Dealing with specials

Responding to members' requests the Society presents practical guidance for pharmacists on professional responsibilities when dealing with the supply of specials

GOOD PRACTICE GUIDANCE ON: THE PROCUREMENT AND SUPPLY OF PHARMACEUTICAL SPECIALS

Background

Pharmacists throughout the whole of the supply chain have a responsibility for procuring and supplying specials in a professional manner. We are aware that the supply chain encompasses manufacturing, prescribing, procuring and dispensing of specials. This guidance only addresses part of that whole process. Other parts need to be considered by other organisations.

Over the last few years pharmacists have increasingly bought in specials rather than prepare products extemporaneously within the pharmacy setting. This practice has arisen from a need to ensure quality in the manufacturing process and to enhance patient safety.

This guidance provides good practice advice on the key professional responsibilities for pharmacists when providing advice about or supplying specials, and support in making appropriate choices for their patients.

There are patients who do benefit from receiving a special and this guidance will help pharmacists in providing the appropriate product and advice for their patients.

n.b: this guidance is specific to the use of specials. It does NOT apply to licensed products used outside the clinical indications of their licence i.e. "off-label" use.

Community, hospital, primary care and industrial pharmacists are encouraged to engage with one another and with prescribers to discuss the issue of specials. This can lead to a more efficient procurement of specials within the locality

Pharmacists also need to raise awareness of prescribers to the issue of specials as they themselves are not always aware they are prescribing a special and therefore will not be aware that as a bespoke special it is likely to be more expensive to procure than a licensed product.

The Society would like to thank the contributors from Hospital, Primary Care and Community practice, specials Manufacturers, NHS Quality Assurance and PSNC for their help in developing this guidance.

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If you have any enquiries about this guidance, please contact the Information and Advisory Service at RPSGB on 0207 572 2302

1. Purpose

This document aims to:

- Provide 'good practice guidance' on the key professional responsibilities for pharmacists when dealing with the supply of specials.
- Encourage pharmacists working in Primary Care Organisations and community pharmacy to work collaboratively with each other and with GPs to update and inform on prescribing policy and support joint working
- Help support clinical governance in pharmacy.

2. General Information about specials (also see Glossary of Terms and Abbreviations)

- The term specials has a number of meanings. In the context of this guidance it can be taken to include:
  - o A medicine manufactured by a specials manufacturer holding a Manufacturer's specials Licence (MS) in multiple quantities with end product analytical testing
  - o A special medicine produced by a specials manufacturer holding a MS as a bespoke medicine without end product analytical testing
  - o Extemporaneously prepared medicines – unlicensed medicines made in a pharmacy under a pharmacist's direct supervision
- Every medicinal product marketed in the UK is issued a Marketing Authorisation (MA) number by the regulatory authority, the Medicines and Healthcare products Regulatory Authority (MHRA) or by the European Medicines Agency (EMEA). The MA, previously known as a Product Licence (PL), or EC/EU authorisation, guarantees that the quality, safety and efficacy of a medicine has been rigorously assessed, and must be displayed on the pack.
- To manufacture specials in the UK, an MHRA Manufacturer's specials Licence' (MS) is required. This guarantees that the sourcing of ingredients, product development, packaging and labelling, as well as the manufacturing and the ex-factory supply processes are all to regulatory standards. There has, however, been no formal assessment of product safety or efficacy. A special is therefore an unlicensed medicine. The manufacturer's MS number must be printed on the label.
- An MS is not required for extemporaneous dispensing as this can be carried out in a registered pharmacy under Section 10 exemption of the Medicines Act but it is not uncommon for manufacturers holding a MS to make small quantities of medicine under the supervision of a pharmacist if they are also a registered pharmacy. There is then no guarantee that the extemporaneous dispensing process has been subject to any formal quality assurance.
- Some medicines licensed in Europe and America may not be licensed in the UK, so if they are imported into the UK they acquire the same legal status as specials.

3. Key Professional Responsibilities

CODE OF ETHICS:

1. MAKE THE CARE OF PATIENTS YOUR FIRST CONCERN

1.5 Seek to ensure safe and timely access to medicines and take steps to be satisfied of the clinical appropriateness of medicines supplied to individual patients.

1.7 Be satisfied as to the integrity and quality of products to be supplied to patients.

2. EXERCISE YOUR PROFESSIONAL JUDGEMENT IN THE INTERESTS OF PATIENTS AND THE PUBLIC

2.3 Make best use of the resources available to you Professional Standards and Guidance for the Sale and Supply of Medicines

3. SUPPLY OF PRESCRIBED MEDICINES Patients are entitled to expect the dispensing service provided to be accurate, accessible and reasonably prompt. Appropriate standard operating procedures must be in place for the dispensing services you provide, or are responsible for and you must ensure that:

3.2 Every prescription is clinically assessed by a pharmacist to determine its suitability for the patient.

3.7 A product with a marketing authorisation is supplied where such a product exists in a suitable formulation and is available, in preference to an unlicensed product or food supplement.

3.13 Reimbursement claims for NHS or other professional services are honest and accurate.

To meet these standards all pharmacists have a professional responsibility to ensure that:

- Patients receive medication that is safe, effective, appropriate for their condition and their circumstances, with minimal clinical risk
- A special is
  - o prescribed (if you are a pharmacist prescriber)
  - o supplied (if you are dispensing it) only when there is no available licensed medicine which fully meets the patient's clinical needs.
  - o The appropriateness of continued prescription of a special is reviewed and that continued supply is justified by continued special clinical need.
  - o Any specials product supplied is fit for purpose – is of the appropriate quality and clinically appropriate for the individual patient
  - o They understand their professional responsibilities when supplying specials i.e. ensure the patient receives a medicine of assured quality
  - o They minimise risk to patients and themselves: the expectation is that pharmacists will supply an unlicensed product only by exception and with the full knowledge of the prescriber and the patient

A pharmacist shares with the prescriber, accountability for supplying a Special to a patient. They must be able to demonstrate that they have acted with due diligence in regards to patient safety, and that they have taken all reasonable steps to ensure

- procurement from an appropriate source
- that the product is of appropriate quality
- that the product meets the particular clinical needs of the patient: this may require dialogue with the manufacturer, and if relevant the hospital pharmacy, about formulation, strength etc
- that relevant records are kept

Case study 1

GOOD PRACTICE

A 4kg neonate was discharged from hospital on Phenobarbital 20mg three times a day (tds) prescribed as 2ml tds of 50mg/5ml alcohol free phenobarbital suspension. The general practice prescribing system included a British Pharmacopoeia (BP) suspension of 15mg/5ml, and the GP prescribed and the pharmacy dispensed 6.8ml (20mg) tds of this suspension. Four days later the child was taken to hospital with lethargy and increased fitting. The 15mg/5ml preparation contains 38% alcohol and the volume of 6.8ml administered was similar to giving the neonate a glass of wine three times a day. As a neonate cannot metabolise alcohol as efficiently as an adult this would have resulted in lethargy and decreased their seizure threshold which explained their increased fitting. In this case a special would have been the preferred option.

The following good practice issues have been highlighted when dealing with specials:

4. Assessing Clinical Need

Practice Tip

Supply of a special is justified only when there is no available licensed medicine which fully meets the patient's clinical needs. (Reference: MHRA Guidance Note 14 – see below)

When considering the clinical need for a special it is good practice to assess the risk associated with this supply and for pharmacists to use their professional judgement. A risk hierarchy, based on guidance from MHRA, is described in Appendix A. A pharmacist should:

- Make sure the prescriber is aware of the unlicensed status, and if requested, to make every reasonable effort to identify a UK licensed product equivalent, or near equivalent product, to the prescribed Special that meets the patient's clinical needs.
- Where no appropriate licensed medicine is available, and it is essential to supply a special, consider options that include, but are not necessarily limited to,: see Case Study 1
  - o Importation of a product licensed in Europe, USA, Canada, Australia or in another MHRA recognised authority
  - o Purchase of a special from an external manufacturer with a MS
  - o Prescription and supply of an alternative licensed presentation such as a soluble or dispersible formulation, transdermal patch or suppository
  - o Extemporaneously dispensing in the pharmacy – this would include crushing of tablets if appropriate information is available
- Choose the option which minimises the risk to the patient, bearing in mind the patient's clinical need
- Where a patient receives prescriptions on a continuing basis, periodically reconfirm with the prescriber that the ongoing use of an unlicensed product is appropriate, having regard to any circumstances that might suggest that a licensed product may become more suitable
- Document any discussions with the prescriber in relation to the unlicensed nature of the product and its suitability.
- Consider the urgency, or otherwise, of the patient's need for the medicine and take reasonable steps to ensure timely supply.

Case study 2

A study of 22 hospitals found that 10 different captopril oral liquids were being used in many strengths: four of the liquids were provided by specials manufacturers, one was manufactured in an NHS pharmacy manufacturing unit, one was imported and four involved crushing tablets and dispersing them in water. Of these 10 products, only the import had comprehensive data on the stability of the products containing this relatively unstable medicine, and bioavailability equivalence had not been investigated at all. As each child moved between tertiary, secondary and primary care, his / her medicine was often swapped with no consideration for the altered effect of this medicine with a narrow therapeutic range, thus leading to changes in symptom control and adverse events.

5. Choosing a Suitable Product

Practice Tip

To ensure quality of the product, always ask for a certificate of analysis or a certificate of conformity with every product, read what the certificate says and cross reference with the prescription and product supplied.

A certificate of analysis should be available for any batch manufactured special manufactured under a MS and is evidence that critical parameters have been confirmed by retrospective physical, chemical or microbiological assay of a sample of the final product. A certificate of conformity is a signed statement by the manufacturer that they believe the product complies with the purchaser's specification and should be available for all specials produced by an MS holder. (please also refer to Glossary)

Pharmacists have a professional responsibility to ensure that the prescriber is

aware of the unlicensed nature of any Special dispensed. This requirement is detailed in MHRA Guidance Note 14: The Supply of Unlicensed Relevant Medicinal Products for Individual Patients 2008. (http://www.mhra.gov.uk/home/groups/comms-ic/documents/publication/con007547.pdf)

Safety and Quality considerations

Whether a special is made under section 10 exemption or under a MS, the pharmacist who supplies the product to the patient remains accountable for its quality and should take all reasonable steps to assure it.

Where a decision is taken to supply a special, the following points around quality should be considered:

- Pharmacists should agree with the supplier what they require, which includes strength, formulation and excipients, where relevant, such as requirements for sugar-free or alcohol free formulations. This will be based on the pharmacist's understanding of the clinical needs of the patient.
- Where feasible the agreed formulation should be confirmed to the manufacturer in a written order.
- Pharmacists should not assume any aspect of quality and take all reasonable steps to ensure that the product supplied:
  - o Is of a suitable standard.
  - o Comes with a certificate of analysis or a certificate of conformity
  - o Is pharmaceutically appropriate and suitable for the patient e.g. check strength, formulation and excipient details on the certificate, and where available, on the label
  - o Has evidence to support the labelled shelf life of the product – the MS details on the label will be evidence that the shelf life is supported as the MHRA requires the manufacturer to have evidence to support the labelled shelf life.
- If the manufacturer can provide further evidence to support the quality, safety or efficacy of a particular product or formulation, this should be taken into account – however, this information may be commercially sensitive.
- Where the product has a patient information leaflet, the pharmacist should provide this to the patient. If written information is not available then verbal advice should be given.
- If the shelf life/expiry date does not allow for the initial supply to cover the full intended duration of the treatment, this should be drawn to the patient's attention and appropriate arrangements for further supplies should be made
- Any adverse reactions to the product reported by patients, should be reported to the MHRA via the 'yellow card scheme' – http://yellowcard.mhra.gov.uk

6. Choosing a Suitable Supplier and placing an order

Practice Tip

Pharmacists are recommended to have a written Standard Operating Procedure (SOP) in place detailing the steps involved in the ordering of specials including risk assessments of the different options available.

When developing an SOP the following should be considered:

- An SOP for ordering specials demonstrates that the pharmacist has understood the need to define a process for this and how this can be achieved
- A written order listing the formula of the product required demonstrates that the pharmacist has understood exactly what is required and communicated that accurately to the supplier.
- For products produced in batches a certificate of analysis confirms that levels of active ingredients have been retrospectively confirmed by testing a sample of the final product.
- For products produced individually, as a one off, a certificate of conformity confirms that, to the best of the knowledge of the signatory, the final product conforms to the specification supplied by the pharmacist.
- An MHRA licensed specials supplier is preferred and details of registered licensed manufacturing sites can be found at www.mhra.gov.uk/Pharmaceuticalindustry/Manufacturingandwholesaling/index.htm. Details of NHS hospital manufacturing departments are listed in the BNF
- Preference should be given to suppliers with a history of satisfactory service to the pharmacy, although new providers and those who come with good feedback from other pharmacies should also be considered, especially if this could secure improvements. A supply chain involving one or more third parties is potentially associated with additional risk and cost.
- When dispensing a repeat supply (rather than a new treatment) aim to continue to use the same supplier if possible, to ensure product consistency, see Case Study 3
- Regularly check that your chosen supplier is offering the best all round service, taking into account quality, promptness of supply and value for money

Responsible Pharmacists can amend or change existing SOPs if they believe that the SOP in its current format does not support best practice as described in this guidance.

Case Study 3

A child with epilepsy was prescribed clobazam tablets which are licensed for eplilepsy for children aged 3 years and older. The mother reported that the child was struggling to swallow the tablets and the GP decided that it was necessary to prescribe a liquid preparation. The BNF for Children confirmed that no licensed liquid was available, so the GP typed out a prescription for the appropriate dose and strength of liquid clobazam. The community pharmacist subsequently dispensed this unlicensed medicine as an extemporaneous product. The mother returned a week later reporting that the child had increased fitting. Although the GP prescribed clozabam liquid at the appropriate dose and strength and the pharmacist dispensed the correct medicine, clozabam is very hard to suspend. This means that unless the unlicensed liquid dispensed has an appropriate formula and production method, and the bottle is shaken well before dosing, the amount of active ingredient that the child will receive in each dose will vary enormously. Indeed, in some bottle, clozabam is so caked on the bottom of the bottle that the strength of the suspension is only 20% of that expected, even after vigorous shaking. While it is hard for the GP to avoid such a problem, advice could be sought from the original prescriber or pharmacist to ensure that the child receives the most appropriate unlicensed medicine. They should also be prepared to closely monitor the patient and warn patients / carers that symptom control may vary when swapping between products that are not licensed. Changing preparations may impact on symptom control and result in adverse events.

7. Good Record Keeping

The MHRA has specific requirements around record keeping for all specials, including those that are imported. In addition, pharmacists should also comply with the RPSGB guidelines on record keeping for unlicensed medicines (http://www.rpsgb.org/pdfs/factsheet5.pdf)

It is recommended to maintain the following records:

TO BE KEPT FOR A MINIMUM OF 5 YEARS* **
A record of the purchase and supply of a Special and the specification of the product agreed with the supplier (see safety and quality considerations) should be documented and kept on file in the pharmacy for at least five years
Documentation to verify the specifications i.e. certificate of analysis or a certificate of conformity from the manufacturer, should be obtained on delivery and must include the batch number and expiry details of the product; kept on file in the pharmacy
Patient details, such as name and address linked to the special should also be maintained to provide an adequate audit trail.
The source of the product i.e. manufacturer details
The quantity of each sale or supply
The batch number and expiry date of the product (listed on certificate of analysis or a certificate of conformity)
If the product is in response to a prescription, the records must also include the patient's details, prescription details and the date of dispensing.
The date the product was supplied (as may differ from the date of manufacture)

**The MHRA requires a minimum of 5 years, but as pharmacies are accountable for the quality, and claims under the Consumer Protection Act may be brought after many years, pharmacists could decide to retain records for longer periods.*

***In hospitals some specials such as fluids are used as standard supplies and are therefore stock at ward level. The Trust formulary takes responsibility for not documenting every patient who receives one of these particular specials so as long as appropriate governance is in place, there may be exceptions to the requirements in the table above.*

9. Glossary of Terms and abbreviations as they are used in this Guidance

Term	Definition
Special	A medicine manufactured by a specials manufacturer holding a Manufacturer's specials Licence (MS) in multiple quantities with end product analytical testing A special medicine produced by a specials manufacturer holding a MS as a bespoke medicine without end product analytical testing Extemporaneously prepared medicines - Unlicensed medicines made in a pharmacy under a pharmacist's direct supervision
Marketing Authorisation (MA)	The Marketing Authorisation (MA) defines the therapeutic or diagnostic purposes (the clinical indications) for which a medicine may be marketed. The MA provides the authority granted under the Medicines Act for the MA holder to promote or sell the product for these purposes. The permitted clinical indications stated in the MA are based on the data submitted by the MA holder during the licence application process. As such the safety, quality and efficacy of the medicine for use in the listed indications has been assessed by the regulator (the MHRA in the UK or the EMEA in Europe). The MA was formally known as the product licence before harmonisation of the Medicines Act with EU law. A product will be issued with a PL number if the MHRA grants a MA.
Certificate of Analysis	A Certificate of Analysis should state: o The laboratory / organisation issuing it o Be authorised by an appropriately qualified person with signature o Be specific to the batch concerned (state the batch number which matches that of the medicine supplied) o Clearly indicate who performed the tests and the date o State the specification against which the tests were performed o State the test results (actual result or 'complies')
Certificate of Conformity	A Certificate of Conformity states that the batch of medicine supplied is in conformance with its release specification i.e. that it is of the appropriate standard. It will not contain any test results and may not be signed or bear a batch number relating to the batch of the product supplied. A certificate of conformity is therefore only of use in assessing the quality of a product if the purchaser knows what the release specification of the product in question actually is – see MA above.

8. Useful Resources

There are several documents which impact on the procurement and supply of specials, as referenced in the text:

RPSGB
Legal and Ethical Advisory Service Fact Sheet 5: The use of Unlicensed Medicines in Pharmacy (http://www.rpsgb.org/pdfs/factsheet5.pdf)
This document summarises the legislation and best practices when issuing unlicensed medicines.

MHRA
Guideline Note 14: The supply of unlicensed relevant medicinal products for individual patients (http://www.mhra.gov.uk/home/groups/comms-ic/documents/publication/con007547.pdf)

Recommendations for the Retention of Pharmacy Records: Hospital Pharmacist 2008; 15: 254 (full text accessible via PJ Online)

Guidance for the purchase and supply of unlicensed medicinal products: Notes for Prescribers and Pharmacists. (http://www.portal.nelm.nhs.uk/QA/default.aspx) You need to be a member of the National Electronic Library for Medicines (NeLM) to view this document.

Academic detail aid for prescribers – choosing medicines for patients unable to take solid oral dosage forms: UK Medicines Information (http://www.nelm.nhs.uk/en/NeLM-Area/Evidence/Medicines-Q--A/QA-307-1-academic-detail-aid-for-prescribers/)

Information and Guidance on the prescribing and use of unlicensed pharmaceutical specials – East of England Collaborative Procurement Hub specials Sourcing Group. http://www.eoecph.nhs.uk/Pharmaceutical_specials.pdf

The Association of Commercial specials Manufacturers website which provides information on their code of conduct and general information on unlicensed medicines, as well as links to member organisations. The address is www.acsm.uk.com

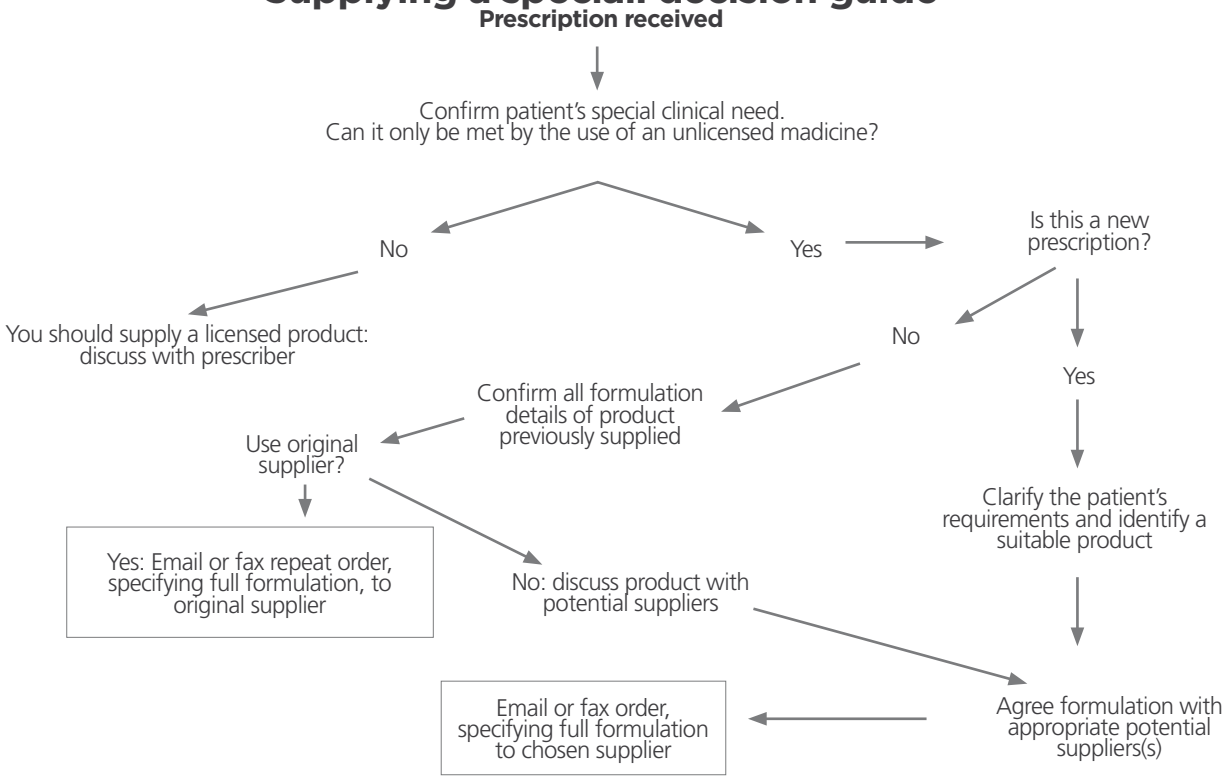
Ref: 'Making medicines safer for children' – guidance for the use of unlicensed medicines in paediatric patients. Guidlines Feb 2009, produced by Connectmedical.

Hierarchy of risk on basis of product origin
(adapted from MHRA guiidance)

Hierarchy may differ in particular patient groups such as neonates

Decision aid/flowchart

Supplying a special: decision guide



Other matters outside the terms of this guidance
The guidance above is intended to ensure that specials are only used when there is no available, clinically appropriate, licensed medicine. All pharmacists are encouraged to ensure that the NHS secures good value from its expenditure, and pharmacists should bear this in mind in procurement of specials.