority with university education, and is located on four locations.

APL also offers development and manufacturing services to pharmaceutical companies.

Eva Sjökvist Saers is the Chairman of the Swedish Academy of Pharmaceutical Scinces, a non-profit association of individual members (approx. 6000) with a professional interest in the e.g. research & development, manufacturing and use of pharmaceuticals – to promote a high professional standard within the field of pharmaceuticals. The Society was first mentioned in the statutes in 1675.

Eva Sjökvist Saers is a member of the board of Karolinska Institutet Holding AB (KIHAB), a company held by Karolinska Institutet, since 2006. The innovation system at Karolinska Institutet is managed by KIHAB.
Dr Thomas ZAPF

Professional Qualifications

1983  Ambulance man with a rescue service
1988  Study of pharmacy at the University of Freiburg i.Br.
1988  Practical Training in a public Pharmacy
1989  Practical Training with Gödecke AG, Freiburg
1990  State license as pharmacist

Professional Functions

1990  Teacher at a Health School, Lahr
1990  Pharmacist at a public pharmacy, Hohberg
1990  Pharmacist at a hospital pharmacy, Osnabrück
1991  Pharmacist at a hospital pharmacy, Remscheid
1995  Scientist (Development and Regulatory Affairs) with Dr Falk Pharma, Freiburg
1995  PhD Thesis at the University of Freiburg
      Title „Dielectric characterisation of surfactants“
2007  Pharmacist at a public pharmacy, Stuttgart
2007  Postdoc at the University of Jena (Sterile Production)
2000  Head of the pharm. technol. Lab with Gebro Pharma, Austria
2003  Scientific assessor at the Federal Institute of Drugs and Medical Devices (Licensing Section – Pharmaceutical Quality)
2003  Scientific officer at the Federal Institute of Drugs and Medical Devices (Head of the Standard Marketing Authorisation Unit)
APPENDIX 3 - LIST OF PARTICIPANTS

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F-93285 Paris St. Denis

Ms Carmen DE LA MORENA
AEMPS
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ES-28022 Madrid

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UHBS
Spitalstrasse 26
CH-4031 Basel

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National Institute of Pharmacy
Zrinyi utca 3
HU-1051 Budapest

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Medicines Products Agency
Uppsala
Sweden

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General Pharmaceutical Inspectorate
38/40 Dlugi St.
PL-00238 Warsaw

Mag. Karin KIRCHDORFER
AKH
Vienna
Austria

Dr Hilda KOESZEGI-SZALAI
National Institute of Pharmacy
Zrinyi utca 3
HU-1051 Budapest

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Swissmedic
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Austrian Chamber of Pharmacists
Spitalgasse 31
A-1090 Vienna

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State Institute for Drug Control
Srobarova 48 100
CZ-10041 Praha

Mr Alemka MITAR BRATANIC
KBC Zagreb
Krspaceva 12
HR-1000 Zagreb

Dr Juta RIEDL
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Hallerstrasse 7
CH-3000 Bern 9

Dr Farshid SADEGHPOOR
Pharmacy HUG
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CH-1211 Geneva 14
Ms Kristine SALMINEN
National Agency for Medicines
Mannerheimintie, 103b
FI-0830 Helsinki

Ms Chrystalla SAVVIDOU
Pharmaceutical Services
Nicosia
Cyprus

Mr Haraldu SIGURJONSSON
Icelandic Medicines Control Agency
Eidistorg 13-15
Seltjarnarnes
IS-170 Seltjarnarnes

Ms Anne Elisabeth SMEDSTAD
Norwegian Pharmacy Association
PO Box 5070
Majorsturen
N-0301 Oslo

Ms Luisa TARNO
AEMPS
Campezzo 1
E-28022 Madrid

Dr Maria TERRACCIANO
Ministry of Labour, Health and Social Affairs
Department of Innovation
Directorate General of Medicines and Medical Devices
Via G. Ribotta 5
I-00144 Rome
APPENDIX 4 – PRESS RELEASE

Medicinal products prepared in pharmacies: Committee of Ministers of the Council of Europe adopts a resolution

The Committee of Ministers of the Council of Europe has adopted on 19 January 2011 a Resolution on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients.

Patients have special needs as regards the medication they need caused by age, medical condition, individual disposition and environmental factors. Medicinal products made available by the pharmaceutical industry cannot always cover these needs: therefore, medicinal products prepared in pharmacies are important elements of pharmaceutical care in Europe.

The preparation of medicinal products in pharmacies is not harmonised throughout Europe.

Patients rightfully expect medicinal products that are of appropriate quality, safety and therapeutic value irrespective of whether they are prepared in a licensed pharmacy by virtue of the pharmacist’s professional qualification or placed on the market by the pharmaceutical industry.

This Resolution is a major breakthrough to protect patient safety and to prevent quality and safety gaps between medicinal products prepared in pharmacies and at industrial scale through outlining assurance principles for structures and processes.

As an innovative approach to assist in the selection of the quality system required for the preparation, the Resolution proposes a model for assessing the risk carried by the preparation.

Resolution CM/ResAP(2011)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients recommends the adaptation of regulations in line with principles inter alia for the:

- added value of pharmacy-preparations and responsibilities of health-care professionals;
- preparation process;
- product dossier;
- labelling;
- reconstitution of medicinal products in health-care establishments;
- authorisation for pharmacies or licences for companies making preparations for pharmacies.

The European Directorate for the Quality of Medicines & HealthCare (EDQM) and its bodies promotes human and animal health through the setting of standards and norms for the quality of medicinal products and their safe and effective use in society.
RESOLUTION CM/RESAP(2011)1
ON QUALITY AND SAFETY ASSURANCE REQUIREMENTS FOR MEDICINAL PRODUCTS PREPARED IN PHARMACIES FOR THE SPECIAL NEEDS OF PATIENTS
(Adopted by the Committee of Ministers on 19 January 2011
at the 1103rd meeting of the Ministers’ Deputies)

The Committee of Ministers, in its composition restricted to the representatives of the States Parties to the Convention on the Elaboration of a European Pharmacopoeia1 (ETS No. 50),

Considering that the aim of the Council of Europe is to achieve greater unity between its members and this aim may be pursued, among others, by common action in the public health field including the adoption of common regulations;

Having regard to the standard-setting carried out under the Convention on the Elaboration of a European Pharmacopoeia and its Protocol (ETS No. 134) which endeavours to promote progress in every way possible, both in the social field and the related field of public health through the harmonisation of specifications for medicinal substances, which, in their original state or in the form of pharmaceutical preparations, are of general interest and importance to the peoples of Europe;

Underlining the need to apply where possible relevant international standards such as those developed by the World Health Organisation and the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S);

Recalling also the chapters and monographs of the European Pharmacopoeia containing general and specific requirements applicable to medicinal products prepared in pharmacies, in particular about standards and methods for the control of the chemical, pharmaceutical and microbiological quality of active substances and excipients, about dosage forms and containers;

Bearing in mind the measures proposed in the Committee of Ministers Resolution ResAP(93)1 on the role and training of community pharmacists, Resolution ResAP(94)1 on the rational use of medicines and Resolution ResAP(97)2 on the development of the function of pharmacists and the adaptation of their initial training, and the need to implement them;

Recalling the measures proposed in the Committee of Ministers Resolution ResAP(2001)2 concerning the pharmacist’s role in the framework of health security, inter alia emphasising that community pharmacists are the health professionals most readily accessible to patients and that they help to personalise the delivery of patient care;

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1 States concerned: Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, “the former Yugoslav Republic of Macedonia”, Turkey and United Kingdom.
Bearing in mind the results of the international symposium “European cooperation and synergy in quality standards beyond the European Pharmacopoeia”, held on 15 and 16 June 2007, and of the expert workshop “Promoting standards for the quality and safety assurance of pharmacy-prepared medicinal products for the needs of patients”, held on 24 September 2009 at the European Directorate for the Quality of Medicines & Health Care (EDQM), Council of Europe, in Strasbourg;

Considering that medicinal products manufactured by the pharmaceutical industry are not always authorised or available to cover the special needs of individual patients;

Noting that medicinal products manufactured on an industrial scale must obtain marketing authorisation issued by the competent regulatory authority before being placed on the market;

Considering that the preparation of medicinal products in pharmacies, which may be required as a consequence of the individual or medical condition of the patient in the absence or unavailability of appropriate medicinal products on the market, is indispensable for accommodating the special needs of individual patients in Europe;

Noting that the preparation of medicinal products in pharmacies is not harmonised throughout Europe and falls under the national competencies of the States Parties to the Convention on the Elaboration of a European Pharmacopoeia;

Considering that pharmacists can legally prepare medicinal products in the pharmacy by virtue of their professional education, professional licence and licensing of the pharmacy’s premises;

Emphasising that patient safety and the achievement of the therapeutic aim require that medicinal products prepared in pharmacies meet appropriate and specific criteria for quality, safety and added value also where no marketing authorisation is required;

Underlining that the requirements for the quality and safety assurance of medicinal products prepared in pharmacies through specific structures and processes, in addition to the relevant pharmacopoeial requirements, are necessary for ensuring appropriate patient safety in Europe and the added value of the preparation of such medicinal products in pharmacies;

With a view to avoiding quality and safety gaps between medicinal products prepared in pharmacies and those prepared on an industrial scale, recommends that the governments of the States Parties to the Convention on the Elaboration of a European Pharmacopoeia adapt their regulations in accordance with the principles set out in the present resolution:

- added value of pharmacy preparations and responsibilities of health care professionals;

- preparation process;

- product dossier;

- marketing authorisation;

- labelling;
- compliance with pharmacopoeial requirements;
- reconstitution of medicinal products;
- authorisation for pharmacies or, if not covered by other national legislation or guidance, licences for companies making preparations for pharmacies;
- transparency and safety;
- rational use;
- surveillance;
- communication and information to patients;
- distribution of pharmacy preparations.

In order to implement the present resolution, States Parties to the Convention on the Elaboration of a European Pharmacopoeia will have to supplement it through additional practical guidance, taking into account the national frameworks.

Appendix to Resolution CM/ResAP(2011)1

1. Field of application

This resolution covers medicinal products for human use only. Other products, such as medical devices or cosmetic products, are outside the scope of this resolution.

This resolution applies to pharmacy preparations also known as unlicensed pharmaceutical preparations, i.e. medicinal products which are prepared for the special needs of patients by community and hospital pharmacies and to comparable processes and preparations of medicinal products as referred to in paragraph 10.2. It applies also to the reconstitution of medicinal products in health care establishments.

The provisions cover all pharmacy preparations, both extemporaneous and for stock, and their applicability depends on the outcome of the risk-assessment of the pharmacy preparation.

2. Definitions

Closed-system procedure for sterile medicinal products: a procedure whereby a sterile medicinal product is prepared by transferring sterile starting materials or solutions to a pre-sterilised sealed container, either directly or by using a sterile transfer device, and without exposing the solution to the external environment (such as intravenous infusion services: services for cytotoxic medical products or total parenteral nutrition (TPN)).

Dispensing pharmacy: the pharmacy which receives the prescription for a patient and which provides the pharmacy preparation to the patient (often, the preparing and the dispensing pharmacies are identical).
External supply (see note 1, model procedure for risk assessment): any supply of pharmacy preparations by the preparing pharmacy other than directly to patients.


Internal supply (see note 1, model procedure for risk assessment): the direct supply of pharmacy preparations to patients by the preparing pharmacy.

Open-system procedure for sterile medicinal products: a procedure whereby a sterile medicinal product is prepared and the solution is exposed to the external environment.

Pharmaceutical equivalent: a medicinal product having the same active substances, irrespective of the excipients used, the same or similar intended purpose, equivalent strength and posology, and the same or similar route of administration.

Preparing pharmacy: produces the pharmacy preparation for a dispensing pharmacy (often, the preparing and the dispensing pharmacies are the same).

Reconstitution: manipulation to enable the use or application of a medicinal product with a marketing authorisation in accordance with the instructions given in the summary of product characteristics or the patient information leaflet.

3. Added value of pharmacy preparations and responsibilities of health care professionals

Pharmacy preparations are of added value if, due to medical, pharmaceutical or personal reasons, they are needed by a specific patient or by specific population groups with particular needs.

3.1. Pharmaceutical equivalents on the national market

Pharmacy preparations are not advisable if a suitable pharmaceutical equivalent with a marketing authorisation is available. Before preparation the pharmacist should verify whether a pharmaceutical equivalent is available on the national market, taking into consideration the pharmaceutical form and the strength.
3.2. **Added value and responsibility of health care professionals**

The professionals involved in patient care should jointly assume responsibility for determining whether a pharmacy preparation could be of added value. They should take into account the medical need of the patient. A pharmacist should be able to refuse a prescription for a pharmacy preparation if a suitable pharmaceutical equivalent is available on the national market, inform the physician that a suitable pharmaceutical equivalent is available and discuss with the physician if there is a specific need to dispense a pharmacy preparation.

If the preparing pharmacy and the dispensing pharmacy are not identical, their different responsibilities, including the sharing of those elements of the product dossier essential for the safe use of the product by the patient, should be defined either in regulations or a contractual agreement. Pharmacy preparations should always be distributed by a dispensing pharmacy because this pharmacy receives the prescription for the patient. The preparing pharmacy should be responsible for ensuring that an appropriate quality assurance system is in place.

4. **Preparation process**

All pharmacy-prepared medicinal products should be prepared using an appropriate quality assurance system. Before preparation, a risk assessment should always be carried out in order to define the level of the quality assurance system which should be applied to the preparation of the medicinal product.

A possible model procedure for risk assessment, described in section 5.2 and in note 1, provides an aid to distinguishing between two risk levels (“high-risk preparations” and “low-risk preparations”) and between two levels of quality system based on a risk-graded application of quality assurance principles.

It is recommended that the GMP Guide be used as a reference for an appropriate quality system for “high-risk preparations”, and that the PIC/S GPP Guide be used for “low-risk preparations”. The application of other guidelines with an equivalent quality level is possible, depending on the national legislation or guidance.

Premises, facilities and pharmaceutical knowledge should be appropriate for the preparation of the medicinal product.

5. **Product dossier**

Product dossiers, as described in note 2, should be required only for stock preparations.

For extemporaneous preparations it will not usually be possible to compile a complete product dossier containing all possible information mentioned in section 5.1. as it could lead to a delay in the supply of necessary medicines. For extemporaneous preparations, however, the pharmacist and the prescriber should always consider the risks for the patient, which include the risks posed by a medicinal product without documentation specifying the added value of the pharmacy preparation and the quality assurance system applied to its production versus the risks related to the unavailability of this medicinal product.
5.1  *Topics to be covered by a product dossier*

The pharmacy should ensure a good balance between all possible disadvantages and the added value of the pharmacy preparation. The product-specific quality properties, as well as the site-specific manufacturing conditions of the preparation should be specified in a product dossier.

A product dossier should cover the following topics:

- **a.** demonstration of the added value of the pharmacy preparation;
- **b.** demonstration that the active pharmaceutical ingredients, excipients and containers meet relevant requirements, taking into account specific patient needs;
- **c.** description of the preparation process including, where appropriate, testing;
- **d.** development and background documentation of the preparation process;
- **e.** use of the product including information for the patient and the prescriber.

The contents and detail of information as mentioned in points a to e above depend on the risk assessment, which should be documented. The product dossier should be more comprehensive for preparations that carry a higher risk than for those carrying a lower risk.

This is taken into account by the model procedure for risk assessment, see note 1.

Alternative risk assessment methods may be applied, provided that an appropriate assessment of the risk is obtained.

More details about the product dossier can be found in note 2.

5.2  *Risk assessment of a pharmacy preparation*

When making a pharmacy preparation, the pharmacist should always undertake an appropriate risk assessment in order to determine the level of the quality system which should be applied to the preparation of the medicinal product.

This risk assessment should consider:

- **a.** dosage form and administration route;
- **b.** amount prepared;
- **c.** pharmacological effect of the medicinal product for the envisaged route of administration;
- **d.** therapeutical window (dose range for therapeutic doses);
- **e.** type of preparation process;
- **f.** supply.
The risk assessment should consider the contribution of active pharmaceutical ingredients and excipients to the safety profile of the pharmacy preparation.

Where appropriate, active pharmaceutical ingredients manufactured according to GMP and analysed according to pharmacopoeial standards should be used.

A risk assessment model can be found in note 1.

5.3. Availability of data for authorities for inspection or upon request

Pharmacies should have chemical, pharmaceutical and microbiological data or information (see section 5.1,a-e), as applicable, concerning the pharmacy preparations available for inspection or upon request of the authorities.

The production of different batches should be documented in individual batch records, which should be included in the product dossier.

6. Marketing authorisation

If the preparation is carried out on a scale comparable to the industrial level, if distribution takes place and if an authorised medicinal product, or a pharmaceutical equivalent (see section 3.1), is on the market, the competent drug regulatory authorities should consider establishing, if they have not already done so, the requirement for obtaining a marketing authorisation, including full compliance with GMP, for pharmacy preparations (see note 1: refer to “high-risk preparation”).

7. Labelling

Correct labelling is essential for patient safety. The label should present the following information, as appropriate:

a. name, address and telephone number of the dispensing pharmacy;
b. name and address of the preparing pharmacy;
c. name of the pharmacy preparation, if applicable;
d. full qualitative composition and the quantity of the active substance;
e. batch number, if applicable;
f. expiry date or information about limits for use;
g. special storage conditions or handling precautions;
h. directions for use, warnings and precautions;
i. route of administration.

8. Compliance with pharmacopoeial requirements
When a pharmacy preparation is needed and if it is applicable, a standard formula should be searched in a national pharmacopoeia or nationally recognised formularies.

Active pharmaceutical ingredients and excipients used for the pharmacy preparations, dosage forms and containers must comply with the relevant chapters and monographs of the European Pharmacopoeia or, in absence thereof, of a national pharmacopoeia of a State Party to the Convention on the Elaboration of a European Pharmacopoeia.

Where no applicable pharmacopoeial individual monographs or general chapters exist, the chemical, pharmaceutical and microbiological quality of the starting materials should be fit for pharmaceutical use and be demonstrated on the basis of validated methods.

9. Reconstitution of medicinal products in health care establishments

In general, reconstitution of medicinal products should preferably take place in a pharmacy, assuming that the requirements concerning the safe preparation of sterile products can be fulfilled. Reconstitution considered to be low risk can be done on the wards.

9.1. Risk assessment for reconstitution

The risk assessment should consider the following topics:

a. complexity of the process and the availability of adequate instructions
   - complexity of the reconstitution process, e.g. the number of steps in the process;
   - processing instructions that define and document the steps to be followed in the reconstitution processes for the different products.

b. premises, equipment and the application of environmental monitoring
   - premises and equipment used;
   - availability of clean areas with the required air classification;
   - availability of laminar air flow systems;
   - environmental monitoring that demonstrates the effectiveness of the measures taken to minimise the risk of contamination of the product by the personnel.

c. nature of the product

Sterile medicinal products

In the case of reconstitution of authorised medicinal products for parenteral administration, the risk assessment should be documented.

System requirements comprise both closed-system procedures or open-system procedures.
d. relevant education and training

Hygienic behaviour and appropriate clothing should be ensured, in accordance with the instructions. Appropriate training must be documented. Qualification of personnel should be checked, based on the results of individual microbiological monitoring.

9.2. Responsibilities of the health care establishment

Based on the above risk assessment (see section 9.1), the health care establishment should decide and document which products should be reconstituted in pharmacies and which products can be reconstituted in the wards.

When reconstitution takes place in the ward, a pharmacist should approve written procedures and ensure that the staff involved in reconstitution are appropriately trained.

9.3. Role of the authorities

As reconstitution is not generally considered a process in the frame of pharmacy preparations, national authorities should develop, in co-operation with the relevant professional bodies, specific legislation or guidance taking into consideration the elements in the present section 9.

10. Authorisation for pharmacies or licences for companies making preparations for pharmacies

10.1. Authorisation for pharmacies

In general, authorisation by the competent authorities or bodies is a prerequisite for a pharmacy to carry out operations.

If considered appropriate to guarantee the quality and safety of pharmacy preparations, the authorities should provide for an additional authorisation or a licence for preparation. An additional authorisation or licence can be granted or suspended, depending on compliance with its conditions.

10.2. Licence for companies

In some countries the preparation of medicinal products is performed at the request of pharmacies by companies which are not pharmacies. In this case, a licence for manufacture (for EU member states, a manufacturing licence and full compliance with GMP) issued by the competent authority should be mandatory.
11. Transparency and safety

11.1. Reporting of quality and safety issues

All quality and safety issues arising from the use or making of pharmacy preparations should be recorded and notified to the competent national authorities. An appropriate system for reporting quality and safety issues should be put in place which allows for a link between this notification, the product, the preparing and dispensing pharmacies, and the preparation process.

11.2. Notification or announcement system

With a view to dealing with high-risk preparations, the competent national authorities should obtain relevant information on the preparation activities performed in each pharmacy. The establishment of an appropriate notification system should be considered.

11.3. Inventory for pharmacy preparations

With a view to transparency as regards pharmacy preparations for stock, the establishment of national inventories is encouraged.

The national inventory should cover the following topics:

a. names of the preparing pharmacies;

b. full composition of the available pharmacy preparations;

c. preparing pharmacies’ portfolio of different preparations.

11.4. Rational use

Based on clinical criteria, member states should be encouraged to engage with clinical experts on rational use of the medicines established in the inventory.

11.5. Surveillance

Based on the information obtained through the above-mentioned notification system, the competent authorities should perform risk-based inspections.

Competent authorities should have powers to suspend preparation activities.

12. Communication and information to patients

Communication to patients and carers of patients receiving pharmacy preparations is of crucial importance.

12.1 Information about the pharmacy preparation

Essential information should be given to the patient, if available, based on the product dossier. A leaflet containing product-specific information to patients is not needed for pharmacy
preparations. General information to patients concerning the therapy and the use of the pharmacy preparation is recommended, including indications in some specific cases.

13. Distribution of pharmacy preparations

13.1. Compliance with good distribution practices (GDP)

Pharmacies or companies preparing medicinal products under their responsibility upon the request of pharmacies should comply with good distribution practices (GDP).

13.2. Export/import of pharmacy preparations

Other than to meet an individual patient’s needs, export/import, of pharmacy preparations from a State Party to the Convention on the Elaboration of a European Pharmacopoeia to other states parties should not take place, unless bilateral agreements exist. As long as no uniform and mutually agreed quality requirements for medicinal products without marketing authorisation are available, and as long as the inspectorates’ competencies are not regulated, export should not take place.

* * *

Note 1: Model procedure for risk assessment

This is a proposed model for risk assessment as to whether a pharmacy preparation carries a high or a low risk as referred to in this resolution. Alternative risk-assessment methods may be applied provided that an appropriate assessment of the risk is obtained.

The risk assessment should also consider the contribution of the active pharmaceutical ingredients, excipients and containers to the safety profile of the pharmacy preparation.

Under the following sections 1 to 5, the decision criteria for the risk assessment of pharmacy preparations are specified. Each decision criterion has a graded risk factor ranging from 1 to 5. The multiplication of these risk factors results in a number, which indicates the level of the quality system required for the pharmacy preparation process. If the number is higher than 100 the preparation is considered a “high-risk preparation”; if the number is equal to or lower than 100, it is considered a “low-risk preparation”. It is recommended that the GMP Guide be used as a reference for an appropriate quality system for “high-risk preparations”, and that the GPP Guide be used for “low-risk preparations”. The application of other guidelines with an equivalent quality level is possible, depending on national legislation or guidance.
Risk-based decision matrix

1. Type of preparation

a. parenteral preparations = 5
b. eye preparations used in trauma or surgery = 4
c. preparations for inhalation = 4
d. dosage forms for sterile digestive administration (such as oral, sublingual and rectal administration) = 4
e. cutaneous and transdermal preparations = 4
f. dosage forms for digestive administration (such as oral, sublingual and rectal administration) = 3
g. eye preparations used on the intact eye = 1
h. cutaneous and transdermal preparations/dosage forms where sterility is not required = 1

2. Amount prepared annually (units)

Depending on the type of preparation and the amount prepared annually, a risk factor between 1 and 5 should be determined, taking into account national legislation or guidance. It is recommended to define a separate set of risk factors (1-5) for the following types of preparation, with a risk factor of 1 for very small amounts:

a. liquid preparations and solid preparations (e.g. powders);
b. oral preparations (solid dosage forms);
c. rectal preparations;
d. cutaneous and transdermal preparations;
e. eye preparations.

3. Pharmacological effect of the active substances

a. very strong = 5
b. strong = 3
c. mild = 1

While grading the pharmacological effect of the active substances, the following criteria should be considered: absence of a pharmacopoeial monograph at European level or at the level of a State Party to the Convention on the Elaboration of a European Pharmacopoeia, carcinogenetic properties, mutagenic properties, ecological toxicity, risk of allergy, therapeutical window,
dosage, stability (light, O₂, temperature, pH changes), and chemical, pharmaceutical and microbiological quality.

4. Preparation process

a. aseptic filling = 5
b. terminal sterilisation = 4
c. dissolving, mixing not for the purpose of reconstitution = 2
d. diluting not for the purpose of reconstitution = 2
e. filling only (non-sterile product) = 1

5. Supply

a. external only = 5
b. mainly external (I:E ≈ 1:2) = 4
c. internal and external (I:E ≈ 1:1) = 3
d. mainly internal (I:E ≈ 2:1) = 2
e. internal only = 1
Note 2: List of topics to be covered in a product dossier, depending on the results of the risk assessment for pharmacy preparations

1. Added value and preparation process of the pharmacy preparation
   a. description of the final preparation process;
   b. demonstration of the added value of the pharmacy preparation.

2. Composition
   a. function;
   b. demonstration that the active pharmaceutical ingredients, excipients and containers meet relevant requirements, taking into account specific patient needs;
   c. specifications and traceability of origin of the starting materials;
   d. specifications of the primary packaging material, etc.

3. In-process controls and quality controls of the finished product
   a. product specific procedures;
   b. records of prepared batches.

4. In-process controls and quality control of finished product
   a. sampling;
   b. analytical methods;
   c. acceptance criteria, etc.

5. Results of test batches (namely, information on the development, background and evaluation of the preparation process, including testing)

6. Validation
   a. of preparation process;
   b. of analytical methods.

7. Stability considerations
   a. a plan for own stability studies;
   b. the evaluation of stability data, etc.

8. Use of the product and information for the patient.