PHARMACY PREPARATION ACROSS EUROPE – IS THERE A LEVEL PLAYING FIELD?

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- Pharmacy standards in the UK
- Preparation in clinical areas
- How does Europe compare?
- EU Resolution on pharmacy preparation Resolution CM/ResAP(2011)1
- EU project on reconstitution
- Impact in the UK

E U (Orange) GMP “Industrial” Guide

- Standards applied across the EU (and beyond) for companies holding Manufacturing Authorisations
- Standards required by the Regulatory Authority in the UK (MHRA) for all hospital preparation that requires* a manufacturing licence – generally a Specials licence (MS)
- * Quantity limits/ conditions apply

CONDITIONS FOR UNLICENSED ASEPTIC PREPARATION
(MCA GUIDANCE TO NHS 1992)

- done by or under the supervision of a pharmacist
- uses closed systems
- ingredients are licensed medicinal products or made in licensed facilities
- expiry of no more than one week (supported by stability data)
- all activities should be in accordance with defined NHS guidelines

The Quality Assurance of Aseptic Preparation Services
Yellow Guide

- ‘defined NHS guidelines’ (Loss of Crown Immunity Guidance MCA, 1992)
- Standards for unlicensed aseptic preparation in UK implemented by EL(97)52 audits

Orange and Yellow Guides

- Standards for audit for unlicensed units operating under S10 exemption
- Risk based inspections by MHRA – as Pharma industry
- For all types of manufacture – sterile and non-sterile
- Audit by Regional QA in line with EL(97)52
- For aseptic preparation only
NPSA Patient Safety Alert 20
Promoting safer use of injectable medicines

- 6 actions for NHS
- Action plans required from all Trusts
- Action 1 - Requirement to identify high risk practices and products prepared
- Joint clinical/pharmacy risk assessment in all clinical areas using development of Beaney and Black* risk assessment tool

*Hospital Pharmacist 2005;12:150-154

NPSA 20 Risk Factors for Assessment of Preparations

- Therapeutic Risk
  - List given
- Use of a concentrate
- Complex Calculation
- Complex Method
- Reconstitution Required?
- Part / Multiple vials
- Use of Rate control device
- Non Standard giving set.

NPSA 20 - Actions for the NHS 1-3

- Undertake a risk assessment of the injectable medicines procedures and products used in their organisation.
- Ensure that there are up to date written protocols and procedures that cover the prescribing, preparation and administration of injectable medicines by all healthcare professional in all near patient areas where injectable medicines are used.
- Ensure the availability of essential information for the safe use of injectable medicines at the point of use in all near patient areas where injectable medicines are used.

NPSA 20 - Actions for the NHS 4-6

- Implement purchasing for safety procurement policies to obtain products that are safer in preference to those that pose patient safety risks in practice.
- Implement a programme of training to ensure that staff are competent to prescribe and use injectable medicines safely.
- Produce an injectable medicines report each year. The report should be communicated to Clinical Governance and Drugs and Therapeutics Committees each year and this information should also be used as part of the performance management process by external organisations.

Never Events February 2011

- Wrongly prepared high-risk injectable medication (new Never Event No 4)
- There are financial penalties to the Trust if a Never Event occurs
- Trusts must know what their high-risk injectable medicines are i.e. must continue to undertake risk assessment
The “Spectrum of Preparation” Concept*  
A.M. Seamey 2005

Sterile Products

<table>
<thead>
<tr>
<th>Preparation in clinical areas</th>
<th>Preparation in unlicensed aseptic unit</th>
<th>Manufacture in pharmacy specials unit</th>
<th>Licensed Product (industry)</th>
</tr>
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<tbody>
<tr>
<td>Scale</td>
<td>Risk</td>
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Pharmaceutical Inspection Co-operation Scheme (PIC/S SCHEME)

- PIC/S now covers 39 countries including EU
- Website: www.picscheme.org
- Promotes exchange of information and harmonisation of standards e.g. mutual training for inspectors, publication of standards documents


- Applies to preparation of medicines for direct supply to patients
- Comprises 9 general sections (QA systems, Personnel, Premises and Equipment, Documentation, Production, QC, Work contracted out, Complaints and Recalls, Self-audits), plus Annex 1 Sterile products Annex 2 Non-sterile liquids creams and ointments
- EU GMP Guide for industrial manufacture

SURVEY* ON QA STANDARDS FOR PREPARATION ACROSS THE EU

- Key findings
  - 16/19 have quality and safety standards for products prepared in pharmacies e.g. EP
  - 7/19 have additional standards for larger batches
  - 8/19 have quality and safety standards for products prepared on wards
  - 15/19 no authorisation needed for pharmacy preparation
  - 13/19 have pharmacies that prepare for other pharmacies i.e. trade across boundaries
  - 4/19 need to justify therapeutic benefit

* PharmEuropa Oct 2010 (Vol 22, No 4) **Reconstitution** of authorised medicinal products is a ‘grey area’ as to whether it falls under the definition of preparation or not.

SURVEY* ON QA STANDARDS FOR PREPARATION ACROSS THE EU

- Wide variation between countries in QA and safety standards for pharmacy preparation
- Quality and safety gap between products prepared in pharmacies and those prepared on wards
- Even fewer quality and safety requirements defined for preparation on wards than for pharmacy preparation
- Reconstitution** of authorised medicinal products is a ‘grey area’ as to whether it falls under the definition of preparation or not.
- Based on 19 countries – UK only sent in GN14 (The supply of Unlicensed Relevant Medicinal Products for Individual Patients)

* PharmEuropa Oct 2010 (Vol 22, No 4) **Reconstitution defined as manipulation to enable the use or application of a product with a MA in line with the instructions in the SPC or the PIL

Council of Europe Resolution on pharmacy preparations for special needs patients Resolution CM/ResAP(2011)1

- Survey led to EU Resolution on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients.
- UK signed up to implement this (DH) - advisory not mandatory c.f. EU Directive
- Aim to protect patient safety - quality and safety gaps between medicinal products prepared in pharmacies and those prepared on an industrial scale.
Council of Europe Resolution on pharmacy preparations for special needs patients
Resolution CM/ResAP(2011)1

To avoid quality and safety gaps between medicines prepared in pharmacies and those prepared on an industrial scale, EU Governments should adapt their regulations to fit with the principles of the Resolution.

- **added value** of pharmacy-preparations; pharmaceutical equivalents NB GN14 responsibilities of health-care professionals
- **preparation process; risk assessment**

HIGH risk – EU GMP LOW risk – PIC/S GPP Guide

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**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

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**Risk-based decision matrix**

1. **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, carcinogenic properties, mutagenic properties, ecological toxicity, risk of allergy, therapeutical window, dosage, stability (light, O2, temperature, pH changes), and chemical, pharmaceutical and microbiological quality.

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**Risk-based decision matrix**

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

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**Risk-based decision matrix**

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.
**Risk-based decision matrix**

- **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

**Council of Europe Resolution on pharmacy preparations for special needs patients** Resolution CM/ResAP(2011)1

- product dossier; for stock preparations only
- marketing authorisation; need MA if prepare on an industrial scale
- labelling; essential requirements given;
- reconstitution of medicinal products;
  - Risk assessment – HIGH pharmacy LOW-wards
  - The Healthcare Establishment should decide where products should be reconstituted
  - National Authorities to develop legislation with relevant professional bodies as reconstitution isn’t preparation

**Product Dossier Topics - depending on risk assessment**

- Demonstration of the added value of the pharmacy preparation
- Demonstration that the active pharmaceutical ingredients, excipients and containers meet relevant requirements, taking into account specific patient needs
- Description of the preparation process including, where appropriate, testing
- Development and backrround documentation of the preparation process
- Use of the product; information for patient and prescriber

**Risk assessment for reconstitution**

- Complexity of process e.g. number of steps and availability of adequate instructions
- Premises e.g. LAF, equipment and application of environmental monitoring
- Nature of the product – open or closed for parenterals
- Relevant education and training (documented)

**Council of Europe Resolution on pharmacy preparations for special needs patients** Resolution CM/ResAP(2011)1

- authorisation for pharmacies or licences for companies
- transparency and safety; reporting of quality and safety issues and rational clinical use
- surveillance; Competent Authorities (MHRA in UK) to perform risk-based inspections
- communication and information to patients; specific leaflet NOT needed for pharmacy preparations, general only required. N.B. RUM
- distribution of pharmacy preparations should follow GDP

**How will this impact on us in the UK?**

- Aim is to harmonise QA and safety standards for pharmacy prepared medicines across Europe
- Implementation is up to individual countries
- Reconstitution is one of the work streams
- Asked by DH to take part in the EDQM (European Directorate for Quality of Medicines and Healthcare) expert working party on reconstitution
- Mix of hospital pharmacists and regulators from different countries
- EAHP is playing an active role and may publish a statement/standard on hospital pharmacy preparation in due course
Summary

- The EU Resolution on Pharmacy Preparation
  Applies to preparation of unlicensed medicines
  for special needs of patients by community and
  hospital pharmacies (either extemporaneously or
  for stock)
- Applies also to the reconstitution of medicinal
  products in healthcare premises
- To implement the Resolution EU countries will
  have to supplement it with additional practical
  guidance taking account national frameworks