QUALITY ASSESSMENT of UNLICENSED MEDICINES

1st Edition

November 2016

This document supersedes the quality assessment element of the NHS Pharmaceutical Quality Assurance Committee's "Guidance for the purchase and supply of unlicensed medicinal products: Notes for prescribers and pharmacists (2004)".

It has been produced on behalf of the NHS Pharmaceutical Quality Assurance Committee, the NHS Pharmaceutical Production Committee and the NHS Pharmaceutical Aseptic Services Group by the NHS Unlicensed Medicines Working Group.
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With thanks to Andrew Barnes for the table of Marketing Authorisation numbers (Appendix 3).

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Quality Assessment of Unlicensed Medicines

1. Introduction

The purpose of this document is to provide detailed guidance on the pharmaceutical quality assessment of unlicensed medicines. The principles are applicable both to unlicensed medicines sourced from other legal entities and unlicensed medicines prepared in house.

Unlike licensed medicines, the quality, safety and efficacy of unlicensed medicines is not formally assessed by the MHRA. This means that there is a potential lack of assurance in relation to quality, safety and efficacy.

Unlicensed medicines may only be prescribed and supplied where there is a defined special clinical need which can't be met by any available licensed medicine. A specification for the medicine will be required that not only defines the drug, strength and presentation but also specifies important aspects of the formulation e.g. alcohol-free; preservative free and may also specify the labelling.

The responsibility for ensuring the quality of any unlicensed medicine lies jointly with the prescriber and the purchasing pharmacist. This means that the quality of unlicensed medicines must be assessed before use. This document aims to guide the reader through a typical assessment process and to provide information that will assist with that assessment.

Purchasing pharmacists, and others with responsibility for assessing the quality of unlicensed medicines e.g. QA staff, may wish to adapt the assessment process depending on the level of risk, e.g. nature of product, patient characteristics supplier and route of administration.

2. Scope

This guidance relates to the assessment of the pharmaceutical quality of the unlicensed medicine to support the decision to purchase. It is also intended to assist in identifying any necessary local control measures. **Identification of a patient's special clinical need, preparing a specification, sourcing unlicensed medicines and clinical assessment of safety and efficacy is outside the scope of this document.**

This guidance only relates to unlicensed medicines either imported from another country, or manufactured in the UK by a Specials manufacturer. It does not relate to products made under Section 10 exemption (e.g. aseptically or extemporaneously dispensed) or to overlabelled and repackaged UK licensed medicines. Food supplements and medical devices are also outside the scope of this guidance.

3. Quality assessment of unlicensed medicines

3.1. Overview

Once the clinical need to purchase an unlicensed medicine has been identified, one or more available medicines may need to be assessed for suitability. The prescriber, and the purchasing pharmacist acting on behalf of the prescriber, is responsible for taking all necessary steps to ensure the medicine is of the required quality, so a quality assessment is required before use.

This should take into account the supplier (and manufacturer, if different) and the product.

Suppliers

The supplier or manufacturer is responsible for ensuring that the unlicensed medicine meets the specification provided by the purchaser, however the purchaser needs to takes steps to ensure that the manufacturer has appropriate licences and is capable of supplying consistently manufactured product. Further information about assessing suppliers and manufacturers is in Section 3.2 below, and in Appendices 1A and 2A.

Products

Medicines that do not have a Marketing Authorisation valid in the UK have not been assessed by a regulator in the UK (MHRA or EMA) so the prescriber and purchaser are responsible for assessing their quality, safety and efficacy.

Imported medicines

Imported medicines licensed in the EEA (see appendix 4) or in a country with a Mutual Recognition Agreement are usually the preferred option because quality, safety and efficacy are assured by their licensed status in their country of origin. The quality assessment confirms the licensed status and security of the supply chain, and takes into account the suitability of the packaging and labelling. If the labelling is not in English there may be an increased risk of medication error. The NHS Pharmaceutical QA Committee's "*National requirements for the overlabelling of foreign (non-English language) imported medicines unlicensed in the UK. Edition 1"* sets out the requirements for English overlabelling.

There is less assurance of quality, safety and efficacy of imported medicines licensed outside these countries, or not licensed in their country of origin, and so the assessment will need to be more robust.

N.B. Importers must notify the MHRA of their intention to import a medicine, and the MHRA will either object or not object, but this is not a formal quality assessment.

UK manufactured Specials

In some cases an imported medicine may not be the safest option e.g. where it is only available as a concentrate and a very small dose must be measured; or where the excipients are not suitable for the patient; or if it is not labelled in English and overlabelling (of a very small container, for instance) is not practicable. In such cases a UK manufactured Special may be preferred.

Early Access to Medicines Scheme (EAMS)

Products approved for use under EAMS have undergone an MHRA clinical assessment but they are remain unlicensed in the UK and should be managed as such by pharmacy staff. There is a need for a local product quality assessment before use as for any other unlicensed medicine, in line with the local unlicensed medicines policy. Since it is unlikely that manufacturers will provide a Certificate of Analysis, this might include scrutiny of a batch release certificate signed by their Qualified Person (QP). The assessment should also include a review of the clarity of labelling and of supporting information provided with the product.

Further information about the purchasing of unlicensed medicines can be found in the Royal Pharmaceutical Society's Professional Guidance for the Procurement and Supply of Specials (2015).

QC testing

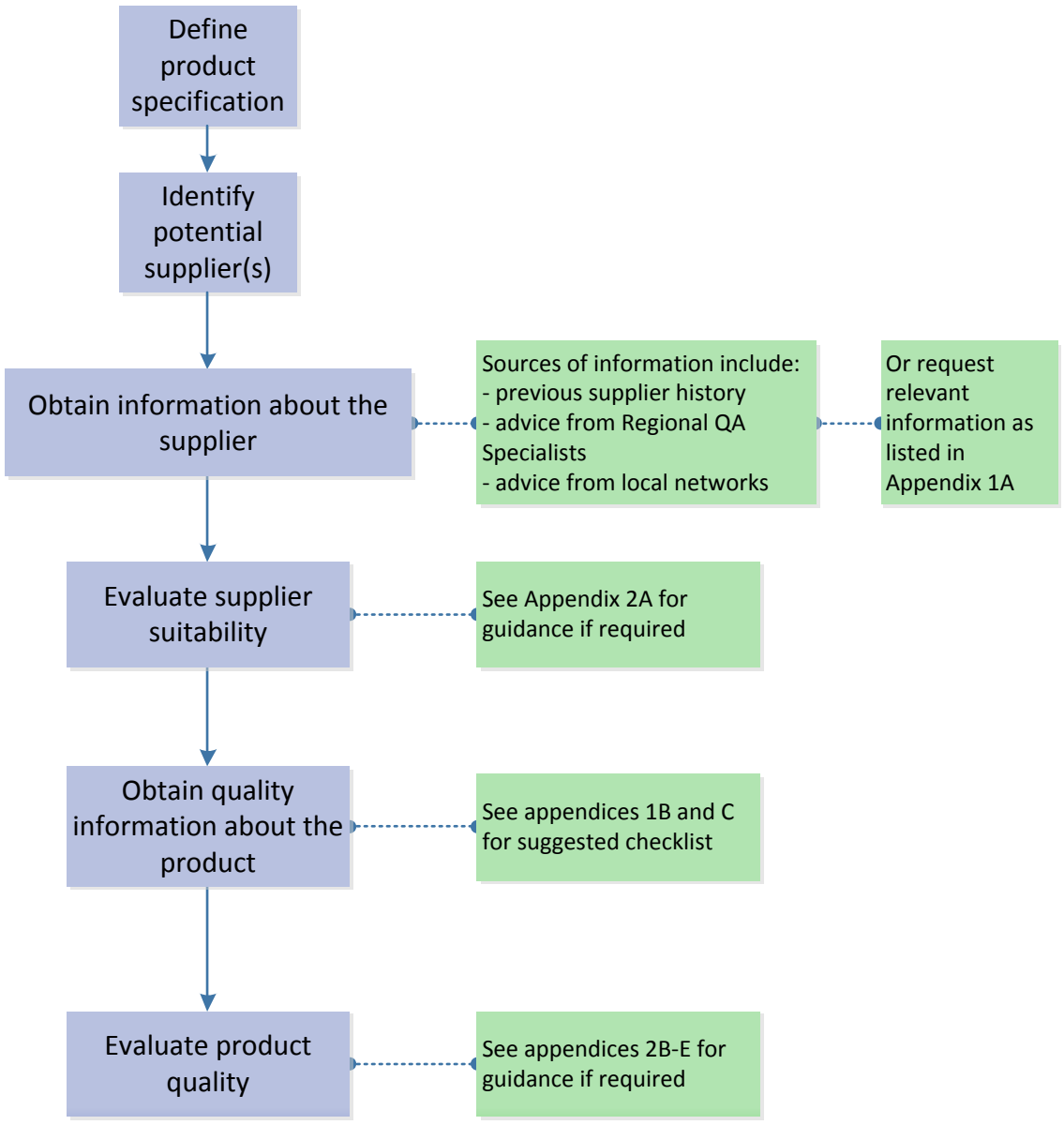
Independent testing of unlicensed medicines is not a substitute for good documentary evidence of the quality of any medicine. Assurance of the quality of any medicine requires evidence that the product is made in such a way that a consistent, uniform product that meets its specification is produced every time. It is not possible to "test quality into the product".

In some cases, however, independent laboratory testing may be recommended following risk assessment e.g.

- as part of an on-going programme of supplier monitoring, especially for new suppliers/manufacturers
- to give additional independent assurance of compliance with a Pharmacopoeial specification

Advice is available from your Regional QA Specialist.

Quality assessment process flow



3.2. Assessment of suppliers and manufacturers

It is recommended that quality assessment of the supplier is performed before purchasing medicines from a new supplier/manufacturer. As a minimum, this should involve checking that the supplier and/or manufacturer have an appropriate licence, and that the licence covers the type of medicine to be purchased. For example:

- A company importing medicines from within the EEA must have a MIA (Imports) licence

- A company importing medicines from outside the EEA must have a Specials manufacturing licence (MS) covering imports.
- A company that manufactures unlicensed medicines in the UK must have a Specials manufacturing licence (MS)
- A company that supplies but does not manufacture Specials must have a Wholesale Dealer Authorisation (WDA)

For routine use of a supplier or manufacturer, the assessment should be more detailed to give assurance of a robust supply of consistently manufactured product. A technical agreement (TA), clearly setting out the responsibilities of the purchasing consortium (if applicable), the purchasing hospital and the contractor should be prepared for all contracts that outsource the preparation of unlicensed medicines. NHS regional and national tenders are supported by the Regional Pharmaceutical QA Specialists who obtain detailed evidence of conformity to tender specifications from manufacturers and often also perform audits.

Before beginning to assess a new supplier, either for occasional or routine use, it is advisable to contact your Regional QA Specialist because there may already be a current NHS QA audit or formal supplier assessment on file. Regional and National tenders for unlicensed medicines involve formal assessment and/or site audit by Regional QA specialists. If a regional or national contract is in place for the product involved, considerable quality assessment will already have been carried out so local assessment may be able to be reduced e.g. to assuring that the product is intact, labelled in line with the specification, any documentation e.g. C of A is acceptable etc.

An information checklist can be found in Appendix 1A and supplier assessment aide memoire in Appendix 2A.

In all cases, assessment of suppliers should be reviewed at intervals to ensure that the supplier or manufacturer still holds relevant licences, and taking into account whether products and services provided have been of an acceptable quality.

3.3. Product quality assessment

The assessment process identifies whether there is a risk of patient harm because:

- the unlicensed medicine does not meet the purchasing specification
- the medicine is not compliant with British Pharmacopoeia (BP) product and general monographs
- there is a risk of medication error (by a healthcare professional or the patient) resulting from inadequate labelling, lack of information or some other feature of the presentation.

The formulation and presentation of an unlicensed medicine should be agreed between the purchaser and prescriber, and the unlicensed medicines manufacturer or importer. In some cases this may mean commissioning a bespoke item or a new product line, but in

other cases hospitals will purchase a product already formulated and offered by a Specials manufacturer or importer. In all cases the purchaser and prescriber will need to ensure that the offered product meets the special clinical needs of the patient concerned, is of the right quality, and is labelled and packaged appropriately.

Further information about this can be found in the Royal Pharmaceutical Society's Professional Guidance for the Procurement and Supply of Specials (2015)

Information gathering

The purchaser and supplier should agree their product specifications to permit assessment ***before*** the products are purchased. Checklists to assist with this information gathering process can be found in Appendices 1B (imports) and 1C (Specials).

If agreement can't be reached with a given supplier, consideration should be given to purchasing from elsewhere or contact your Regional QA Specialist for assistance.

Assessment of different product types

The tables in appendices 2B-E list the quality indicators that should be taken into account when assessing the suitability of unlicensed medicines of different types. Explanatory notes are also given, with some cross references to other sources of information.

If there are difficulties in interpreting the information received, contact your Regional QA Specialist for assistance.

4. Risk control and risk acceptance

Where risks are identified, it may be possible to agree alterations to the product to ensure it meets the purchaser's specification e.g. reformulating without the excipient of concern; bespoke labelling.

Otherwise, it may be necessary to put measures in place to control those risks locally. For example,

- medicines that are not labelled optimally could be overlabelled in the dispensary provided appropriate controls are in place;
- clinical teams may need to provide additional information to the patient;
- additional monitoring of the patient could be introduced. For example, a change in formulation may require closer monitoring of the patient. This is especially important for medicines with a narrow therapeutic index.

If there is a critical need for the medicine but there is a lack of information about the medicine, or risks cannot be fully controlled/no suitable alternative(s) exist, then a risk/benefit assessment should be made in conjunction with the clinical team. This could be documented on a D&T submission form or in the patient's notes, according to the local Unlicensed Medicines Policy.

Once a product has been assessed as suitable for use, an internal hospital specification should be prepared detailing

- The manufacturer's specification and ordering details, to ensure the correct product is requested
- The accompanying documentation to be requested with every order
- The necessary checks to be performed on receipt of the medicine.

The specification should be recorded in the form of a worksheet or checklist to support robust and auditable processes for ordering, quarantining on receipt, and release for use.

5. Periodic risk review and reassessment

Arrangements should be in place to ensure the continuing validity of the risk assessment.

- The suitability of the unlicensed medicine should be reviewed in the light of feedback from patients and clinical teams. This will include positive experiences, as well as recording adverse drug reactions, defects, administration difficulties, errors and near misses. An example form is in appendix 5. It is particularly important to report suspected ADRs and defective medicines via the Yellow Card system.

- The relevant licences of suppliers and manufacturers should be re-checked at intervals. Hospitals with Wholesale Dealer Authorisations must carry out bona fide checks according to Good Distribution Practice, and it is recommended that a similar approach is taken by all purchasers of unlicensed medicines.

- Systems should be in place to ensure that, if a licensed medicine becomes available, it is used wherever appropriate. The MHRA publishes a monthly list of granted Marketing Authorisations, and there should be a system in place to check this periodically.

- There should be a method in place for reviewing formulations in the light of changes (e.g. new BP Monographs; advice from the National Institute for Health and Care Excellence (NICE)) and feedback from patients and clinical teams.

- Systems should be in place to ensure that any changes made to the unlicensed medicine (e.g. a change in formulation or labelling) are agreed in advance. Ideally, a TA should be in place between all parties involved in the supply chain and this should specify responsibilities in relation to change control.

Document History	Issue date and reason for change
Edition 1	Issued November 2016
Edition 2	
Edition 3	
Edition4	

Appendix 1A: Checklist for supplier and/or manufacturer assessment

This checklist can be used to assist with gathering the information needed to assess the suitability of a supplier. Additional notes to help with interpretation of the information can be found in Appendix 2A.

<table>
<tr><td>Name and address of Supplier/manufacturer</td><td colspan="4"></td></tr>
<tr><td rowspan="3">Licence number(s)

This can be checked on the MHRA's lists of wholesalers and manufacturers</td><td></td><td>Scope</td><td colspan="2"></td></tr>
<tr><td></td><td>Scope</td><td colspan="2"></td></tr>
<tr><td></td><td>Scope</td><td colspan="2"></td></tr>
<tr><td>Assessment available from Regional QA?</td><td></td><td colspan="2">Scope of assessment is relevant to the medicine(s) to be purchased?</td><td></td></tr>
<tr><td colspan="5">If an audit has been performed or an assessment made by Regional QA and the scope of the assessment is relevant to the medicine(s) to be purchased, further information may not be required, provided that the audit/assessment conclusion was satisfactory.</td></tr>
<tr><td colspan="5">Further information which may be requested to assist with the assessment, depending on the product type, the quantity to be purchased and the history of the supplier.

☐ Copy of most recent NHS QA audit

☐ Details of most recent MHRA inspection Date of inspection
o Evidence of closure
o Anticipated date of next inspection

☐ Copy of Site Master File (SMF) (e.g.for Specials manufacturers) or Quality Manual(QM) (e.g. for WDA holders)

☐ If not covered by the SMF or QM, procedures for or description of

o Change management and change control
o Receipt of orders from customers
o Use of sub-contractors (including technical agreements with manufacturing sub-contractors)
o Deviations/quality exceptions, complaints, recalls, corrective and preventive actions (CAPA)
o Self-inspection and audit
Where the supplier is also the manufacturer:

☐ If not covered by the SMF or QM, procedures for or description of:

o Any automated equipment in use e.g. mixing vessels, compounders, pumps etc.
o Validation of facility, equipment, manufacturing processes, cleaning and sanitisation processes, and personnel.
o Finished product approval and release
o Maintenance of cold chain (if applicable)

☐ For aseptically manufactured medicines

o If medicines are released before all microbiological results are available, an explanation of how out-of-specification results are managed for products already released.
o An outline of the programme of finished product testing and end of session media filling
o A brief description of the facilities used, types of clean air devices and method of transfer sanitisation.</td></tr>
</table>

Appendix 1B: Checklist for Imports

This checklist can be used to assist with gathering the information needed to assess the suitability of an imported medicine. Additional notes to help with interpretation of the information can be found in Appendix 2B.

Name of product			
Form		Concentration	
Pack size		Diluent (if applicable)	
Strength		Container (if applicable)	
Other details			
Country in which product has a marketing authorisation		MA equivalent number (See Appendix 3)	
Name & address of MA holder		Name and address of manufacturer (if different)	
Country of manufacture		Country from which imported	
Name & address of importer		Import licence number	
Contact details for importer	Name	Telephone	Email

Documentation and samples that may be required.

☐ Sample of product (if possible)

☐ Photograph or artwork of all faces of secondary packaging and primary container

☐ Copy of original SmPC

☐ Copy of original patient leaflet

☐ Copy of most recent MHRA "non-objection" to import (including conditions)

☐ Details of how any relevant temperature controlled storage is maintained between manufacturer and final recipient

☐ Details of how importer will supply the product i.e. will it be overlabelled in line with NHS requirements and whether English translations of PILs or other patient information will be supplied with the pack

If product is not labelled in English:

☐ Copy of validated translations of all leaflets (if required by requesting pharmacist)

☐ Sample overlabel(s) in English

If product is not licensed in the EEA, Switzerland, Australia, Japan, New Zealand or Canada

☐ TSE certification

If product is not licensed in the EEA, Switzerland, Australia, Japan, New Zealand, Canada or the USA

☐ Certification of GMP compliance for the manufacturer from an EU member state

☐ A certificate of analysis or a QP certificate for the batch to be imported

Appendix 1C: Checklist for Specials

This checklist can be used to assist with gathering the information needed to assess the suitability of a UK manufactured Special. Additional notes to help with interpretation of the information can be found in Appendices 2C, D and E.

Name of product			
Form		Concentration	
Pack size		Diluent (if applicable)	
Dose		Container (if applicable)	
Other details			
Name & address of supplier		Name and address of manufacturer, if different	
Licence number of supplier		Licence number of manufacturer, if different	
Contact details for supplier	Name	Telephone	Email

Documentation and samples that may be required to give assurance that the medicine meets the prescriber's requirements, depending on the medicine and the history of the supplier.

- ☐ Specifications for starting materials including excipients
- ☐ Details of method of manufacture
- ☐ Brief explanation of in-process controls (e.g. supervisory and QC checks and tests)
- ☐ Method of sterilisation (for sterile products)
- ☐ Method of transfer sanitisation (for aseptic products)
- ☐ Release criteria including finished product testing
- ☐ Certificate of analysis or certificate of conformity (example or batch-specific)
- ☐ Shelf life and storage requirements
- ☐ Shelf life once opened (oral and topical liquids) or at room temperature (infusions)
- ☐ Stability data summary supporting shelf life (un-opened and in use)
- ☐ Packaging specification for primary and secondary packaging, including the closure if relevant
- ☐ Sample label
- ☐ Photograph of finished product (primary and secondary containers, where applicable)
- ☐ Details of how any relevant temperature controlled storage is maintained between manufacturer and final recipient
- ☐ Sample C of A

Appendix 2A: Aide memoire – supplier assessment

This aide memoire can be used to help to interpret the information received from suppliers (see Appendix 1A)

	Quality indicator	Notes
1	The supplier/manufacturer holds the appropriate licence from the MHRA for the service to be provided	Manufacturers of Specials must hold a Manufacturing Authorisation (Specials) licence (MS). This permits them to manufacture and to sell the Specials they make. Brokers and suppliers of Specials must hold a Wholesale Dealer Authorisation (WDA(H)). Importers of unlicensed medicines must have a Manufacturer/Importer's licence (MIA). If there is an overlabelling stage, the overlabeller must have a MS licence. The scope of the licence (i.e. the product types covered by the licence) must cover the type of products they are making or supplying. The scope of each licence is listed on the MHRA's lists of wholesalers and manufacturers.
2.	MHRA inspection closure and frequency	The MS holder or importer of the medicine should be able to supply the date of the most recent MHRA inspection, a closure letter or certificate indicating that the inspection is closed, and the date that the next inspection is anticipated. The MHRA operate a risk-based inspection programme and schedule the frequency of inspections based on their assessment of risk. Frequencies vary between 6 monthly and every 2.5 years; if the assessment frequency is short additional information may need to be sought. Contact your Regional QA Specialist for advice.
3.	NHS QA audit	NHS Regional Quality Assurance specialists audit or otherwise assess some suppliers of unlicensed medicines and these reports, whilst confidential to the NHS, are usually available to the other Regional QA Specialists. Suppliers themselves may provide the reports to hospitals on request. The audit report will conclude whether the supplier or manufacturer is considered to be a suitable supplier to the NHS, and may make further recommendations for action. It is important to check that the audit scope is relevant to the type of product to be purchased and that any follow up actions have been satisfactorily completed if this is a condition of approval. N.B. The absence of a NHS QA audit does not indicate that the supplier is unsuitable, just that an audit has not yet been undertaken.
4.	The supplier can demonstrate GMP compliance, robust quality system processes, and the technical capability to produce medicines according to agreed specifications.	Where a supplier is being formally assessed e.g. as part of a tender process, evidence of suitability is required. This may be obtained as statements from the supplier, the site master file or quality manual, and/or from other policies and SOPs. Tender specifications should specify in detail the evidence required. An example of a specification for Specials manufacturing sites is included in the Homecare Medicines and Services Template Specification from the Commercial Medicines Unit.
5.	Supplier performance is satisfactory	When supplier approval is renewed, or when a new supplier is being formally approved, the performance history of the supplier (reliability, defects, complaints handling etc.) should be considered.

Appendix 2B: Aide memoire - Imported medicines licensed in their country of origin

This aide memoire can be used to help to interpret the information received about imported medicines (see Appendix 1B)

	Quality indicator	Notes
1	There is no objection from the MHRA to importation, and whether any special conditions have been imposed by the MHRA	The MHRA issues a non-objection statement to the importer: a copy of this should be available on request. If conditions are applied by the MHRA, the purchaser should ensure that the supplier complies with the conditions, and the prescriber is informed.
2	The product is licensed in the EEA (see appendix 4), or in a country with a Mutual Recognition Agreement (Canada, Japan, Switzerland, Australia, New Zealand or Israel), or in the USA.	Pharmaceutical quality is assured if the medicine has a marketing authorisation in one of the listed countries. See appendix 3. NB. The Mutual Recognition with Canada and Japan does not extend to biologicals or blood products. There is no Mutual Recognition with the USA, but **medicines** that are approved by the FDA (i.e. medicines with an ANDA or NDA number) comply with standards equivalent to EU GMP. NB an NDC number on the packaging is not evidence that a product is a licensed medicine in the USA, but the NDA number can be used to search the FDA's National Drug Code directory to determine whether the drug is FDA approved. Different countries use different MA number formats, and sometimes these are not on the packaging. If in doubt refer to your Regional QA Specialist for advice. In some cases it may be appropriate to use a medicine that is not licensed in its country of origin. However, assurance of quality varies widely between countries (within and outside the EEA) depending on their regulatory arrangements. Contact your Regional QA Specialist for advice. Additionally, the prescriber should be informed that the medicine is not licensed in its country of origin so that they can make a risk/benefit analysis for the particular patient that they are treating.
3	Certification of compliance with the TSE regulations is provided (for countries outside the EEA and the Mutual Recognition countries).	Compliance with the TSE regulations is assured in EEA countries or those with Mutual Recognition, so no additional certification is needed. This is not the case for the USA and the rest of the world, so documentary evidence of compliance with the TSE regulations is essential.
4	A certificate of GMP compliance is available (for countries outside the EEA, the Mutual Recognition countries and the USA).	A specific manufacturer outside the EEA may be granted a certificate of GMP compliance by an EEA member state. This certifies that the manufacturer complies with the principles of EU GMP. Certificates should be available on request.
5	A certificate of analysis is available (for countries outside the EEA, the Mutual Recognition countries and the USA)	Because arrangements for finished product release may differ in countries outside the EEA, the mutual recognition countries and the USA (FDA approved medicines only: see (2) above), a certificate of analysis for the finished product should be obtained. This should demonstrate compliance to the finished product specification.

	Quality indicator	Notes
6.	A certificate of analysis or a QP certificate of batch release is available for medicines **not** licensed in their country of origin	A certificate of analysis or QP certificate of batch release may provide assurance that a medicine is of the required quality. In the case of EAMS medicines which may be manufactured in the EEA or a Mutual Recognition country a C of A is unlikely to be available, but it should be possible to obtain a QP certificate of batch release.
7	The cold chain (if applicable) has been maintained up to the point of delivery	The supplier should be able to provide certification for all cold chain items.
8	The medicine is suitably packaged and labelled.	For non-English language imported products, overlabelling may be required, depending upon the department to which the product is to be supplied, and whether the generic name and dose are clearly understandable on the original pack. Excipients of known effect (and all excipients in injectable medicines) should be included on the label, so this should also be considered. Some importers may offer bespoke labelling as defined by the purchaser, but other importers may offer their standard overlabelled pack. In this case it is essential to check that the wording on the label meets the requirements of the prescriber. Alternatively, the medicine could be overlabelled locally. Refer to the NHS Pharmaceutical QA Committee's "*National requirements for the overlabelling of foreign (non-English language) imported medicines unlicensed in the UK. Edition 1"* Also measuring devices provided may not be suitable if not marked with standard UK measurements.
9	Suitable technical and patient information is available	Technical and patient information is essential. For non-English language imported products, translated leaflets (PILs, SmPCs or equivalent) should be requested. This is essential to ensure that the • prescriber has all the necessary information about the formulation, dosage and administration to determine whether the medicine is suitable for the patient's clinical need • healthcare professional has the information required to administer the medicine safely • Patient has the information required to take the medicine safely Importers should be able to provide evidence that they use a validated translation service complying with EN-15038:2006. In some cases, the information provided for the healthcare professional or patient may not be sufficient or appropriate e.g. the pack may not contain patient information, or the medicine is to be used for a different indication from that for which the medicine was licensed. Local patient or technical information may therefore need to be prepared.

Appendix 2C: Aide memoire - Non-sterile "Specials" from the holder of a Manufacturing Licence (Specials).

This aide memoire can be used to help to interpret the information received about UK manufactured non-sterile Specials (see Appendix 1C)

	Quality indicator	Notes
1	The product has been made under the manufacturer's Specials licence	The MS holder's name and MS number should be stated on the label. This can be verified by checking the MHRA's list of licence holders. The scope of the licence must cover the type of product that is being purchased. N.B. Where the supplier is a wholesaler or broker, not manufacturer, the product *may* state the supplier's name, and *must* state the manufacturer's name and MS number.
2	The product complies with the relevant BP monograph, if applicable	There are several BP monographs for specific unlicensed medicines, a general monograph (see appendix 4) for Unlicensed Medicines and general monographs for specific dosage forms. The product specification should state compliance with the relevant monographs.
3	The product is made from pharmaceutical grade starting materials, using a validated method with in-process controls which gives assurance of a consistently made product, every time.	Products may be made in different ways e.g.: - In bulk from active pharmaceutical ingredients (API)s - In small batches or single items from APIs - In small batches or single items by altering licensed dose forms The identity of all starting materials should be stated. The product specification should state which preparation method is used. It should also state how accuracy and uniformity are assured e.g. use of validated mixing methods; second-checking; automated verification of measurements; in-process sampling etc. dependent on the product and preparation method.
4	The finished product is QC tested before release	Product made in batches should be subject to finished product testing prior to release. This should demonstrate conformity to the BP or other defined specification. Where very small batches or single items are produced, finished product testing is unlikely to be performed A testing programme involving occasional analysis should, however, be in place. The absence of finished product testing is not necessarily a barrier to purchasing, provided that the manufacturing method, in-process controls and product quality monitoring methods are validated and robust (see below). However, if a batch manufactured and fully tested product that meets the patient's special clinical needs is available, this should always be purchased in preference.
5.	The release process is robust	The release process should take into account any in-process or finished product checking and testing, and correct functioning of plant and equipment, in addition to documentation checks.
6	Certificates of analysis are provided with every batch	A Certificate of Analysis is a batch-specific certificate of finished product testing. It should detail the tests performed, required results, actual results, and the laboratory which issued it. A Certificate of Conformity is a declaration of conformity only, which is not supported by end product batch testing. A Certificate of Conformity will only state that the medicine was made under the MS Licence, according to GMP. Without an agreed product Specification, a Certificate of Conformity is of limited value.

	Quality indicator	Notes
		All certificates should be signed by an authorised person independent of production, such as someone working in a quality discipline e.g. Quality Assurance or Quality Control.
7.	The stability data supports the shelf life (during storage and in-use, where applicable)	Stability statements should relate specifically to the product being purchased, taking the formulation and the primary container into account. Sources of data should be stated. Stability studies should be stability indicating. Where shelf life is extrapolated from existing studies, the rationale for doing this should be fully explained. Refer to the NHS Pharmaceutical QA Committee's "*A Standard Protocol for Deriving and Assessment of Stability. Part 3 - Oral Liquid Medicines (Solutions, Emulsions, Suspensions and Syrups) - Edition 1, August 2014*" This requirement also applies to those products made on a 'bespoke' basis, not just those that are batch produced.
8.	The labelling and packaging is suitable for the patient or healthcare professional, and meets the general requirements of the BP.	Labels should be compliant with the BP general monograph and should be designed to minimise the likelihood of errors. There is no requirement for Specials manufacturers to provide patient or technical information leaflets. If they are provided these must not imply that the product is licensed, and may not be suitable for the special clinical need of the patient(s) for whom the medicine is purchased.
9.	For cold chain medicines, there is evidence of cold chain maintenance to the point of delivery.	This may be a cold chain certificate provided on delivery or on request after delivery, or evidence of validation of insulated packaging.

Appendix 2D: Aide memoire – Terminally sterilised "Specials" from the holder of a Manufacturing Licence (Specials).

This aide memoire can be used to help to interpret the information received about UK manufactured sterile Specials (see Appendix 1C)

	Quality indicator	Notes
1	The product has been made under the manufacturer's Specials licence	The MS holder's name and MS number should be stated on the label. This can be verified by checking the MHRA's list of licence holders. The scope of the licence must cover the type of product that is being purchased. N.B. Where the supplier is a wholesaler or broker, not manufacturer, the product *may* state the supplier's name, and *must* state the manufacturer's name and MS number.
2	The product complies with the relevant BP monograph, if applicable	There are several BP monographs for specific unlicensed medicines, and a general monograph (see appendix 4) for unlicensed Medicines and general monographs for specific dosage forms. The product specification should state compliance with the relevant monographs.
3	The product is made from pharmaceutical grade starting materials, using a validated method with in-process controls which gives assurance of a consistently made product, every time.	The product specification should state which preparation method is used. It should also state how accuracy and uniformity are assured e.g. use of validated mixing methods; second-checking; automated verification of measurements; in-process sampling etc. dependent on the product and preparation method.
4.	The product is sterilised using a BP method	Medicines must be sterilised in according to a validated British Pharmacopoeial method. Wherever possible this should be by autoclaving in their final container.
5.	The finished product is QC tested before release	Product should be subject to finished product chemical and sterility testing prior to release. This should demonstrate conformity to the BP or other defined specification.
6.	The release process is robust	The release process should take into account any in-process or finished product checking and testing, and correct functioning of plant and equipment, in addition to documentation checks.
7	Certificates of analysis are provided with every batch	A Certificate of Analysis is a batch-specific certificate of finished product testing. It should detail the tests performed, required results, actual results, and the laboratory which issued it. It should be signed by an authorised person independent from production, such as someone working in a quality discipline, e.g. Quality Assurance or Quality Control.
8.	The stability data supports the shelf life (during storage and in-use, where applicable)	Stability statements should relate specifically to the product being purchased, taking the formulation and the primary container into account. Sources of data should be stated. Stability studies should be stability indicating. Where shelf life is extrapolated from existing studies, the rationale for doing this should be explained. Whilst not the same scope as for terminally sterilised medicines, the following may contain some information which may be applicable: *"Standard Protocol for Deriving and Assessment of Stability; Part 1: Aseptic Preparations (Small Molecules) Edition 3, 2015,"* issued by the NHS Pharmaceutical QA Committee.
9.	The labelling and packaging is suitable for the patient or healthcare professional, and meets the general requirements of the BP.	Labels should be compliant with the BP general monograph and should be designed to minimise the likelihood of errors. There is no requirement for Specials manufacturers to provide patient or technical information leaflets. If they are provided these must not imply that the product is licensed, and purchasers should ensure that any leaflets are relevant to the patient(s) for whom the medicine is purchased.
10.	For cold chain medicines, there is evidence of cold chain maintenance to the point of delivery.	This may be a cold chain certificate provided on delivery or on request after delivery, or evidence of validation of insulated packaging.

Appendix 2E: Aide memoire - Aseptically manufactured "Specials" from the holder of a Manufacturing Licence (Specials).

This aide memoire can be used to help to interpret the information received about UK aseptically manufactured Specials (see Appendix 1C)

	Quality indicator	Notes
1	The product has been made under the manufacturer's Specials licence	The MS holder's name and MS number should be stated on the label. This can be verified by checking the MHRA's list of licence holders. The scope of the licence must cover the type of product that is being purchased. N.B. Where the supplier is a wholesaler or broker, not manufacturer, the product *may* state the supplier's name, and *must* state the manufacturer's name and MS number.
3	The product is made from UK licensed sterile medicines, using a validated method with in-process controls which gives assurance of a consistently product, every time.	The product specification should state the nature of the starting materials. If it is necessary to use unlicensed starting materials (i.e. sterile Specials or sterile imported medicines), this should be clearly stated in the agreed product specification and the quality of the unlicensed starting material should have been assessed by the manufacturer in the same way as outlined in this document. The specification should also state the preparation method used, and whether intermediates are produced either as part of a single process or as a discrete manufacturing step. It should also state how accuracy and uniformity are assured e.g. use of validated mixing methods; second-checking; automated verification of measurements etc. dependent on the product and preparation method.
4.	Sterility is assured	The specification should include a description of sterility assurance measures e.g. facility in which the product is prepared; transfer sanitisation measures; in-process monitoring; process validation, programme of finished product sterility sampling or media fills.
5	The release process is robust	The release process should take into account any in-process or finished product checking and testing, and correct functioning of plant and equipment, in addition to documentation checks.
6.	Certificates of conformity are available	Certificates of conformity to specification should be available for each batch.
7	The stability data supports the shelf life (during storage and in-use, where applicable)	Stability statements should relate specifically to the product being purchased, taking the formulation and the primary container into account. Sources of data should be stated. Stability studies should be stability indicating. Where shelf life is extrapolated from existing studies, the rationale for doing this should be explained. Refer to *"Standard Protocol for Deriving and Assessment of Stability; Part 1: Aseptic Preparations (Small Molecules) Edition 3, 2015,"* issued by the NHS Pharmaceutical QA Committee.
8.	The labelling and packaging is suitable for the patient or healthcare professional, and meets the general requirements of the BP.	Labels should be compliant with the BP general monograph and should be designed to minimise the likelihood of errors.
9.	For cold chain medicines, there is evidence of cold chain maintenance to the point of delivery.	This may be a cold chain certificate provided on delivery or on request after delivery, or evidence of validation of insulated packaging.

Appendix 3 – Marketing authorisation numbers

Country	Status*	Licence number examples	Searcheable databases	SPC (or equivalent if non-EU) description	Approximate meaning	Name of regulator	Address	Website
Australia	Other (Full MR)	AUST R 16273		ARTG Number	Australian Register of Therapeutic Goods Number	Therapeutic Goods Administration	136 Narrabundah Lane Symonston ACT 2609 Australia	http://www.tga.gov.au/index.htm
Austria	EU	Z. Nr.: 1-22175 Z.Nr: 15.434	https://aspregister.basg.gv.at/aspregister/faces/aspregister.jspx?_afrLoop=27040843693017830&_afrWindowMode=0&_adf.ctrl-state=tke627idc_4	Zulassungsnr	Registration no.	Austrian Agency for Health and Food Safety	Spargelfeldstraße 191 1220 Wien Austria	www.ages.at
Belgium	EU	BE217271 922 IS 32 F3	http://bijsluiters.fagg-afmps.be/?localeValue=en	NUMMER VAN DE VERGUNNING NUMÉRO (S) D'AUTORISATION	Authorisation number	Federal Agency for Medicines and Health Products	EUROSTATION II Place Victor Horta, 40/ 40 1060 Brussels Belgium	http://www.fagg-afmps.be/
Canada	Other (Part MR)	DIN 00260428	http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp	Drug Identification number DIN		Health Canada	Address Locator 0900C2 Ottawa, Ontario K1A 0K9 Canada	http://www.hc-sc.gc.ca/index-eng.php
Croatia	EU	UP/I-530-09/09-01/459	http://www.almp.hr/?ln=hr&w=lijekovi	KLASA RJEŠENJA O ODOBRENJU ZA STAVLJANJE GOTOVOG LIJEKA U PROMET	Classification number	Agency for Medicinal Products and Medical Devices	Ksaverska cesta 4 10 000 Zagreb Croatia	http://www.almp.hr/

Country	Status*	Licence number examples	Searcheable databases	SPC (or equivalent if non-EU) description	Approximate meaning	Name of regulator	Address	Website
Czech Republic	EU	Reg ČÍSLO 14/190/01-C	http://www.sukl.cz/modules/medication/search.php	REGISTRAČNÍ ČÍSLO	Registration number	State Institute for Drug Control	Šrobárova 48 100 41 Praha 10 Czech Republic	www.sukl.cz
Estonia	EU	713910 EE 357701 *(May be Baltic multistate packaging)*	http://193.40.10.165/register/register.php?keel=eng&inim_vet=inim	MÜÜGILOA NUMBRID	Marketing number	State Agency of Medicines	Nooruse 1 50411 Tartu Estonia	www.sam.ee
EU (Centralised procedure)	EU	EU/1/04/276	http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/medicines/medicines_landing_page.jsp&mid=WC0b01ac058001ce7e			European Medicines Agency	30 Churchill Place Canary Wharf London E14 5EU	http://www.ema.europa.eu/ema/
France	EU	Médicament autorisé nº 343 663-7 Méd Aut 34009 343 663-76 *(New 13 digit format from 2008)*	http://agence-prd.ansm.sante.fr/php/ecodex/index.php#result	NUMERO(S) D'AUTORISATION	Authorisation number	National Agency for the Safety of Medicine and Health Products	ANSM 143-147 bd Anatole France 93285 Saint-Denis cedex France	www.ansm.sante.fr
Germany (drugs)	EU	Zul-Nr 3003264.00.00 *(8-digit number being introduced from 2013. 7-digit numbers may be preceeded by a 0)*	https://www.pharmnet-bund.de/dynamic/de/arzneimittel-informationssystem/index.html Click "Rescherche für Midizinische Laien". On bottom of next page click "akzeptieren"	Pharmazentral-nummer		Federal Institute for Drugs and Medical Devices	Kurt-Georg-Kiesinger-Allee 3 53175 Bonn Germany	www.bfarm.de

Country	Status*	Licence number examples	Searcheable databases	SPC (or equivalent if non-EU) description	Approximate meaning	Name of regulator	Address	Website
Germany (biologicals such as vaccines)	EU	PEI.H.03166.01 86a/97 *(PEI = Paul-Erlich-Institut)*	http://www.pei.de/DE/arzneimittel/weitere-arzneimittel/weitere-arzneimittel-node.html	Zulasssungsnummer	Registration number	Paul Ehrlich Institute	Paul-Ehrlich-Straße 51-59 63225 Langen Germany	www.pei.de/
Greece	EU	ΑΡ.ΑΔ.ΚΥΚΛ: ΕΛΛΑΔΑ 19940/30-5-2002 Αρ.Αδειας Κυκλ. ΕΟφ: 35986/01/002		Την με αρ. Πρωτ	The ref number	National Organization for Medicines	Messogion Avenue 284 15562 Athens Greece	www.eof.gr
Ireland	EU	PA0179/003/006A	http://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results?showadv=true&list=HM			Irish Medicines Board	Kevin O'Malley House Earlsfort Centre Earlsfort Terrace Dublin 2 Ireland	www.imb.ie
Italy	EU	A029485099 On bar code coupon				Italian Medicines Agency	Via del Tritone, 181 00187 Roma Italy	www.agenziafarmaco.it
Japan	Other (Part MR)	22300AMX00548000 *(See accompanying information from Japan Ministry of Health, Labour and Welfare)*				Pharmaceuticals and Medical Devices Agency, Japan	Shin-Kasumigaseki Building 3-3-2 Kasumigaseki, Chiyoda-ku Tokyo 100-0013 Japan	http://www.pmda.go.jp/english/

Country	Status*	Licence number examples	Searcheable databases	SPC (or equivalent if non-EU) description	Approximate meaning	Name of regulator	Address	Website
Latvia	EU	05-0084 LV 00-0245 *(May be Baltic multistate packaging)*	https://www.zva.gov.lv/zalu-registrs/?lang=en	REĢISTRĀCIJAS NUMURS(I) Reģistrācijas apliecības numurs:	Registration number(s) Marketing authorization number	State Agency of Medicines	15 Jersikas Street 1003 Riga Latvia	www.zva.gov.lv
Liechtenstein	EU	Does not licence - automatically approves Swiss and Austrian medicines				Office of Health / Department of Pharmaceuticals	Äulestr 512 9490 Vaduz Liechtenstein	www.llv.li
Lithuania	EU	LT/1/94/0478/005 LT 01/7555/9 LT/1/2000/0464/001	http://extranet.vvkt.lt/paieska/index.php	Rinkodaros teisės (registracijos) pažymėjimo numeris:	Marketing (registration) certificate number	State Medicines Control Agency	Žirmūnų g. 139A 09120 Vilnius Lithuania	www.vvkt.lt
Malta	EU	082/04401	http://www.medicinesauthority.gov.mt/advanced-search			Medicines Authority	Sir Temi Zammit Buildings Malta Life Sciences Park San Gwann SGN 3000 Malta	www.medicinesauthority.gov.mt
Netherlands	EU	RVG 26707 RVH = *homeopathic*	http://www.geneesmiddeleninformatiebank.nl/ords/f?p=111:1:0::NO:SESSION:P0_DOMAIN,P0_LANG:H,NL	NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN	Marketing authorisation number	Medicines Evaluation Board	Graadt van Roggenweg 500 3531 AH Utrecht The Netherlands	http://www.cbg-meb.nl/ www.igz.nl

Country	Status*	Licence number examples	Searcheable databases	SPC (or equivalent if non-EU) description	Approximate meaning	Name of regulator	Address	Website
Poland	EU	Pozwolenie nr R/0949 Pozwolenie nr 9588	http://pub.rejestrymedyczne.csioz.gov.pl/?AspxAutoDetectCookieSupport=1 http://bil.aptek.pl/servlet/leki/search	Pozwolenie nr:	Permit number	Office for Registration of Medicinal Products, Medical Devices and Biocidal Products	Al. Jerozolimskie 181C 02-222 Warsaw Poland	www.urpl.gov.pl
Spain	EU	Reg AEM y PS no Reg 71.685 604751.4 CN 656733.33	http://www.aemps.gob.es/cima/fichasTecnicas.do?metodo=detalleForm			Spanish Agency for Medicines and Health Products	Parque Empresarial Las Mercedes Edificio 8C/. Campezo, 1 28022 Madrid Spain	www.aemps.gob.es
Sweden	EU	MTnr 42106	http://www.lakemedelsverket.se/Sok-efter-lakemedel-och-mediciner-i-Lakemedelsfakta/			Medical Products Agency	Dag Hammarskjölds väg 42 / Box 26 751 03 Uppsala Sweden	www.lakemedelsverket.se
Switzerland	Other (Full MR)	41940 Highlighted on the human readable numbers under the barcode, above the word "SWISSMEDIC"	http://www.kompendium.ch/search/de (Pack photos may be viewable)	Zulassungsnummer	Approval number	Swiss Agency for Therapeutic Products	Hallerstrasse 7 P.O. Box CH-3000 Bern 9 Switzerland	http://www.swissmedic.ch/index.html?lang=en
Turkey	Candidate Country	Ruhsat Numerası: 21.04.2011 - 231/6		Ruhsat Numerası	Permit number	Ministry of Health of Turkey Directorate of Pharmaceuticals and Pharmacy	Mithatpaşa Cad. No : 3 06434 Sıhhıye Ankara	http://www.saglik.gov.tr/TR/ana-sayfa

Country	Status*	Licence number examples	Searcheable databases	SPC (or equivalent if non-EU) description	Approximate meaning	Name of regulator	Address	Website
United Kingdom	EU	PL 00057/0963 PL 3265/0003R	http://www.medicines.org.uk/emc/browse-documents http://www.mhra.gov.uk/spc-pil/		Marketing Authorisation	Medicines and Healthcare Products Regulatory Agency	151 Buckingham Palace Road Victoria London SW1W 9SZ United Kingdom	https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency
USA	Other (No MR)	**The Licensed status of the medicine cannot be confirmed from the label - the NDC number shown is NOT a Licence number. Search on FDA website using NDC number to determine status.**	http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194955.htm			US Food and Drug Administration	10903 New Hampshire Avenue Silver Spring, MD 20993 USA	http://www.fda.gov/Drugs/default.htm

*MR = Mutual recognition of GMP inspections. For specific details see:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000248.jsp&#section1

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Additional links to drug databases from Infolinks: http://pharm-infolinks.webnode.cz/drug-databases/national-drug-databases-eu/
Version Number 3 2nd August 2016, Pharmacy Quality Assurance Specialist Services, East of England and Northamptonshire.

Appendix 4 – Countries in the EEA

Austria
Belgium
Bulgaria
Croatia
Cyprus
Czech Republic
Denmark
Estonia
Finland
France
Germany
Greece
Hungary
Iceland
Ireland
Italy
Latvia
Lithuania
Luxembourg
Malta
Netherlands
Norway
Poland
Portugal
Romania
Slovak Republic
Slovenia
Spain
Sweden
United Kingdom

Source:
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004445.pdf

Appendix 5 – example feedback form

Warrington and Halton Hospitals NHS
NHS Foundation Trust

PATIENT SAFETY FEEDBACK FORM FOR UNLICENSED MEDICINES
This form is for use within the Trust. It should be completed and returned to Medicines Management, Pharmacy Department

MEDICINES MANAGEMENT, PHARMACY DEPT	DATE: REFERENCE NUMBER:
Patient details	
Initials:	Hospital No:
D.O.B.:	Gender:
Prescriber details	
Name:	Contact No:
Division:	Grade:
Unlicensed Medicine details	
Medicine name:	
Form	
Strength	
Route	
Dose	
Indication for use	
BNF category	
Date medicine was requested	
Date medicine was prescribed	
Unlicensed Medicine category	
Licensed Import	☐
Batch manufactured special	☐
Non-batch manufactured special (section 10 exemption)	☐
Unlicensed Medicine feedback (please comment as appropriate)	
Was there acceptability of administration of the medicine, for example, oral medicine did not sediment, able to administer via PEG, solution for IV administration reconstituted without problems? Please comment.	
Was patient acceptability of the medicine satisfactory, for example, acceptable taste, formulation, storage? Please comment.	

Warrington and Halton Hospitals NHS
NHS Foundation Trust

MEDICINES MANAGEMENT, PHARMACY DEPT	DATE: REFERENCE NUMBER:
Has the patient obtained a good or acceptable clinical response? Please comment.	
As appropriate, has the course of treatment been completed? If not please detail briefly why.	
Has the patient experienced any adverse effects or intolerance to the medicine? Please comment.	
If the patient has experienced any problems taking the medicine does this require further investigation.	