Why specials manufacturing units are needed now as much as they ever were

In this special feature, Zoë Gross provides an update on specials, in terms of their clinical and technical aspects, addresses what is going on in practice and looks at some recent and future developments.

A special is an unlicensed medicine manufactured in response to a prescription for an individual patient for whom a licensed product is not available. It is a bespoke, or specially prepared, product manufactured to meet a specific patient's specific requirements.

Specials may be used to meet a variety of patient needs, for example, for babies, children and older people, and in specific areas such as dermatology and palliative care. However, because they are unlicensed products, there are associated unknowns around patient safety since such products do not bring with them the guarantees of product quality, safety and efficacy that are taken for granted in a licensed medicine.

(2) This list is not exhaustive

Uses of specials

Panel 1 provides examples of situations where specials may be prescribed and supplied. For babies and children, specials are often required because of the lack of licensed formulations to meet specific paediatric needs and a lot of work is currently going on in this area. The use of specials in babies and children is discussed in Panel 2. Many older people, and those who are terminally ill, have difficulty swallowing medicines and, by prescribing a special, doctors are able to prescribe unlicensed liquid formulations to improve compliance. In dermatology, various strengths and vehicles may be required to formulate unlicensed liquid formulations to improve compliance. In dermatology, various strengths and vehicles may be required to formulate unlicensed liquid formulations to improve compliance.

Specials are manufactured in Medicines and Healthcare products Regulatory Agency licensed NHS manufacturing units or commercial manufacturing units and each unit must comply with a number of legal, regulatory and quality standards. Strictly speaking, specials are only manufactured in licensed facilities. Such specials are regularly manufactured in batches and to formulae that have been subjected to at least quality control and final release by a Qualified Person and are made for stock (in anticipation of a prescription) under conditions which comply with current Good Manufacturing Practice. Batch manufactured specials are usually supplied with a certificate of analysis.

Definitions of specials

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Panel 1: Examples of when a special may be used¹

Specials may be prescribed and supplied, when an alternative licensed product is not available, for patients who:

- Cannot or will not swallow tablets and need a liquid formulation — eg, babies, children, older people, terminally ill patients, those who have recently undergone throat surgery or are incapacitated
- Are allergic to product excipients present in licensed medicines and need a modified formulation (such as preservative- or additive-free)
- Require medicines that are in different concentrations, formulations or strengths from those available as licensed medicines — eg, children who need a particular strength of a medicine
- Require specific formulations of intravenous or intrathecal treatment — eg, critically ill patients in intensive care
- Have specific intravenous nutritional needs — eg, critically ill patients in intensive care
- Are taking or need continued treatment with a particular licensed medicines which has been discontinued or is out of stock

This list is not exhaustive.

Section 10 exemption

A product extemporaneously prepared in an unlicensed unit operating as a registered pharmacy, or in the dispensary under supervision of a pharmacist, is likely to be a one-off product and is not under strict legal definition a special — these are extemporaneous preparations made under section 10 exemption of the Medicines Act. There are also unlicensed compounding units and services in the NHS that dispense products, such as parenteral nutrition and epidurals, for use within the NHS and such products are given a maximum shelf-life of seven days. Unlicensed products imported from outside the UK also do not meet the legal definition of a special.

It should, however, be noted that there is a blurring at the overlap between specials and section 10 exemptions.

NHS manufacturing units

There are around 40 manufacturing units in the NHS that hold a manufacturer’s (specials) licence issued by the MHRA. A list of special-order hospital manufacturing units can be found in the British National Formulary.

Among the specials manufactured in specials units are products such as parenteral nutrition, epidurals and patient-controlled...
Panel 2: Paediatrics

Studies published in the Bmj over the past few years have highlighted the common use of unlicensed and off-label prescribed medicines in children. One reason why a doctor may prescribe a special for a baby or a young child is that babies cannot, and young children often will not, co-operate when taking medicines in a licensed tablet formulation. Thus a liquid formulation that is available in a taste that children are familiar with, like strawberry, will often make it easier for them to take their medicine. Another reason for prescribing a special is that the younger the baby or child, the more important it is to give an accurate fraction of the dose and solid dosage forms are often difficult to manipulate into child-specific or baby-specific doses. A liquid formulation is therefore often required to provide a fraction of an adult dose. In the UK market, it is relatively unusual for a new medicine to be launched in a liquid formulation that is specifically suited to meet a child’s needs, so palatable oral liquid formulations for children are often made up as specials, according to the ACSM. In terms of injectables, doses may again not be customised to meet needs and thus specials maybe used to rectify the problem.

A number of commercial manufacturing units will have been set up to represent the interests of the industry. To date, 11 licensed commercial manufacturing units are members of the association. Among its roles, the ACSM seeks to “safeguard prescriber choice and ensure individual patients continue to have access to the most appropriate and convenient medicines at the point of need” and to “ensure that health care professionals continue to have access to information and choice in supplying the needs of patients requiring specials”. A spokesperson for the association says “The ACSM and its members are working with a number of stakeholders to ensure that specials will meet the future needs of individual patients and the NHS”. Further information and a list of commercial specials manufacturers are at the association’s website (www.acsm.uk.com) or by contacting Andy Low, ACSM business manager (tel 01279 504 254).

NHS and commercial co-existence

The National Implementation Board takes the view that there is a role for “happy co-existence of both NHS and non-NHS units”, according to Tim Root, joint project manager of the board and London specialist pharmacist, clinical governance and technical services. Explaining this role he said that at one end of the spectrum are the one-off, low-volume products with poorly defined formulae and a lack of stability data that are tailored to meet the needs of individual patients or small groups of patients. He added that he be-
lieved the NHS “is probably better placed” to supply such preparations. As the scale of production increases and the formulation becomes established, either NHS or commercial units can meet the demand.

However, he went on to say that at the other end of the spectrum are the routine-use, large scale specials with established formulas and shelf-lives, and commercial manufacturing units may be best suited to manufacture and supply these products. For those products that are produced in sufficiently large quantities, that are commercially viable, and whose use becomes routine and widespread, the aim should be to achieve a licensed product, he commented.

Andrew Tittershill, commenting on behalf of the ACSM on the place of the NHS in the supply of extemporaneous preparations, suggested that “commercial manufacturers are a logical first port of call for low-volume, one-off products because of the industry’s formulation expertise, flexibility and responsiveness, resulting in the patient receiving her or his medicine in a timely manner”.

**Procurement**

A special can be supplied in one of the following ways:

- A registered pharmacy (hospital or community) receives a prescription for a special and decides to supply the product by extemporaneous dispensing under its pharmacy registration.

Once a prescription for a special has been written, a pharmacist will decide whether a special is actually required or whether there is a licensed preparation that could be used instead. If a special is required, it is then a matter of where to obtain it from.

Whether pharmacists choose to obtain specials from a licensed NHS manufacturing unit or a commercial manufacturing unit is entirely their choice. According to Mr Root, usually in secondary care, but by no means always, pharmacists will either have the product prepared in-house or purchase it from an alternative NHS manufacturing unit that holds a specials manufacturing licence.

Dr Tittershill offered an alternative perspective, suggesting that NHS hospital trust-based pharmacists frequently adopt a pragmatic view, recognising the role that the commercial sector can play in supplying specials medicines in various dosage formats to meet patients’ needs.

In community pharmacy, when sourcing a special, community pharmacists may either choose to go to their usual commercial specials manufacturer or, if it is a hospital-initiated item, they may choose to approach that particular hospital provided it has a licensed manufacturing unit. Mr Root added that there are concerns that would-be purchasers, especially in primary care, have limited access to robust, comprehensive information about the specials in common use and which manufacturing units make them — this is something the National Implementation Board is starting to address.

It should be noted that there is also a growing home care sector for which specials are used — examples where specials may be used are antibiotics for cystic fibrosis, intravenous nutrition and the treatment of thalassaemia. These treatments may be sourced either from an NHS or commercial specials supplier.

From the manufacturer’s perspective, once a request has been received for a special, a choice will then have to be made as to
whether to formulate the special from scratch or whether any of the formulation, all or part, can be obtained from another supplier. Written records of manufacture or assembly and supply must be kept for five years.1

Numbers of specials

An estimated total number of different unlicensed products in different formulations being manufactured somewhere in the N H S is thought to be around 3,000 to 4,000. In the community, it is harder to gauge exactly how many unlicensed preparations are being purchased and how many are extemporaneously dispensed, but it is thought that an increasing number of such preparations are now being bought in from special manufacturers. A study carried out in 2003 to find out whether community pharmacists extemporaneously dispense or use special manufacturers found that out of 82 community pharmacies, 41 per cent ordered from special manufacturers and 31 per cent extemporaneously dispensed. Items most commonly ordered from special manufacturers were various preparations of preservative-free eye drops, topical coal tar preparations and diluted glyceryl trinitrate ointment.8

Role of the pharmacist

A special should only be prescribed when a suitable licensed medicine is not available and when such a product is thought, on clinical or oncological grounds, to be clinically appropriate. In both the community and hospital sectors, pharmacists can play a key role in advising and influencing doctors on the use of specials and will often initiate prescribing. However, the intention is to have more pharmacist input at the point of prescribing so that a special is not prescribed unnecessarily.

As of April 2005, specials and unlicensed products were specifically added to the list of items that can be prescribed by supplementary prescribers. This has allowed pharmacists to be involved in nutrition oncology and dermatology to prescribe specials for their patients and for supplementary prescribers to prescribe on home care prescriptions for these items. Commenting on this, Rebecca Whitley, lead pharmacist for nutrition and surgery for Oxford Radcliffe Hospitals NHS Trust, said: “Extending supplementary prescribing rights to allow for the prescription of specials and unlicensed products has made parenteral nutrition prescribing possible for the recently qualified pharmacist and nurse prescribers working in this area. This has a positive impact on clinical risk management as prescribing responsibility transfers to a more experienced member of the team.”

MHRA guidance updated

MHRA Guidance Note 14 on the supply of unlicensed relevant medicinal products for individual patients was revised in May 2005. Although some advice has been strengthened in the guidance, there are no fundamental differences from the previous version, Mr R Root said. However, he pointed out that the guidance now emphasises the supplier’s responsibility to specify clearly on paperwork whether a particular product has been supplied as a special or was dispensed under Section 10 of the Medicines Act. Mr R Root pointed out that the Medicines Act bans advertising of unlicensed medicines. Guidance Note 14 states “A ‘special’ manufacturer or wholesaler may advertise the service he provides but particular ‘specials’ must not be advertised. He may, however, respond to requests for information on specific products.”

Mr R Root commented: “This is a sound principle which I support but it inevitably conflicts with the need to ensure that pharmacists and doctors have comprehensive, detailed information to enable rational choice.”

To help provide this information, the National Implementation Board has put together a database, “Pro-File”, containing details of all products known to be manufactured in the N H S and whom they are manufactured by — the aim is eventually to include details of commercial specials manufacturers as well. Although access to the database, which is expected to be up and running in the second quarter of next year, will be restricted to registered N H S pharmacy staff in secondary care to start with, access for community pharmacists is on the agenda.

Adding to Mr R Root’s comments about access to information, Dr Tittershill advised that commercial manufacturers are also interested in providing appropriate information on specials. “The ACSM is developing an information service, with some individual member companies also developing product databases,” he said.

Reimbursement arrangements

A Department of Health consultation has been seeking views on the proposal to list the top 150 prescribed specials, and a reimbursement price for each one (including out-of-pocket expenses) in the Drug Tariff. The proposed changes would apply to England only and the closing date for responses to this consultation was 30 November.1

Other initiatives

A number of initiatives are under way to improve the quality and use of specials. In addition to those already mentioned in this article, the National Implementation Board is currently working with the British Association of Dermatologists to reduce the number of dermatological specials in use by agreeing on preferred presentations and formularies. The board is also working alongside the Royal College of Anaesthetists to reduce the lack of both standardisation and stability data for anaesthetics and analgesics, such as bupivacaine and opioid analgesics used in epidurals and for patient-controlled analgesia pumps. It is also developing monographs and diluent data for anaesthetics and analgesics. A Department of Health consultation has been seeking views on the proposal to list the top 150 prescribed specials, and a reimbursement price for each one (including out-of-pocket expenses) in the Drug Tariff. The proposed changes would apply to England only and the closing date for responses to this consultation was 30 November.1

Conclusion

The supply of specials appears to be complicated. There may be many benefits of using a special where a licensed product is not appropriate or available, but there is less overall quality assurance than with a licensed product. Nevertheless, pharmacists should satisfy themselves with the standards of their sourcing arrangements and usual specials supplier. The use of specials for babies and children is being addressed. However, a problem still exists with liquid medicines because there are no appropriate licensed products. Although the use of specials is preferred over extemporaneous preparations, there is a need for more licensed medicines on the market. “If the number of products manufactured as specials can be reduced from the 4,000 currently manufactured by N H S hospital pharmacies then, over time, better validated products will be produced. This will also enable stability data and shelf-life data to be collected and lead to the possession of better data to support the use of specials and higher quality products being produced. That can only enhance patient safety,” according to Mr R Root. Dr Tittershill added: “The specials medicines sector is complex, and defies easy and convenient classifications and rules on how the sector should work in theory. The specials market has been changing, and the advent of initiatives such as BN F for Children and the Drug Tariff to 150 products is likely to see the rate of change increase still further. He added: “All stakeholders will have a challenging role to play in ensuring that patients continue to have timely access to appropriate, high quality specials medicines.”

References