Bespoke pharmacy:

TAILORING MEDICINES TO THE NEEDS OF PATIENTS — the pharmacy production unit's role

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Hospital pharmacy production units are responsible for making a wide range of products. In this part of the special feature, the author describes the challenges presented by an increasingly patient-focused approach to care within the National Health Service

The production unit: when patients need individual items not available elsewhere, "in-house" production is necessary

The National Health Service production unit today is responsible for producing a wide range of products for individual hospital patients, often in addition to the classical manufacturing of "specials". These products range from oral suspensions and dermatologicals to cytotoxic preparations, intravenous nutrition feeding solutions and other central intravenous additive service (CIVAS) products.

Individual prescriptions for named products, which are prepared in response to a doctor's prescription, must be carried out by, or under, the supervision of a pharmacist (Section 10, Medicines Act 1968). A production unit is required to be licensed by the Medicines Control Agency (MCA) for manufacture of specials if supplying to patients outside its trust or legal entity. There is provision in the guidance to the NHS on licensing requirements of the Medicines Act,[1] for unlicensed "preparation for stock". This allows preparation of medicines — in anticipation of patient prescriptions — to be made without the need for a manufacturer's licence. However, such activity is limited in batch scale and frequency of manufacture and must still be carried out in accordance with good manufacturing practice (GMP).

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EXTEMPORANEOUS PREPS

Patients may need individual prescription items that require extemporaneous preparation. Before preparation, consideration should be given to the possible use of an alternative licensed product that is clinically equivalent. If there is no alternative, the availability of an unlicensed "special" from an MCA licensed "specials" manufacturing unit or importation of a licensed product may be worth considering.

In-house preparation requires a risk assessment and consideration of facilities, formulation, stability and shelf-life. Other factors to be considered include the availability of the necessary raw materials, how soon the product is required and the likely duration of use. If it is for long-term use, the resource implications and convenience for the patient in obtaining further supplies must be considered. For provision of such services, a comprehensive quality assurance system should be in place since there is limited scope for end product testing of individual preparations. Appropriately trained staff and standard operating procedures (SOPs) are required. These SOPs cover the general procedure for extemporaneous preparations, use of balances for weighing, use of other equipment, cleaning of glassware and operation of computer systems for labelling.

For the preparation of non-sterile extemporaneous preparations, a dedicated area, preferably with a controlled environment minimum European Union Guide grade D is required with fume extraction for hazardous materials.[2] The design should preferably comply with current GMP for non-sterile preparation and any equipment used should have been tested, calibrated and validated as appropriate. Regulations regarding health and safety and control of substances hazardous to health should be observed.

Documentation should include a daybook to record patients' names, dates and preparations made, and a structured standard worksheet, which can be copied to avoid transcription errors.

WORKSHEET REQUIREMENTS

The following is a list of requirements that should be shown on the worksheet:

- Approval by pharmacist
- Formula (cross-referenced to published source or a validated formula)
- Shelf-life of unopened container

- Raw materials including quality, eg, British Pharmacopoeia (BP) standard or full chemical description
- Record of quality control (QC) raw material specification and QC lot number used
- Record of calculations
- Spaces for control numbers, operator and checker signatures
- Health and safety risks and precautions
- Site clearance check declaration before starting preparation
- In-process record of weights and volumes by operator and checker
- Step-wise method of manufacture
- Defined container and closure system
- Means of label reconciliation
- Specimen label and printer reference
- Final check by pharmacist

Formulation

How does the production pharmacist formulate the drug into a suitable medicine, which is stable, palatable if an oral product, and with a reasonable shelf-life? It is not easy in modern medicine when published information on the newer drug entities is sparse. In the past, traditional established drugs had monographs in the Pharmaceutical Codex or the British Pharmacopoeia, with suggested formulae and methods of preparation for medicines. Nowadays, the BP drug monographs are of the open type and provide few specific formulation details.

The pharmacist must use his or her own scientific knowledge and formulation skills to produce a suitable preparation. There are some collated stability studies available within the NHS but it is noted that these have not been actively updated in recent times. It is hoped that modernisation of NHS pharmaceutical manufacturing services will provide resources for research and development, and facilitate sharing of information.

Assigned shelf-lives need to reflect both chemical and microbiological stability. They should also acknowledge the worst-case conditions of storage after opening and the nature of use. When a dosage form is altered, the stability of the drug may be affected. As a general rule, the rate of degradation of a drug increases once it becomes dissolved. The principal degradation mechanisms are oxidation and hydrolysis. This, however, may be much less significant for suspended particles of crushed tablets or opened capsules.

Even where chemical stability has been validated, the requirements for preservative efficacy as defined in the BP may not be met. It is therefore advisable that a maximum shelf-life of 14 days after opening be given, unless compliance with the preservative efficacy test can be demonstrated.

Raw materials Raw materials used may be licensed marketed products, eg, crushed tablets, "specials" supplied by a manufacturer, pharmaceutical quality materials or non-pharmaceutical materials purchased as reagent chemicals. The last type should be avoided if possible, and indeed, some suppliers will refuse to supply such materials if they are intended for drug or human use. However, it is now becoming increasingly difficult to procure pharmacopoeial quality materials because several traditional suppliers have recently withdrawn from the market. It is often necessary to purchase from importers at higher cost and with longer delivery times. One company quotes a standard delivery time of 42 days for raw materials, which in most cases is impracticable. Raw materials should be purchased from approved suppliers and tested for identity. Certificates of Analysis should be obtained where possible, particularly for non-pharmacopoeial chemicals. In an effort to share information, the NHS pharmaceutical production committee is currently preparing a database on raw materials and suppliers.

Where tablets are to be crushed or capsules opened to provide a source of raw material, it is important that the physicochemical properties of the active ingredient are understood. For example, if the drug substance is water-soluble it may dissolve in the vehicle, and only the excipients will need to be suspended. For a sparingly soluble drug, it is important that it is ground to an acceptable particle size to achieve an adequate suspension. Tablets and capsules that have been formulated to have a modified release, or which are intended to be used sub-lingually, should not be used. Furthermore, products that contain local anaesthetic drugs should not normally be formulated into an oral liquid presentation.

Suspending vehicles manufactured by "specials" units are often purchased and used as a base for the preparation of suspensions. Suspending bases using xanthan gum 0.5 per cent and methylcellulose 2.5 per cent have osmolalities less than or equal to plasma osmolality. Vehicles of low osmolality are preferred in liquid formulations especially for neonates, where hyperosmolar solutions have been shown to cause a variety of adverse effects. Users need to be aware of the formulation pH of the suspending vehicle, which might range from pH 4 to 7, and this could be critical to drug stability.

It should be noted that xanthan gum is incompatible with polyvalent metal ions and some tablet film coatings. Methylcellulose is compatible with tablet film coatings but may precipitate in high concentrations of electrolytes.

Preservatives Choice of preservatives does present problems, particularly for preparations with a pH above 7.0. Due to a lack of suitable preservatives, it is often still necessary to use chloroform, which is recognised as toxic and potentially carcinogenic. The use of chloroform as a preservative has been prohibited in the United States since 1976. Regulatory pressure on manufacturers regarding the use of preservatives in products has inhibited the development of new and more effective agents.

It is often necessary to prepare medicines for administration to patients by nasogastric (NG) or percutaneous endoscopic gastronomy (PEG) tubes. Tubes may become blocked by poorly suspended solid medicines or because of drug-feed interactions caused by pH changes . The bioavailability of the drug may be reduced by such interactions or by adsorption onto the tube itself. Certain types of medicines are unsuitable for administration by this route, eg, enteric-coated and modified-release preparations. Hyperosmolar liquids, including some injections that are suitable for oral use, can cause diarrhoea and abdominal cramps. Dilution with water immediately before administration may avoid this.

Paediatric dispensing

Preparation of medicines for children, particularly small infants, requires additional considerations. Alcohols can present problems and should be avoided; for example, ethanol effects the central nervous system, drug absorption and metabolism; and benzyl alcohol is regarded as toxic to neonates. Injections for oral administration should be used with caution since hypertonic solutions have been shown to be associated with necrotising enterocolitis and the possible presence of antioxidants and preservatives could be harmful. Flavouring and sweetening of preparations for paediatric use is important to ensure successful administration.

Retention of records

Manufacturing worksheets and records are required to be retained for at least five years as part of GMP. However, it should be noted that product liability extends this to 11 years after expiry of the product and in paediatrics up to 28 years (maturity plus 10 years).

Aseptic compounding

Aseptic compounding and dispensing are high-risk processes and present the greatest challenge to patient safety. This was recognised as far back as 1976 in the Breckenridge report,[3] which recommended that drug additions to intravenous infusions should be made in pharmacy departments and not on wards. In acknowledgment of the growth in aseptic preparation of medicines, the Farwell report in 1994[4] set out guidelines and standards required to achieve good practice.

In 1996, the Department of Health instigated an inspection by the MCA of a sample of unlicensed pharmacy aseptic facilities. Following a review of the findings of this survey, Executive Letter (96) 95,[5] required all units undertaking non-licensed aseptic preparations to carry out an internal audit of their activities and standards. The outcomes of this audit were summarised in 1997 in Executive Letter (97) 52,[6] which additionally required a programme of external audit by regional quality assurance specialists and NHS trusts to address reported deficiencies.

The publication 'Quality assurance of aseptic preparation services',[7] sets out the required standards to which unlicensed aseptic units should be audited. These are reinforced by criterion five for aseptic dispensing of controls assurance standards for medicines management.[8]

In addition to complying with GMP, unlicensed aseptic preparation must be in accordance with the following conditions:

- Aseptic activity is carried out by or under the supervision of a pharmacist, who takes full responsibility for the quality of the product
- Closed systems are used, ie, there is addition of sterile ingredients to a pre-sterilised closed container via a system closed to the atmosphere
- Licensed sterile medicinal products are used as ingredients or the ingredients are sterile manufactured in licensed facilities
- Products are allocated a shelf-life of no more than one week and shelf-life must be supported by stability data
- Activities should be in accordance with defined NHS guidelines

These conditions apply to all products prepared aseptically for administration to patients. Such products include total parenteral nutrition (TPN) solutions, cytotoxic injections, radiopharmaceuticals and additives for parenteral administration. For the preparation of these products, an isolator or laminar flow cabinet providing an EU Guide grade A environment is required.

TPN Some adult and paediatric patients will require intravenous feeding with TPN. These TPN preparations are a complex mixture of amino acids, carbohydrates, fats, essential elements, electrolytes and vitamins. They are usually prepared specifically for each patient according to their nutritional, fluid and electrolyte requirements. As a consequence of their complexity, the shelf-life of such preparations is short and daily manufacture is required. Adult TPN solutions were traditionally made from the individual components of glucose, amino acids and lipid, but now compartmentalised "off the shelf" licensed manufacturers' products are available and are becoming used increasingly as bases in the bags. These have helped to save on processing time and reduce aseptic processing risk.

Neonate and paediatric TPNs are still manufactured from individual components or using base bags purchased from "specials" units. Intravenous feeding solutions for small babies are a particular challenge because the formulation is often required in a small volume and with the presence of lipids this can cause stability problems. Risk of calcium phosphate precipitation can be high, depending on the concentration of calcium and inorganic phosphate, the pH and the temperature. As a consequence of stability issues, two component lipid and glucose/amino acid TPN solutions are prepared and administered separately.

Panel 1: Dose banded cytotoxic drugs

- Fluorouracil
- Cyclophosphamide
- Methotrexate
- Doxorubicin
- Epirubicin

Cytotoxics Cytotoxic preparations are made on a daily basis and require suitable facilities providing both protection to the product from microbial contamination and cross contamination, and health and safety protection to staff. This is commonly achieved with negative pressure isolators. Cytotoxic doses are calculated on body weight or surface area, and are prepared for immediate administration to the patient. In some units, there is now a dose-banding approach for some drugs (Panel 1), which allows the clinician to use a standard strength solution and an approximation of dose obtained from calculations using the body surface area of the patient. In dose banding, standard doses are prepared in prefilled syringes, which are supplied against the prescription. This saves time and resources, and minimises handling of the product.

CIVAS CIVAS products that are prepared for individual patients include elastomeric devices, infusors, syringe drivers, epidurals, patient-controlled analgesia, syringes and minibags, irrigations and eye preparations. Many of these products have limited physicochemical stability.

With more patient-focused care, it is expected that the demand for CIVAS and the preparation of cytotoxic chemotherapy will increase. It is anticipated that the impetus from modernisation of NHS pharmaceutical manufacturing services will provide the investment for upgrading and modernising aseptic facilities to meet these needs.

Developments

Monoclonal antibodies are prominent among the new types of therapeutic agents being used in clinical practice. They are different in chemical structure and pharmacological activity from traditional drugs. The potential hazards of these products and their handling have been summarised in a joint statement by the National CIVAS group and the British Oncology Pharmacy Association.[9] Aseptic facilities that are used for other types of products may be used for these therapeutic antibodies. Where antibodies are intended for the treatment of malignancy, cytotoxic preparation facilities may be used.

Gene therapy is a technique by which a functioning gene is inserted into a human cell to correct a genetic error or to introduce a new function to a cell. Genes are introduced into the cells by means of viral or non-viral vectors. Because viruses are pathogenic and gene therapy involves manipulation of human genetic material, handling of such agents requires a risk assessment. It would be expected that a dedicated aseptic facility and *en suite* rooms for patients are needed for safe handling and use of gene products.

Conclusion

A more patient-focused approach to provision of NHS services has resulted in an increased workload to meet the requirements of individual patients. The challenge presented to production units is to maintain standards and capacity in order to provide for the expected increase in the use of specialised medicines in patient care.

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