



Compounding in hospital pharmacies in Europe

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Compounding has been the bedrock of a pharmacist's activities for centuries. However there have been dramatic changes in the last 15 years. These have been more akin to revolutionary rather than evolutionary changes and the profession will struggle to adapt.

Public safety became a political issue after such high profile cases as thalidomide and the need to control the marketing of medicines became a priority. Firstly, licensing of medicines is standard these days, so much so that we are now wary of unlicensed medicines. Secondly, in an increasingly risk-averse society, the need to abide by peer-agreed standards, and to prove that they have been abided by, is an imperative for all professionals. Thirdly, the increasing pharmacological and pharmaceutical complexity of modern medicines is requiring a new breed of pharmacists to devote their time to the clinical environment (at the bedside of the patient) thus abandoning the pharmaceutical inheritance of previous generations of the profession.

All these factors are leading to a move away from the compounding and preparative skills, opening a worrying black hole into which the individual needs of particular patients of the future are disappearing. To believe that all patients' needs will be satisfied by products with a Marketing Authorisation is naive. The industry, which is efficiently geared for mass production of those products needed by 98%, discounting paediatrics and geriatrics, of the population mostly outside the hospital will never deal with the last 2%, and in hospital pharmacy this will be significantly more than 2%. If we are to satisfy those needs pharmacists must retain their compounding and preparative skills and achieve those standards which society requires of us.

However, to be clear about that which we are speaking, we need to define terms and the environments in which they are to be applied. Many of the words used to define the process by which medicines are made are interchangeable in the English language and are only understood correctly in context. Occasionally this leads to conflicting definitions. For example, the PIC/S guide, see Eur J Hosp Pharm Prac. 2007; 13(2):87, has attempted to define activities

Do you differentiate between compounding and production or is all preparation considered the same?

Yes, compounding is understood to refer to special requests for small quantities of a medicine in Denmark. However we tend more to think of "service production" which primarily covers ready-to-use products for individual patients, including both compounded and commercial products. To us "production" refers more to products with a longer shelf life.

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associated with the making of a medicine in a non-licensed facility as *preparation* in order to differentiate the activity from that which is expected from the pharmaceutical industry making licensed medicines on a very large scale - *manufacturing*. This has led to the difficulty of differentiating between the activities carried out in an approved and dedicated pharmacy unit, a dispensary and the activity that takes place at the bedside. Please take a look at the definitions we have prepared for you on page 91.

This survey is the second of two into how pharmacists are managing the sourcing of unlicensed medicines. In the last article we focused on the process which we describe as the large scale preparation of medicines in the hospital setting. Here we focus on the compounding of medicines for the immediate use of particular patients.

In the UK there is a definite separation between individual compounding for a particular patient and the preparation of an unlicensed product. The level at which this cut off occurs is dependent on the quantity and type of product. It also depends on whether or not the product is for a patient of the pharmacist or if it is for a supply to a pharmacy for stock. The term "compounding" is popularly understood in the Republic of Ireland to mean aseptic reconstitution of products under a validated protocol after the underpinning knowledge has been researched. Using the definition as given, compounding would solely consist of extemporaneous compounding for the initial requests for a product. Then, depending on how much would be required and the expiry date, the product would be sourced to the private sector or we would develop a validated protocol and produce the item ourselves.

In Finland compounding is understood to mean for individual patients, but is covered by the same rules as production (preparation for stock).

In Spain compounding is understood to mean for the individual patient. *Oficinalis* preparations are for many patients and could be considered as production. In practice, we don't differentiate between compounding and production, always making things in large quantities. But legally, there are differences between compounded and *oficinalis* preparations.

Do you have the equivalent of a “good dispensing guide” to cover compounding by a pharmacist?

In Denmark we compound only a small amount of medicines. Facilities at the different hospital pharmacies vary greatly, but we share knowledge and products as much as possible. We are obliged to follow EudraLex - The Rules Governing Medicinal Products in the European Union [1]. These rules are explained by the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme, jointly referred to as PIC/S [2]. The components in a drug must be described in monographs, for example [3].

The Royal Pharmaceutical Society of Great Britain had issued, in their Code of Ethics, the steps that a pharmacist would be expected to follow when compounding a medicine. This code has undergone a revision in the last year and guidelines are being moved to a separate booklet.

There is no “good dispensing guide” to cover compounding by a pharmacist in Ireland.

If someone in Spain has never compounded a preparation, we have a national formulary, in which we have information to acquire the knowledge and skills necessary to do it.

In Finland there is a national formulary *Dispensatorium Fennicum*. A nationwide project is currently under way in

Finland to create Safe Pharmacotherapy guidelines for all public and private social and healthcare units. As a part of these guidelines an assessment has to be conducted on wards to establish if there are any microbiological or occupational health risks in making ready-for-use products. Then these products could be prepared in the hospital pharmacy.



Does compounding take place in all pharmacies or is it confined to specialist units?

Hospital pharmacies cooperate as much as possible in Denmark, sharing knowledge and trading products when possible. Therefore only a few drugs are compounded in more than one pharmacy. The pharmacies vary very much in size and not all have facilities to meet the demand from the wards, but it is often possible to buy from another pharmacy.

In the UK patients have very occasionally died as a consequence of a compounding error. In these cases the police initiated manslaughter/murder charges against the individual pharmacists. For that reason many pharmacists will not now compound and will turn to others who are specially licensed.

Compounding within the broad definition identified takes place in all pharma-

cies in Ireland. There is a production area in all Spanish hospital pharmacies.

In most Finnish hospital pharmacies compounding is an essential function. Pharmaceutical products are prepared extemporaneously if no commercial products are available. Usually production is divided into preparation for stock, extemporaneous preparation and patient-based preparation (compounding for an individual patient). Nowadays the trend is towards amalgamation of hospital pharmacies and towards centralisation of preparation.

Are there national laws/regulations governing preparation? Do they apply equally to all types of production?

When requested to compound a special mixture in Denmark a lot of questions have to be answered before the drug is ready to compound. We are not allowed to manufacture drugs that are identical to a commercial product. The law and the pharmacopoeia outline the procedures regarding aseptic, terminally sterilised and non-sterile production in all the aspects from facilities, raw material requirements, to personnel training and education and quality assurance. The shelf life of the drug determines which tests and documentation are needed. For products with a shelf life of more than 24 hours, documentation on stability and content is necessary.

In the UK when *preparing* (under the definition on page 91) a batch of an unlicensed product then the activity must take place in a facility licensed by the Competent Authority. This applies to all types of preparation and the licensing requirements equate to those which apply to industry. For aseptic preparation separate guidelines, written with the knowledge of the Competent Authority, have been issued by the NHS quality control pharmacists.

There are no national regulations governing the practice of pharmacy for inpatients in Irish hospitals. Professional ethics rules would naturally apply to the pharmacist's practice.

Decree 175 of 23 February 2001 sets out approved procedures for production and quality control in Spain. Different standards are in place for sterile or non-sterile formulations.

Official publications such as European Pharmacopoeia, EU GMP, PIC/S guidelines and the normative national guideline "Preparation in Pharmacies" are followed in Finnish hospital pharmacies. The rules apply to aseptic, terminally sterilised and non-sterile production.

Do you coordinate preparation of pharmaceuticals between hospitals?

In Denmark the pharmacies with the largest production facilities are those connected with university hospitals, and most of the products are ready to use, e.g. cytotoxics, analgesics and antibiotics.

The coordination of services has been actively pursued since 1974 in the UK and was originally based on health regions. Over time these have evolved and changed. In the past four years the English health regions have been centrally funded with approximately GBP 59 million (Euros 71 million) to bring the centres up to modern standards.

There is also a very active private industry developing to supply unlicensed medicines to retail and hospital pharmacies.

Prepared pharmaceuticals are not provided to other hospitals in Ireland. Our Lady's Hospital for Sick Children in Crumlin, Dublin has prepared and distributed to all other hospitals and retail pharmacies a guide on regularly prescribed paediatric products that require extemporaneous production.

Production is common in Spain. All hospitals engage in this activity.

Under Finnish law preparation in hospitals is allowed only for individual hospitals or individual hospital districts. Preparation for another hospital needs permission from the National Agency for Medicines. Now it is time for nation-

al discussion because very expensive investments will be required for clean areas. More cooperation and coordination are needed in preparation activities.

Is there a career structure for pharmacists in compounding? Is it considered a core subject in undergraduate teaching?

All pharmacists educated in Denmark study production to some extent, but not many continue a career within this field. In hospital pharmacies right now, it is "hotter" to be a clinical pharmacist than a production pharmacist.



In the UK the regional structure developed above was designed with the career structure and specialisation as a main aim. However, production and quality control is diminishing in popularity with the current emphasis on clinical pharmacy. Without a change in emphasis there is some doubt from where future graduates with the necessary skills will come.

There is no career structure in compounding as such in Ireland. Extemporaneous compounding comes under the remit of dispensary services and would be managed by the pharmacist in charge. The day-to-day preparation under the validated protocols in this area may be under the remit of a senior technician. The level of compounding activity is negligible in many hospitals

when commercially available specials (unlicensed products) are obtainable. The volume is significant in paediatrics and neonatology as commercially available products are not available for this patient cohort. There is an increasing demand for compounding in elderly care due to nasogastric or PEG feeding or discontinuation of older products. In Ireland manufacturing is not popular. Pharmaceutical technology is a core subject on the undergraduate course for pharmacists and a core module for pharmaceutical technicians.

Hospital pharmacists are already specialists in Spain, but we don't have further specialisation in compounding. Nevertheless, pharmacists who work in this area are highly qualified because they usually have much experience. There is a national group for production that holds a lot of meetings for pharmacists who work on production. The activity of production in hospitals is growing in importance due to the cost saving it generates in many cases. It is part of the standard syllabus for pharmacy students in Spain.

In Finland undergraduate students are able to choose pharmaceutical technology as a main subject, which is not, however, a requirement for working in the preparation area. Orientation and authorisation are workplace specific. Between 1994 and 2005 postgraduate pharmacists had the possibility to specialise in hospital and health centre pharmacy, but at the moment there are no resources to organise the specialisation.

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Acknowledgements

Thank you very much to those who contributed to this article.



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Glossary of terms used to describe compounding in hospital pharmacy

A product which is requested routinely, frequently, and in larger quantities, is expected to be prepared in a hospital GMP-approved facility according to locally approved standard operating procedures. The Pharmaceutical Inspection Convention (PIC/S) has produced a suggested outline for an all-Europe standard to cover this function.

A product which is requested routinely but in very low quantities may be prepared by a pharmacist for an individual patient for immediate use. The pharmacy would, however, be expected to have a developed standard method of preparation and follow acceptable professional practice in the preparation. This can also be defined as *extemporaneous dispensing*.

The first time a pharmacist is asked for a product for which there is no Marketing Authorisation, and none of the above will satisfy the order, then the pharmacist will need to *compound* the medicine using his/her professional knowledge and judgement before extemporaneously dispensing the product.

The first stage in compounding, and the precursor to the previous two activities, is

to *formulate* a suitable recipe which will be appropriate to the need of the patient and the chemical entities being used.

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/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.

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.

Preparation

Preparation is a general term which includes all operations of purchase of materials and products, production, quality control, release, storage, distribution of medicinal products and the related controls.

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.

These terms are mostly taken from the PIC/S guide (see Eur J Hosp Pharm Prac. 2007;13 (2):87).