Status: Effectivity information can only be shown for content published to the website.

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Unlicensed Medicines

Details for the public consultation of this monograph are as follows:

Expert Advisory Group ULM:	**Unlicensed Medicines**
Contact Details	fiona.swanson@mhra.gov.uk
Deadline for Comment	31st March 2022
Target Publication Date (subject to change)	BP 2023
Notes:	Revised monograph: Labelling statement amended to reflect MHRA Best Practice Guidelines on the Labelling and Packaging of Medicines.

This monograph describes the minimum quality standards required for Unlicensed Medicines for human use. The statements in this monograph are intended to be read in conjunction with individual monographs for unlicensed medicines or formulated preparations in the Pharmacopoeia, together with relevant General Notices, Appendices and Supplementary Chapters.

Individual monographs are intended to apply throughout the period for which the formulation is expected to be satisfactory for use.

DEFINITION

An unlicensed medicine is one which is prepared, at the request of an authorised healthcare professional, to address patient medicinal requirements, unmet by current licensed medicines, according to the Human Medicines Regulations 2012 (see Supplementary Chapter V). Such products will be manufactured under a Manufacturer's 'Specials' Licence or prepared extemporaneously under the supervision of a pharmacist.

SCOPE

This general monograph applies to those dosage forms that are routinely manufactured or prepared as unlicensed medicines and are usually presented as conventional-release formulations. These include:

— Capsules

— Liquids for Cutaneous Application

— Ear Drops and Lotions

— Eye Drops

— Preparations for Irrigation

— Nasal Preparations

— Oral Liquids

— Oral Powders

— Parenteral Preparations

— Rectal Preparations

— Tablets

— Topical Semi-solid Preparations

— Vaginal Preparations

PRODUCTION

The production of unlicensed medicines should only be undertaken by competent staff, within suitable facilities and using equipment appropriate for the scale of manufacture and the specific dosage form.

In the UK, batch manufacture should be undertaken in facilities holding a UK Manufacturer's 'Specials' Licence in compliance with the standards of Good Manufacturing Practice.

LABELLING

The following requirements are applicable to unlicensed medicines manufactured or prepared in accordance with medicines legislation. They are not intended to apply to repackaging and assembly activities.

Best practice guidance on the labelling and packaging of medicines advises that certain items of information are deemed critical for the safe use of the medicine (see "Best Practice Guidance on the Labelling and Packaging of Medicines"; MHRA, 2020). These critical items of information, which should be located together on the pack and appear in the same field of view, are: name, strength, route of administration, dosage and warnings (highlighted in bold).

1. **The common name of the product**.
2. **The full name of the medicine should appear on at least three non-opposing faces of the pack to aid accurate identification of the drug.**
3. **A statement of the active ingredients expressed qualitatively and quantitatively per dosage unit or for a given volume or weight**.
4. **Route of administration**.
5. **Instructions for use, including any special warnings**.
6. The pharmaceutical form.
7. The contents of the container by weight, volume or by number of doses.
8. Excipients of known effect. For injectable, topical (including inhalation products) and ophthalmic medicines, all excipients.
9. 'Keep out of reach and sight of children'. [Note 1]
10. The expiry date expressed in unambiguous terms (dd/mm/yy).
11. Any special storage precautions.
12. The manufacturer's MS number, where appropriate.
13. The manufacturer's name and address.
14. The batch number.

15. Statutory warnings required by The Human Medicines Regulations 2012 for particular actives, e.g. paracetamol (Schedule 25, Part 4 of the 2012 Regulations).

For small containers certain details may be omitted, but the label should contain, as a minimum, the following information:

1. The common name of the product.

3. A statement of the active ingredients expressed qualitatively and quantitatively per dosage unit or for a given volume or weight.

4. Route of administration.

7. The contents of the container by weight, volume or by number of doses.

10. The expiry date expressed in unambiguous terms (dd/mm/yy).

14. The batch number.

In such cases, the label for the outer packaging should contain all the relevant label information.

Note 1: This is a statutory requirement for relevant medicinal products.

MEDICINAL SUBSTANCES AND EXCIPIENTS

Where such a monograph is available, the medicinal substance and any excipients must comply with the specific monograph requirements of the Pharmacopoeia.

The medicinal substance and any excipients must also comply with the General Monograph for Substances for Pharmaceutical Use and, where appropriate, the provisions of Supplementary Chapter IV J on the Control of Impurities in Substances for Pharmaceutical Use and the General Monograph for Products with Risk of Transmitting Agents of Animal Spongiform Encephalopathies.

FORMULATED PREPARATIONS

Unlicensed medicines must comply with the requirements of the General Monograph for Pharmaceutical Preparations, the requirements of the General Monograph for Unlicensed Medicines and with the requirements of the relevant General Monograph for the specific dosage form.

While it is required that the formulated preparation will demonstrate compliance with the Pharmacopoeia when tested, it is recognised that it might not be practicable to carry out the pharmacopoeial tests routinely. In such instances other suitable methods may be used to provide assurance that the preparation is of the appropriate quality.

Where a BP monograph for a formulated preparation is available, the product must comply. In addition, where specified, the product must comply with the following tests.

Sterility

All batches of aseptically prepared unlicensed medicines should undergo a sterility test. In cases where the in-use period is before the expectation of the sterility test result, then the test will be retrospective and become a developing and continuing assurance of the process and batches produced. The test should not delay the release of product(s) with a short shelf-life (less than 90 days).

Where an aseptic preparation has been prepared individually by aseptic manipulation, the batch size is effectively one. However, since a sterility test on a batch of one is not manageable, a batch for this purpose is defined as “all preparations prepared during one session”. A “session” is defined as “a continuous period with the same operators, environment, equipment and materials”.

Batch samples may be represented by (i) dummy samples, of the same form and size as the batch items, that have been introduced at the end of the session, (ii) returned items (unused) and (iii) direct samples from the session, where the batch allows.

Further guidance can be found in the MHRA Question and Answers document for holders of a Manufacturer's 'Specials' Licence[1]. This guidance states that "The minimum expectation is one sterility sample per operational work station per week." In addition, the guidance states "The use of a suitably designed 'end of session media fill simulation' may be considered as an alternative to sterility testing of the finished product as part of an on-going monitoring programme."

ORAL LIQUIDS

PRODUCTION

In the manufacturing, packaging and storage of oral liquids, suitable measures are taken to ensure their microbial quality complies with Pharmacopoeial requirements throughout shelf-life; recommendations for microbial limits are provided in the section on *Microbiological Quality of Pharmaceutical Preparations* (*Appendix XVI D*). If necessary, an antimicrobial preservative may be added unless the formulation is required to be preservative-free.

During the preparation, storage and use of preservative-free oral liquids, due consideration should be given to the additional risks of microbial contamination that exist for such preparations. Numbers of viable organisms in starting materials and primary packaging materials should be minimised. Storage conditions of the finished product should prevent contamination and inhibit microbiological proliferation. The product shelf life during storage and use should be based on the risk and probability that the product may fail to meet the requirements of Appendix XVI D.

Acidity or alkalinity

A test to determine the pH of the oral solution or oral suspension may be applied. As the pH may be formulation dependant, limits are only included in specific monographs in cases where the stability of the active substance is affected by pH.

ORAL SUSPENSIONS

Dissolution

Carry out the test for dissolution described under *dissolution test for tablets and capsules*, Appendix XII B1, using Apparatus 2. Unless otherwise stated in the individual monograph use 900 mL of an appropriate dissolution medium (as suggested in Supplementary Chapter I E) and rotate the paddle at 50 rpm.

Shake the container containing the oral suspension being examined for 30 seconds and accurately remove, by syringe, a volume containing one dose at a depth of 1 cm below the meniscus. Introduce the dose by placing the syringe vertically into the dissolution medium as low as possible, not less than 1 cm from the vessel wall, and allow the sample to reach the bottom of the vessel. If sink conditions cannot be obtained, testing a partial dose of the suspension (10% to 20% of the usual dose) is preferable to using a surfactant.

Operate the apparatus at the specified rate. Within the time interval specified, or at each of the times stated, withdraw a specimen from a zone midway between the surface of the dissolution medium and the top of the rotating paddle, not less than 1 cm from the vessel wall. Where multiple sampling times are specified, replace the aliquots withdrawn for analysis with equal volumes of fresh dissolution medium at 37° or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the

calculation. Keep the vessel covered for the duration of the test and verify the temperature of the medium at suitable times. Perform the analysis using a suitable assay method. Repeat the test with a further five additional doses.

Unless otherwise specified in the individual monograph, the value of Q is 75% of the stated amount at 45 minutes.

Homogeneity of Suspension

Allow a suitable volume of the oral suspension being examined to settle, undisturbed, for 24 hours. Shake the container for 30 seconds and accurately remove one dose (usually 5 to 10 mL) at a depth of 1 cm below the meniscus. Shake the container again for 10 seconds and remove another dose. Repeat this procedure until 10 doses of the suspension have been removed. Assay the 10 doses individually according to the method specified in the individual monograph.

The preparation complies with the test if the content of each individual dose is between 85% and 115% of the average content. The preparation fails to comply with the test if the content of more than one individual dose is outside these limits or if the content of one individual dose is outside the limits of 75% to 125% of the average content.

INTRAOCULAR INJECTIONS

DEFINITION

Intraocular injections are sterile preparations intended for administration by injection into the eye.

Several categories of intraocular injection may be distinguished. The requirements of this monograph apply to the most commonly used intraocular injections: intracameral injections (administered into the anterior chamber of the eye) and intravitreal injections (administered into the vitreous chamber of the eye).

Intraocular injections are supplied either in a glass vial or ampoule that allows the contents to be drawn up into a sterile syringe, in pre-filled syringes with a luer lock connector and a blind hub or in pre-filled syringes with a luer slip connector.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

TESTS

Acidity or alkalinity

A test to determine the pH of the injection is carried out, Appendix V L.

Osmolality

A test to determine the osmolality of the injection is carried out, Appendix V N.

Bacterial endotoxins

A test for *bacterial endotoxins* is carried out, Appendix XIV C. Recommendations on the limits for bacterial endotoxins are given in Supplementary Chapter I C.

ASSAY

A suitable procedure to determine the amount of active ingredient(s) is carried out.

STORAGE

Intraocular injections should be stored in a sterile, airtight, tamper-evident container. The containers and closures comply with the requirements for Containers, Appendix XIX A.

LABELLING

The label states (1) the quantity of active ingredient in a suitable dose-volume; (2) the route of administration; (3) for pre-filled syringes, whether the outside surface of the syringe is sterile.

Annex

This section is non-mandatory; it provides guidance on typical limits for Content, pH and Osmolality in Intraocular Injections.

Content

95.0 to 105.0% of the stated amount of the active ingredient, unless otherwise justified.

Acidity or alkalinity

For intracameral injections

pH, 6.8 to 8.2, Appendix V L.

For intravitreal injections

pH, 3.0 to 8.0, Appendix V L.

Osmolality

For intracameral injections

250 to 350 mosmol/kg, Appendix V N.

For intravitreal injections

270 to 330 mosmol/kg, Appendix V N.

1 MHRA Guidance for 'Specials' Manufacturers, January 2015 (sections 3.6.2 and 3.6.3).