Quality, Safety and Sourcing in Unlicensed Medicines

with Andrew Trouton
Managing Director, UL Medicines

UL Medicines
A Quantum PHARMA GROUP COMPANY

THE UNLICENSED EXPERT

In partnership with APTUK

Association of Pharmacy Technicians UK Founded 1952

Agenda

- Welcome
- What is an unlicensed medicine?
- When should you consider using an unlicensed medicine?
- Accountability / Responsibilities in the pharmacy
- Risk assessment
- Sourcing
- Documentation
- MHRA – latest updates / useful resources
- Q&A
- Close

What is an unlicensed medicine?

- Any medicinal substance without a Marketing Authorisation (MA) is an **'unlicensed medicine'**

- In the UK the licensing of medicines is regulated by:

  - Medicines and Healthcare Regulatory Agency (MHRA)
  - European Medicines Agency (EMA)

- The fundamental nature of an unlicensed medicine means they have not been through the same approval process by UK authority

- The unlicensed medicine may have been through a regulatory assessment by a recognised authority in another country i.e. an unlicensed import

When should you consider using an unlicensed medicine?

- When there is no equivalent licensed medicine available in the UK to meet the special need of the patient
- If a licensed medicine is available but **not** in a suitable formulation / presentation (e.g. oral liquid form in paediatrics)
- When the equivalent licensed medicine is likely to be unavailable for a significant period (e.g. manufacturing difficulties)
- For commercial reasons - either the licence has been relinquished or is maintained without the product being marketed

Accountability

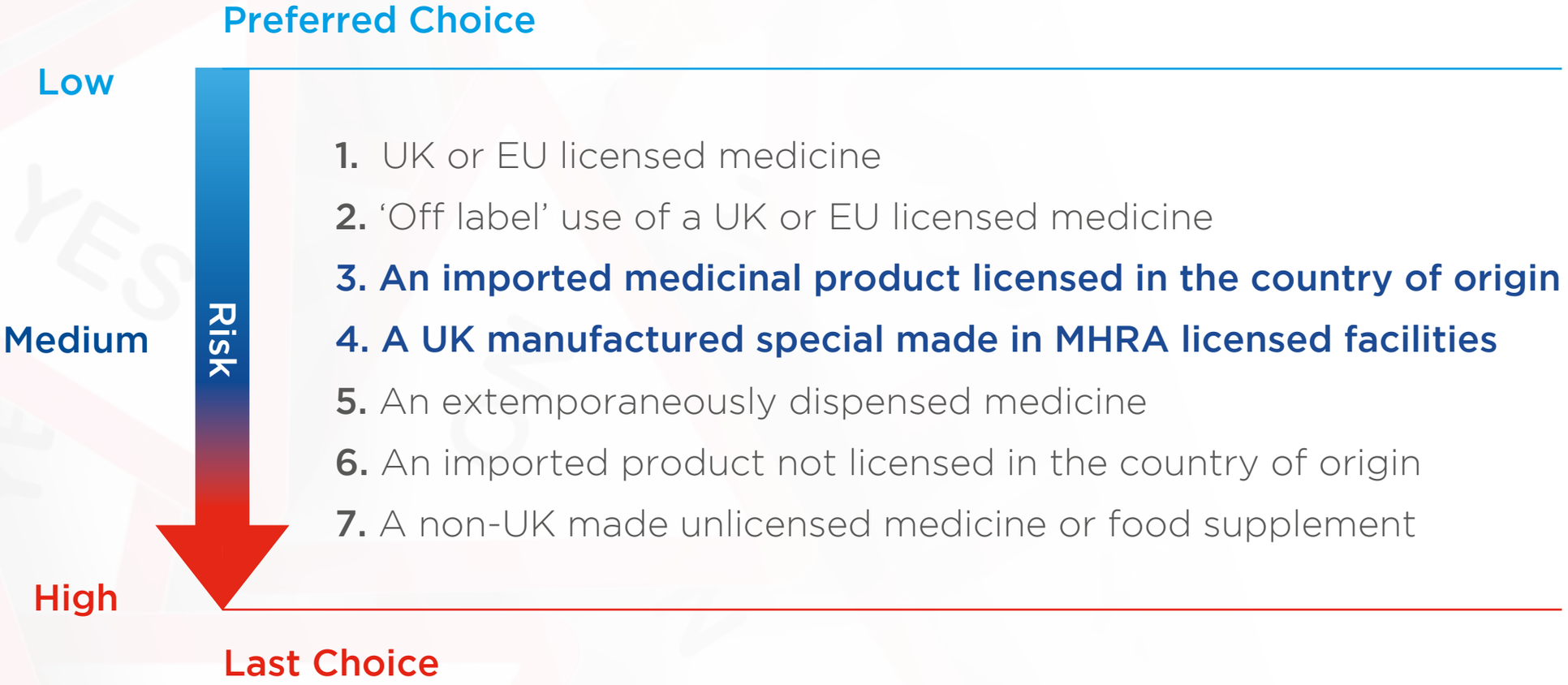
You must ensure:

- Prescribers are always aware that the requested medicine is only available as an unlicensed product
- The manufacturer holds the appropriate licence to manufacture that product and complies with the product specification
- Professional accountability for any harm caused by a defect in the medicine as a result of their own actions or omissions
- The supplying pharmacist is responsible for the quality of the products dispensed

RISK ASSESSMENT

Safeguarding pharmacist and patient

Where do unlicensed medicines fit in the MHRA hierarchy of risk?



*Adapted from MHRA guidance. Hierarchy may differ in particular patient groups, such as neonates.

Risk assessment

1. Assess the evidence

2. Ensure the quality of the unlicensed medicine meets appropriate standards

3. When an unlicensed medicine is being ordered, there needs to be a critical, evidence-based evaluation for its use:

Calculating overall risk

CLINICAL RISK is the primary consequence(s) of receiving an underdose or overdose

TECHNICAL RISK lies in the quality of the formulation and production of the product

CLINICAL RISK + TECHNICAL RISK = OVERALL RISK

Calculating overall risk

Is the product fit for purpose?

A product **should not** be supplied if you are not totally **satisfied**

Clinical risk assessment considerations:

1. Is there a clinical need?

2. Is there an equivalent licensed product available?

3. Where's the evidence?

4. Does the product have a product licence (PL) or EMEA MA?

5. Is the product licensed for the specified indication?

6. Are other NHS Trusts using this medicine?

7. What are the risks to the patient of not using this medicine?

8. What could go wrong?

Your ongoing responsibility

Once the product has been obtained and supplied, your responsibility doesn't end there. **You must ensure:**

There are systems in place to review and/or monitor the effectiveness and safety of the treatment

You understand any primary care implications

You maintain a record for 5 years including:

- The source of the product
- Who it was supplied to?
- Quantity supplied
- Batch number
- Any adverse events

What's the difference?

The pharmacist should ensure that both the patient (and carer) and any other HCP involved **understands the differences** between an unlicensed medication (import, bespoke and batch) and the usual licensed pharmaceutical product.

Quality and safety assurances

Good Manufacturing Practice (GMP)

GMP is the minimum standard that a medicines manufacturer must meet in their production processes. Although GMP inspections of unlicensed manufacturers is not product specific, **products must:**

- Be of consistent high quality
- Be appropriate to their intended use
- Meet the requirements of the marketing authorisation (MA) or product specification

Ref: www.gov.uk/guidance/good-manufacturing-practice-and-good-distribution-practice

Quality and safety assurances

Good Distribution Practice (GDP)

GDP requires that medicines are obtained from the licensed supply chain and are consistently stored, transported and handled under suitable conditions, as required by the MA or product specification.

Ref: www.gov.uk/guidance/good-manufacturing-practice-and-good-distribution-practice

Knowledge check

SOURCING

Maintaining quality and compliance

How to choose the right supplier?

Before ordering an unlicensed medicine make sure to check the credentials and licences of your supplier:

Ensure you refer to your own NHS Trust framework agreement*

Choose a business that sources its products and raw materials from reputable suppliers

Base your purchase decisions on quality and safety above all else

*This must be reviewed on an ongoing basis

Standards and checks

Compliance

1. The supplier should hold appropriate MHRA licences	**2.** They must comply with GMP/ GDP	**3.** A wholesaler licence is required to import unlicensed medicines from the EU	**4.** An MS licence is required to manufacture and assemble specials, and import unlicensed medicines from non-EU countries	**5.** Ask whether the supplier conducts their own quality checks and risk assessments prior to supplying a product

A QP is not required to be named on a manufacturer's wholesaler licence for release of a finish licensed product

Where is the unlicensed medicine to be sourced from?

Who is the supplier?

NHS Specials Unit	Specials manufacturer	Licensed importer	Licensed pharmaceutical wholesaler

Where is the supplier manufacturing?

UK	EU/EEA	**if not**	Ensure this country has a mutual recognition agreement with the UK for the manufacture of medicinal products

Does the importer have a Wholesaler and/or MS Licence?

Think about service - can they deliver?

1. What is the quoted delivery time?

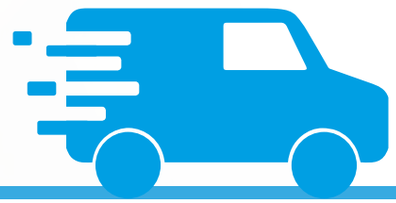
2. What quantity is to be ordered?

3. Are there any delivery charges?

4. Are there any problems associated with continuity of supply?

5. What are the costs involved in obtaining this medicine?

6. Can they provide translated documentation?



Knowledge check

DOCUMENTATION

Quality in black and white

Know your documents

Have you received the supporting documentation?
It's your responsibility to check

UK manufactured unlicensed medicines may include:

- Certificates of Analysis (CofA)
- Certificates of Conformity (CofC)

Imported unlicensed medicines may include:

- Summaries of Product Characteristics (SPC)
- Patient Information Leaflets (PIL)

Certificate of Analysis (CofA)

If a <u>batch-made</u> unlicensed medicine is supplied, then a CofA should accompany the order

The CofA confirms that a sample of the final product has been tested and levels of active ingredients have been retrospectively verified

A CofA should:

- Confirm the laboratory / organisation issuing it
- Be authorised by a QP (i.e. Quality Assurance or Quality Control personnel) and include their signature
- Show the specific batch number that matches the medicine supplied
- Indicate exactly who performed the tests and the date
- State the specification against which the tests were performed
- Give the required test results and the actual results – a result in full or 'complies' may be shown

Certificate of Conformity (CofC)

Individual products produced as a one-off, such as bespoke specials, should come with a CofC

A CofC should:

- Ensure the final product conforms to the specification supplied by the pharmacy team. It should be signed by a suitably authorised person

PLEASE NOTE:

- The CofC is best viewed in conjunction with the original specification given in your order. The CofC will simply confirm that the product was manufactured under a Manufacturing Specials (MS) licence, in accordance with GMP

Imported products

- The MA holder will supply the appropriate paperwork with the product, such as the PIL and SPC
- The importing unlicensed medicine supplier must be able to link the batch number and MHRA Import Licence Number
- Products with non-English packaging, may be over-labelled by the supplier. Translated labelling and PILs help ensure the medicine is taken correctly by the patient

Over-labelling

Patients (and carers) and HCPs will expect to understand what is written on the packaging and the PIL.

Without clear instructions, they could be at risk of taking the medicine incorrectly or overlooking any relevant side effects or contraindications.

For the majority of products clear instructions come as standard, but ask what measures are in place for unlicensed medicines sourced from other countries.

Here are some key factors to consider:

- Do labels comply with British Pharmacopoeia standards and NHS QA Guidelines?
- If not in English, is the unlicensed medicine accompanied by a **version-controlled**, professionally translated label and PIL?
- Are the English translations professionally certified?

Additional evidence of safety

Transmissible Spongiform Encephalopathies (TSE)

The importation of unlicensed medicines from certain countries must comply with the TSE guidelines, which are provided by the MHRA.

The pharmacy team should not expect to be supplied with any TSE documentation, but importers must ensure the manufacturer is compliant and keep records to that effect.

Record keeping

Batched documents should be kept for at least one year after expiry or 5 years after release, whichever is longer.

Many products are acceptable by default:

- Licensed products from within the European Union (EU) / European Economic Area (EEA)
- Products manufactured and licensed in non EU/EEA countries with relevant Mutual Recognition Agreements (MRAs) with the EU
- Products with statements of absence of TSE risk

MHRA Update

Latest from the MHRA: Notification to MS licence holders

The GMDP Inspectorate are aware that some unlicensed medicine manufacturers do not always receive written orders from pharmacists for an unlicensed medicine, this mainly appears to apply to non-sterile medicines.

Latest from the MHRA: Notification to MS licence holders

The GPhC and RPS state:

Pharmacists and their teams agree with the supplier what they require to meet the prescription, this includes strength, formulation and, where relevant, requirements for excipients e.g. sugar-free or alcohol-free formulations, and flavourings. This is based on the pharmacist's understanding of the clinical needs of the patient. Where necessary the agreed formulation is confirmed to the manufacturer in writing.

GMDP inspectors will be assessing the application of this guidance in all future inspections of unlicensed medicine manufacturers to ensure consistency in expectations for placing orders.

Knowledge check

Q&A

- Where do unlicensed medicines fit within the MHRA's hierarchy of risk?
- When is it acceptable to prescribe an unlicensed medicine?
- The responsibly of the pharmacy team vs. the manufacturer/supplier
- Considerations in choosing a supplier/manufacturer of unlicensed medicines
- Your responsibility in reviewing supporting documentation
- Why mutual recognition agreements (MRAs) are important in unlicensed medicines?

Resources

MHRA Guidance Note 14, The supply of unlicensed relevant medicinal products for individual patients. MHRA, London, 2014

Guidance for the Purchase and Supply of Unlicensed Medicinal Products - Notes for prescribers and pharmacists. NHS Pharmaceutical Quality Control Committee. 3rd edition. June 2004, (superseded by Good Practice in Prescribing Medicines (2013) GMC)

Rules and Guidance for Pharmaceutical Manufacturers and Distributors (The Orange Guide). MHRA, London. 2015

The Medicines (Standard Provisions For Licences And Certificates) Amendment Regulations 1999, Statutory Instrument SI 1999/4

Drug Safety Update April 2009 Vol 2 Issue 9. Off-label or unlicensed use of medicines: prescribers' responsibilities

Handbook of Extemporaneous Preparation. A Guide to Pharmaceutical Compounding 1st Edition. Published 24th May 2010, updated 1st March 2016. NHS Pharmaceutical Quality Assurance Committee

MHRA Blog Notification to MS licence holders due to compliance concerns Michelle Rowson, 15 April 2016

ASPM How specials can deliver value to the NHS without compromising patient safety - a case study approach June 2015

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