



THE PREPARATION AND PRODUCTION ACROSS EUROPE

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Parmacists are the custodians of a nation's medicines and historically have prepared many of them. This need has lessened over the past 50 years with the growth of the pharmaceutical industry. This has been a spectacular and welcomed change, without which the mass improvement to public health could not have occurred. Nevertheless such production, by its very nature, is focused on the mass market and therefore not every individual's pharmaceutical needs will be satisfied by the system. For that very reason a backbone of production has remained in the profession specifically in hospital pharmacy. In this arena it has become a speciality to a varying extent across Europe.

There are a number of reasons why production/preparation has and should remain in hospital pharmacy. Not only are a few patients' needs not met by the marketed products but there is a strategic need to fulfil an immediate need in times of shortage. In the uncertain world in which we live pharmacists will be expected to supply in emergencies (e.g. Tamiflu in the case of an outbreak of bird flu). EU legislation has deliberately created room for this (see the paper from Dr Gerard Lee, EJHP 2007;13(1):67-70).

In order to achieve this objective in a professional and safe manner, to ever increasing quality demands, there is a need to maintain an experienced and trained workforce supported by modern, validated facilities and equipment. The justification and maintenance of such a system is best made at a level higher than the single hospital level. This will be a challenge to a number of Member States where there is little or no coordination between hospitals; others have come together and created viable specialist units. Speaking from my own point of view

I am pleased to note that the NHS in England has recognised the strategic need for production in hospital pharmacy and invested £59 million (€87.5 million) to renovate the leading regional centres in order to bring them up to standard and equip them to meet the needs of the modern service.

The standards with which such units are to comply is a topic much debated across Europe. What is agreed is that patient safety cannot be compromised. Where the debate is concentrated is whether or not the EU Good Manufacturing Practice (GMP), designed around large scale production using processes fully validated on specific products (which themselves should have undergone a rigorous validation programme) is the standard to use. The relation of such processes to the preparation of individually prepared dosages for the particular use of specific patients is currently under discussion. Each country has very different circumstances whether of equipment, facilities, staff training or expectations. The one common factor is the outcome – patients should benefit from, and not be harmed by the medicine.

But if the medicines and the processes themselves are not validated there can be no proof of which is the most acceptable method to produce the wanted objective. In the UK enlightened discussions are taking place between the national inspectorates and hospital pharmacists. In the overviews that follow each of the respondents is considering a 'hospital' GMP. Such discussions are to be welcomed and once some agreement is reached within Member States we will need to reach a compromise across States such that we can speak with one voice across Europe. The path will be long and tortuous but the end point is required.

We await with interest the outcome of the

consultation over the proposed guidelines from the pharmaceutical inspectors' convention, PIC/S, GMP document. The standards on offer in the document are to be taken seriously as they come from experienced external auditors. However hospital pharmacists must offer their practical experience and give honest comment on where the standards can be applied. Whatever the outcome any guidelines produced will only be guidelines and not the law. Standards must be relevant and applicable to the situation to which they are being applied.

In this article we bring you a flavour of how production/preparation is carried out in European Hospital Pharmacy.

There is a general trend to reduce large scale production and move towards individual patient preparation, much of this is due to the industry supplying products that are not patient ready. Pharmacist involvement in the preparation will produce a safer product due to a reduction in errors from miscalculations, picking errors, and microbial contamination.

There is also a general trend across Europe to move towards centralisation of units between groups of hospitals. Such a movement is to be welcomed as it is the only way to create a workforce of sufficient size to justify a suitable career structure to attract and retain the high calibre of pharmacist required to run and develop such a specialist service. Where Member State rules forbid the inter-hospital cooperation and supply of products they should be questioned as to whether or not such rules are in the best interest of the patients, given the huge investments that will be required to fulfil all regulations.

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OF PHARMACEUTICALS IN HOSPITAL PHARMACY

Germany

The production of medicinal drugs is an essential function of German hospital pharmacies as is that of medical devices and reagents for laboratories. However, there has been a noticeable change since the seventies and eighties: batch production has decreased. On the other hand there is increasing demand for the production of individual prescriptions (e.g. cytotoxics, pumps for analgesics, solutions for parenteral nutrition). There are also frequent demands for unavailable pharmaceuticals as well as for drugs which are no longer produced by the pharmaceutical industry. Moreover, a hospital pharmacy is required to guarantee the supply of medicinal drugs in exceptional situations (e.g. disaster prevention).

Under German law, each producer has to hold a "permission to manufacture" for the preparation of drugs. For pharmacies an exception exists: "...if frequent pre-

scriptions by a physician or a dentist can be demonstrated daily production of up to hundred packs is permitted". The regulations distinguish dispensing against individual prescriptions, pharmacy stock production as described above and "Large Scale Production".

Medical devices and cosmetics have to be produced in accordance with the regulations for medical devices and the decree for cosmetics. There are currently no exceptions for pharmacies for these products.

The pharmacopoeias are of course binding for the production and analysis of drugs (European and German Pharmacopoeia). Further guidelines are based on Good Manufacturing Practice (GMP). A special collection with instructions for production is the ADKA hospital formulary "*Herstellungsvorschriften aus Krankenhausapotheken*".

At present hospital pharmacies make everything that it is possible to make with the standard equipment (capsules, solutions, suppositories, ophthalmic products, ointments, injectables, etc.). However, there are calls for the rules to be tightened in the future due to more stringent requirements for rooms, documentation and analytical methods, so only specialised pharmacies will be allowed to produce special drugs in future.

The areas being discussed for preparation in hospital pharmacies are the production of drugs for children and the preparation of clinical trial medication.

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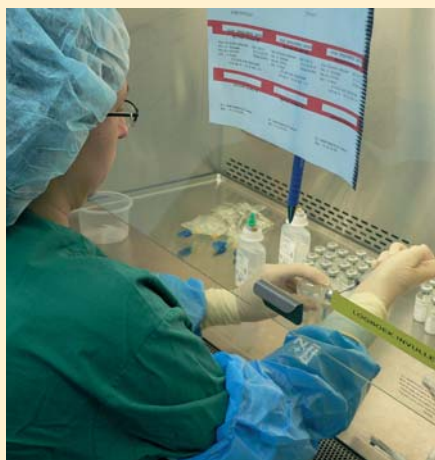
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Italy

Most Italian hospitals operate a preparation department, managed by a hospital pharmacist with the co-operation of the nursing staff. Current ways of working do not entail coordination between different hospitals, but national regulations do permit the preparation of pharmaceutical products for different hospital pharmacies. This service is intended for the preparation of orphan medicines (drugs for rare conditions that cannot be obtained commercially) and as a means of preparing medicines for hospitals that do not have the facilities for preparing medicines to the modern standards required today. The preparation of pharmaceuticals that are commercially available is forbidden by the Official Pharmacopoeia both in hospitals and community pharmacies.

The pharmacists must adhere to and respect the Italian Official Pharmacopoeia (FU Ed XI). This text includes a chapter of "Good Manufacturing Rules", the most important reference for pharmacists who prepare and distribute medicines, with

procedures to guarantee high quality in preparation, equivalent to the GMP rules for the pharmaceutical industry. The same



rules are applied to the preparation of sterile and non-sterile pharmaceuticals.

Courses and training are provided for students at the pharmacy schools at universities of pharmacy and the preparation departments serve both undergraduate and postgraduate training programmes. Preparation is therefore considered to be of

primary importance for those wishing to specialise in hospital pharmacy.

In our country, preparation technicians or pharmacy technicians are not yet recognised as having professional qualifications. From early 2007 a postgraduate course for preparation laboratory technicians will be made available to provide specialist training for the nursing staff or biomedical laboratory technicians, who at the moment perform pharmaceutical preparation under the supervision of a hospital pharmacist.

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France

Type of preparation: In France, pharmaceuticals are prepared in hospital pharmacies if there are problems with the supply of drugs by pharmaceutical companies. The drugs concerned are mainly orphan drugs, or special dosages of standard agents (paediatric patients, cancer treatments). Sometimes formulations have to be adapted to the administration conditions in order to decrease the risk of microbiological contamination (parenteral nutrition admixtures) and to improve protection of personnel and environment (cytotoxic drugs, radiopharmaceuticals).

Regulations: Under French Law batch hospital preparations are distinguished from individually dispensed preparations, which are also allowed. *“Hospital preparation concerns all pharmaceutical drugs prepared in the event of the lack of available or adapted marketed drugs following a prescription from the Pharmacopoeia, prepared in the hospital pharmacy and dispensed to one or a group of patients.”*

French Law distinguishes two categories of duties of hospital pharmacies: compulsory and optional. Individually dispensed preparations are included in the compulsory duties, whereas batch hospital preparations are included in the optional duties. It is recognised that special resources may be required for hospital preparations which explains their optional character. Hospital preparations have to be declared. The objective of the declaration is to validate the grounds for using the preparation and to require substitution if the drug is available commercially and secondly to push pharmaceutical companies to develop commercially available drugs if there is a need for them. By this procedure, a “top 20” list of hospital preparations prepared in French hospital pharmacies has been established and as a result, 14 active substances (five from the “top 20” list) commercially available on the international market have been required to replace the hospital preparations.

Preparation of pharmaceuticals has to be done under the responsibility of a pharmacist, respecting good manufacturing practice (GMP).

Good Manufacturing Practice: Specific GMP requirements for hospital preparations were written and publicly scrutinised in July 2002 but have not yet been published officially by the French Ministry of Health. GMP for hospital preparations includes general chapters (preparation, control, documentation) and specific guidelines (for individually dispensed preparations, preparations for investigational medicinal products, preparation of sterile drugs, preparation of toxic drugs, and preparation of radiopharmaceuticals).

The main points of the GMP for hospital preparations are:

Feasibility: The pharmacist must perform a feasibility study of the preparation in accordance with internationally published data. The pharmacist has to validate the pertinence of the indication and the efficiency/tolerance balance before agreeing to make the preparation. Moreover, the pharmacist must have appropriate means with which to prepare the item and to ensure its quality. For example, injectable drugs may only be prepared if specific facilities, equipment and ventilation equipment (isolators, clean rooms) are available.

Starting materials: For solid forms the raw material must be used. The use of additives should be as near as possible to that of the marketed formulation. However, for sterile formulations, the recommendation is to start from supplied drugs. Identity checks are required on raw materials.

Shelf life: An appropriate shelf life must be determined after stability studies or taken from appropriate international stability studies.

Records/release: Hospital preparations are made in batches. Only a pharmacist is able to release or reject the batch.

Reference sample of the batch: Reference sampling is performed for each batch and samples should be retained till one year after the expiry date.

Quarantine: Quarantine is employed for the raw materials, packaging and finished products.

Quality control: Each batch must be

checked in conformity with the Pharmacopoeia.

Complaints, recall: All non-conforming products must be recorded and analysed so that corrective measures may be taken.

Qualification, validation: All materials and equipment should be qualified following the general rules of 4-step qualification (Design, Installation, Operation and Performance).

Documentation: Procedures must be followed for the whole process from reception of the starting materials to batch release.

Sterile preparations: For the preparation process, the definition of aseptic preparation with regards to the microbiological risk of contamination gives the fundamentals of the facilities required. A low risk of microbiological contamination (transfer of a solution from a sterile supplied drug to a final sterile container using only sterile disposable, sterile needles or transfer tubing) means that the use of laminar airflow grade A in a grade C clean room environment or a positive air pressure isolator in an uncontrolled environment is allowable.

Preparation of toxic drugs: Personnel and the environment must be protected. Additional requirements are specified for ventilation equipment. A positive air pressure isolator for sterile preparation is recommended combined with additional measures. For preparations involving powders (i.e. capsules) a negative pressure isolator is recommended.

Individually dispensed preparations: The same general GMPs should be followed but exemptions are allowed.

All in all, the guidelines are quite similar to those of the pharmaceutical industry except that they take into account the particularities and constraints of hospital production.

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Sweden

The preparation of extemporaneous pharmaceuticals is strictly regulated when it comes to manufacturing sites. Non-sterile pharmaceuticals (e.g. ointments, solutions and capsules) are no longer compounded in hospital pharmacies. Instead production is centralised to four production units that have a higher degree of large-scale processes. Today, only sterile parenterals are manufactured by hospital pharmacies in Sweden. There are 34 compounding hospital pharmacies and no compounding retail pharmacies. The hospital pharmacies give a fast, high quality and individual compounding service to hospital wards. When the order size of a specific pharmaceutical is large and when the shelf life allows, the hospital pharmacy always tries to centralise manufacturing to the one production unit specialised in sterile compounding to make the most of the large-scale advantages. Note that all pharmacies and production units in Sweden belong to the same chain, Apoteket AB.

No products are made that are available in a licensed form from the industry.

Under Swedish law, quality regulations are based on the European Commission rules governing medicinal products (Eudralex), however there are also national adaptations. National regulations cover Aseptic, Terminally Sterilised, and non sterile production.

In my opinion, the speciality of compounding is very popular among young pharmacists. Undergraduate courses often include a lot of preparation theory in conjunction with practical exercises. Some elective courses are available.

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The Netherlands

The Netherlands has a long history of preparation of pharmaceuticals. Both stock production and dispensing were part of the tasks of the pharmacy for decades.

Until the beginning of the '90s it was not uncommon to produce 30% of the total drug turnover in a Dutch hospital pharmacy. This was mainly driven by economic reasons.

Today, the perspective has changed. Increasing quality standards mean that production in the pharmacy is no longer profitable and the volume of production has dropped dramatically. In the Netherlands, it is generally agreed that GMP-Hospital pharmacy (GMP-H) is the minimum standard for production. GMP-H requires huge investments in education of people, quality systems and adequate facilities.

Therefore, the Dutch hospital pharmacist has to make choices or has already made them: investment in production facilities or closure of the stock production and sticking to individual dispensing only.

Availability is the main reason for production: when a product is needed in patient care and is not commercially available or not available in the required

dosage form / strength, it can be produced by a hospital pharmacy. In the Netherlands, the delivery of products from one hospital pharmacy to another is allowed under the following conditions:

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

To date, we already have a number of relatively large hospital pharmacies with several related clients. Expectations are that in the near future stock production will take place in academic centres and a few large regional production centres only. All other hospital pharmacies will limit production to dispensing for individuals and obtain the other necessary products from the production centres. An advantageous "side effect" of this development is that more manpower is becoming available for direct patient oriented care.

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GLOSSARY OF TERMS USED IN RELATION TO PHARMACY PRODUCTION

Glossary of terms used for small scale production activities in hospital pharmacies, based on the draft Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide to good practices for preparation of medicinal products in pharmacies (PE 010).

Batch

Batch is a defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous.

Batch number

Batch number is a distinctive combination of numbers, symbols and/or letters which specifically identifies a batch.

Clean area

An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.

Closed procedure

A closed procedure is a procedure whereby a sterile pharmaceutical product is prepared by transferring sterile ingredients or solutions to a pre-sterilised sealed container, either directly or using a sterile transfer device, without exposing the solution to the external environment.

The use of a solution from a sealed container can be regarded as a closed procedure when a single withdrawal is made from the container, immediately after opening, using a sterile syringe and needle or equivalent device.

The above assumes that, for aseptic preparation and dispensing activities, all closed procedures are performed within an PIC/S and EU GMP for industrial manufacture Grade A environment.

Compounding

A term that reflects the art implied in the Latin phrase “Secundum Artem”, whereby a pharmacist uses his 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.

Controlled work area

An enclosed work area constructed and operated in such a manner and equipped with appropriate air handling and filtration systems to reduce to a pre-defined level the introduction, generation and retention of contaminants. A controlled work area may also be used to protect the external environment from the materials being handled in it, e.g. vaccines or cytotoxics.

Critical zone

That part of the controlled work area where containers are opened and the product is exposed. Particulate and microbiological contamination should be reduced to levels appropriate to the intended use.

Dispensing

To label from stock and supply a clinically appropriate medicine to a patient/client/carer, usually against a written prescription, for self-administration or administration by another professional, and to advise on safe and effective use. (Source: NHS prescribing standards).

Extemporaneous preparation

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

Manufacturing

Large scale production of licensed products.

Preparation

Small scale production activities in hospital pharmacies.

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.

Production supervisor

The person responsible for supervision

should be in the department where the production takes place. He/she is aware of what is going on and able to ensure that the process is carried out in the prescribed manner.

Products for immediate use

Products to be administered immediately after preparation, which undergo neither holding nor storage.

Products for short term use

Products that have a maximum shelf life of 24 hours.

Products for longer term use

These are products that have a proven shelf life of more than 24 hours.

Responsible pharmacist

The pharmacist who is legally responsible for all aspects of the preparation of medicinal products including the release of these products, having the necessary scientific and technical education and experience.

Self inspection

A self inspection is an audit, undertaken under the responsibility of the same organisation in order to monitor the validity of the quality assurance system and the compliance with standards like GMP or the PIC-S guide. It can be conducted by designated competent person(s) from the organisation or assisted by external experts.

Stock preparation

A product, which is prepared for stock, available for dispensing.

Validation

Validation is the risk based, systematic, GMP compliant and documented evidence that a defined process actually leads reproducibly to the required results.