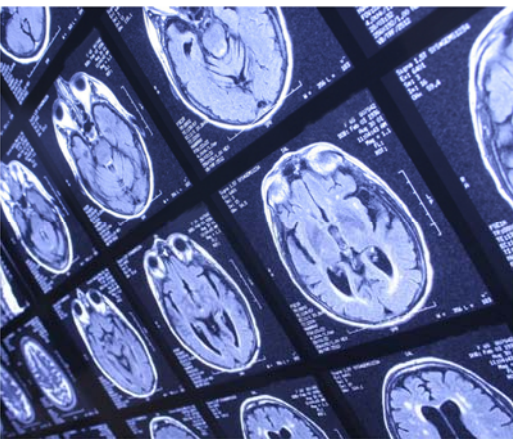




Medicines & Healthcare products
Regulatory Agency



The supply, manufacture, importation and distribution of unlicensed cannabis-based products for medicinal use in humans ‘specials’



This document applies to the supply, manufacture, importation and distribution of unlicensed cannabis-based products for medicinal use in humans 'specials'.

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Contents

Scope

Classification and scheduling of cannabis

Definition

Requirements of the amended 2001 Regulations

The GMC Specialist Register

1. Introduction	7
2. Special clinical needs	8
3. Persons authorised to procure unlicensed CBPMs in the UK	9
4. Active Substance registration	10
5. Manufacture and assembly in the UK	10
6. Importation into the UK	12
7. Record keeping	13
8. Distribution	14
9. Storage requirements for controlled drugs	14
10. Labelling	14
11. Advertising	16
12. Pharmacovigilance and reporting of Adverse Drug Reactions (ADR)	17
Appendix 1 Flowchart	19
Appendix 2 Guidance on the hierarchy for the use of unlicensed medicines	20
Appendix 3 Packaging requirements: specific provisions for the dispensing label	21
Appendix 4 Supply Chain Checklist	22

Scope

The purpose of this document is to provide specific guidance in relation to unlicensed cannabis-based products for medicinal use in humans following the rescheduling of cannabis under [The Misuse of Drugs \(Amendments\) \(Cannabis and Licence Fees\) \(England, Wales and Scotland\) Regulations 2018](#)¹ (the '2018 Regulations'), which amend the Misuse of Drugs Regulations 2001 (S.I.2001 / 3998) to allow its use for medical purposes.

The rescheduling of cannabis under the Misuse of Drugs legislation enables unlicensed cannabis-based products for medicinal use in humans to be available under the provisions for "Specials" under Regulation 167 of the Human Medicines Regulations 2012.

For ease of reading unlicensed cannabis-based products for medicinal use in humans are referred to hereafter as 'unlicensed CBPMs'. The regulation and licensing of unlicensed CBPMs in the UK are undertaken by the Home Office, DHSC and the MHRA. This guidance is designed to provide information on supply, manufacture, importation and distribution of unlicensed CBPMs which have been specially manufactured or imported to the order of a Specialist doctor for the treatment of his/her individual patients.

Classification and scheduling of cannabis

Cannabis, cannabis resin, cannabidiol and cannabidiol derivatives are classified as a Class B drugs under the Misuse of Drugs Act 1971, based on a harms assessment. This classification dictates the penalties for committing offences with the drug such as possession and intent to supply and is used to prioritise the law enforcement response. The classification of the drug is entirely separate from its scheduling.

The Misuse of Drugs Regulations 2001 ('the 2001 Regulations') provides the legal framework for access to controlled drugs for legitimate purposes. Cannabis (the plant material, excluding the stalks and seeds), cannabis resin, cannabidiol and cannabidiol derivatives are listed under Schedule 1 of the 2001 Regulations. These definitions cover, amongst other chemical constituents, the cannabinoid THC². THC is the principal psychoactive constituent of cannabis.

By law, the cultivation, production, supply and possession of cannabis under Schedule 1 is only permitted under a Home Office licence. For more information on Home Office Licensing, see <https://www.gov.uk/guidance/controlled-drugs-licences-fees-and-returns>.

With effect from the 1 November 2018, Cannabis Based Medicinal Products for Use in Humans ("CBPMs") will be listed in Schedule 2 to the 2001 Regulations. Only forms of cannabis – and the associated controlled products – which meet this definition will fall into Schedule 2.

Cultivation of cannabis, irrespective of THC content and/or medicinal purpose can only be carried out under Home Office licence.

¹ Separate but parallel legislation is being prepared in Northern Ireland.

² For the definition of Cannabis see section 37(1) of the Misuse of Drugs Act 1971. For the definition of cannabidiol derivatives see Part IV, Schedule 2 to the Misuse of Drugs Act 1971. The 1971 Act can be accessed here: <https://www.legislation.gov.uk/ukpga/1971/38>

Definition

The definition of unlicensed CBPMs is in the Misuse of Drugs Regulations 2001 ('the 2001 Regulations') as amended by the Misuse of Drugs (Amendments) (Cannabis and Licence Fees) (England, Wales and Scotland) Regulations 2018.³

A 'Cannabis-based product for medicinal use in humans' is defined as:

“cannabis-based product for medicinal use in humans” means a preparation or other product, other than one to which paragraph 5 of part 1 of Schedule 4 applies, which—
(a) is or contains cannabis, cannabis resin, cannabidiol or a cannabidiol derivative (not being dronabinol or its stereoisomers);
(b) is produced for medicinal use in humans; and—
(c) is—
(i) a medicinal product, or
(ii) a substance or preparation for use as an ingredient of, or in the production of an ingredient of, a medicinal product;”;

A number of substances are specifically exempted from this definition. This includes the product known as Sativex (the substance controlled in paragraph 5 of part 1 of Schedule 4 of the 2001 Regulations) as well as synthetic dronabinol (separately Scheduled in the 2001 Regulations).

Requirements of the amended 2001 Regulations

The Misuse of Drugs Regulations 2001, as amended by the Misuse of Drugs (Amendments) (Cannabis and Licence Fees) (England, Wales and Scotland) Regulations 2018, provide that the prescriber must be a Specialist doctor registered on the General Medical Council (GMC) Specialist Register to be able to issue prescriptions for unlicensed CBPMs. Once a substance receives Marketing Authorisation this prescribing restriction will no longer apply, and the product is available for patient use as other Schedule 2 drugs. See Regulation 16A of the 2001 Regulations.

As with other Schedule 2 drugs, organisations wishing to possess, supply, produce or manufacture these products will require a Home Office Controlled Drug licence to lawfully undertake these activities unless a limited 'exemption' applies. A Home Office licence will also be required to import or export these controlled drugs.

All information needed to apply for the relevant Home Office licences is available on the website at <https://www.gov.uk/guidance/controlled-drugs-licences-fees-and-returns>.

The GMC Specialist Register

The GMC Specialist Register is a list of doctors who are eligible to take up appointment in any fixed term, honorary or substantive consultant post in the NHS excluding foundation trusts.⁴

If a doctor is on the GMC Specialist Register it will say so as part of their status on the medical register. The Specialist Register also shows:

³ The Misuse of Drugs (Amendments) (Cannabis and Licence Fees) (England, Wales and Scotland) Regulations 2018 <http://www.legislation.gov.uk/ukxi/2018/1055/regulation/3/made>

⁴ The Specialist Register – General Medical Council <https://www.gmc-uk.org/registration-and-licensing/the-medical-register/a-guide-to-the-medical-register/specialist-registration>

- the specialties (and sub-specialties) the doctor is qualified in
- the date the doctor joined the Specialist Register in each specialty.

Checks on the Specialist doctors registered on GMC Specialist Register can be made on the GMC 'List of Registered Medical Practitioners' link:

<https://www.gmc-uk.org/registration-and-licensing/the-medical-register/a-guide-to-the-medical-register/specialist-and-gp-application-types>

1 Introduction

MHRA is responsible for ensuring that medicines and medical devices work, are safe and of an appropriate quality. MHRA's primary aim is to safeguard public health through a system of regulation. Pharmaceutical manufacturers and distributors operating in the UK marketplace are subject to a system of licensing and inspection, which ensures that licensed medicinal products conform to internationally-agreed standards, and that those medicines are manufactured/imported, stored and distributed in compliance with the required regulatory standards.

The regulation of medicines on the UK market is undertaken by MHRA in accordance with the Human Medicines Regulations 2012 (SI 2012/1916).

Unless exempt, a medicinal product must be the subject of a marketing authorisation (product licence) before being placed on the market. Regulation 167 of the Human Medicines Regulations 2012 provides an exemption from the need for a marketing authorisation for a medicinal product which is supplied under specific conditions:

- in response to an unsolicited order;
- manufactured and assembled in accordance with the specification of a person who is a doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber;
- for use by a patient for whose treatment that person is directly responsible in order to fulfil the special needs of that patient; and meets the conditions specified in regulation 167(2)-(8).

In the interest of public health, the exemption is narrowly drawn because these products, unlike licensed medicinal products, may not have been assessed by the Licensing Authority against the criteria of safety, quality and efficacy.

This document provides advice on the supply, manufacture, importation and distribution of unlicensed CBPMs which have been specially manufactured or imported to the order of a Specialist doctor for the treatment of individual patients.

Unlicensed CBPMs

- *Under Regulation 16A of the 2001 Regulations, unlicensed CBPMs must be manufactured and assembled in accordance with the specification of a person who is a registered doctor listed on the GMC's Specialist Register (a 'Specialist doctor').*

- *The unlicensed CBPM is a ‘Specials’ medicinal product, formulated in accordance with the specifications of a Specialist doctor, and for use by an individual patient under his direct personal responsibility.*
 - *The prescriber should follow the GMC’s guidance on ‘Good practice in prescribing and managing medicines and devices’⁵ paying special attention to section ‘Prescribing unlicensed medicines’ as well as provide information for patients about the licence status for their medicines.⁶ Additionally, the prescriber should refer to the Flowchart process for prescribing, supplying and importing unlicensed CBPMs (see Appendix 1) as well as the guidance on the hierarchy for the use of unlicensed medicines (see Appendix 2). This hierarchy is provided for guidance only and each case should be considered on its individual merit. The prescriber should satisfy themselves of the following with respect to the product being prescribed: that the product is specified by brand/supplier; cannabis strain and content of THC/CBD (and ratio of THC/CBD where relevant), as appropriate.*
 - *Route of administration and dosage instructions.*
 - *That the product is being procured from a manufacturer/importer with a GMP certificate authorised by the Licensing Authority*.*
 - *That the producer/supplier will provide a certificate of Analysis (CoA) including parameters appropriate to define product quality.*

*The Licensing Authority, for the purposes of the Human Medicines Regulations 2012 and this guidance, refers to the UK Ministers⁷ designated by the Regulations, acting either alone or jointly. MHRA is the Government body set up to discharge the responsibilities of the Licensing Authority, under powers delegated by those Ministers.

2 Special clinical needs

Regulation 167 of the Human Medicines Regulations 2012 sets out the exemption from the requirement for a medicinal product, placed on the market in the UK to hold a marketing authorisation. This exemption flows from Article 5(1) of Directive 2001/83/EC, which states:

‘A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised healthcare professional and for use by an individual patient under his direct personal responsibility.’

An unlicensed CBPM may only be supplied in order to meet the special needs of an individual patient. This product should not be supplied where a licensed medicinal product can meet the special needs of the patient. Responsibility for deciding whether an individual patient has “special needs” which a licensed product cannot meet should be a matter for the doctor listed on the GMC Specialist Register, responsible for the patient’s care.

The requirement for a “special need” relates to the special **clinical** needs of the individual patient. It does not include reasons of cost, convenience or operational needs (see Section 10 of MHRA Guidance Note 14)⁸. Anyone supplying an unlicensed CBPM where an equivalent licensed medicinal product is available must be satisfied as to the existence of a

⁵ GMC guidance on Good practice in prescribing and managing medicines and devices - <https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/prescribing-and-managing-medicines-and-devices>

⁶ GMC guidance on Prescribing unlicensed medicines - <https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/prescribing-and-managing-medicines-and-devices/prescribing-unlicensed-medicines>

⁷ The Secretary of State and the Minister for Health, Social Services and Public Safety.

⁸ MHRA Guidance Note 14- The supply of unlicensed medicinal products ‘specials’, Section 10 - European Court cases <https://www.gov.uk/government/publications/supply-unlicensed-medicinal-products-specials>

special need for the unlicensed CBPM.

MHRA expects that documentary evidence that the requested supply is for clinical need that cannot be met by an unlicensed medicine be obtained by manufacturers, importers or distributors and that this evidence should be made available on request of the Licensing Authority. This may take the form of a prescriber's letter, however an alternative fully documented audit trail through the supply chain confirming special need may be acceptable:

- To include clinical therapeutic use/clinical indications
- Why this product is chosen over licensed medicines
- Confirmation of the clinical indication for what the product will be used
- The decision to prescribe has been made by a doctor on the GMC Specialist Register

The unlicensed CBPM may only be supplied to third parties if ALL of the following apply:

- *there is an unsolicited order from a Specialist doctor;*
- *the Importer must have a Home Office import and domestic licence. The wholesaler / manufacturer must have a Home Office Domestic Licence and MHRA Wholesaler or Manufacturer licence for possession and supply of unlicensed CBPMs;*
- *the product is manufactured and assembled in accordance with the specification of a person who is a doctor on the GMC Specialist Register, responsible for the patient's care;*
- *the product is for use by a patient for whose treatment that person is directly responsible in order to fulfil the special needs of that patient that cannot be met by existing licensed medicines; and*
- *the product is manufactured and supplied under specific conditions (see Sections 3 to 12).*

3 Persons authorised to procure unlicensed CBPMs in the UK

They are:

- a) Doctor on the GMC Specialist Register
- b) Specialist Importer with a Home Office Domestic licence and MHRA licence
- c) Registered pharmacies or retail pharmacy businesses (with Home Office Domestic licences, where appropriate)⁹;
- d) Licensed wholesale dealers for supply to the order of any of the above;

UK licensed manufacturers and wholesale dealers should take reasonable steps to establish that persons supplied satisfy the requirements of regulation 167, and intend to use the product in a way which falls within the specified terms. This could be achieved, for example, by the person ordering the "special" confirming their professional status and the nature of the special need of the individual patient concerned, making clear that where a licensed alternative is available, why that is not clinically appropriate. There is no legal requirement for the individual patient's name to be supplied (see Appendix 2).

All involved in the supply chain should be aware of the unlicensed status of the CBPM. It should be clear from the product's packaging that the product is unlicensed because there will be no marketing authorisation/product licence number on it. However, a prescriber may not have sight of the CBPM, for example, where it is ordered by a hospital pharmacist and

⁹ Some pharmacies will NOT need a domestic licence – as pharmacies and retail pharmacy business are able to produce / supply in accordance with their practice. However, if they are wholesale dealing the policy is that they do need a licence.

administered by a nurse. In such cases the pharmacist should ensure before the product is ordered and administered that the prescriber is fully aware of the unlicensed status of the CBPM. Healthcare providers (such as Health Boards, NHS Hospital Trusts, Clinical Commissioning Groups and independent hospitals) will have existing policies on the commissioning and use of unlicensed medicines which should be referred to.

4 Active Substance registration

Active Substances (AS) are responsible for the therapeutic effect of medicinal products and are often referred to as active pharmaceutical ingredients (APIs) or drug substances (DS).

If you manufacture, import or distribute an active substance and you are based in the UK you must register with the Medicines and Healthcare Products Regulatory Agency (MHRA). You can do this through the [MHRA Portal](#).

The MHRA has produced a [flowchart on the registration requirements](#) (PDF, 37.9KB, 1 page) requirements to help you decide what kind of registration you need.

Refer to MHRA Guidance on Medicines: register to manufacture, import or distribute active substances <https://www.gov.uk/guidance/medicines-register-to-manufacture-import-or-distributor-active-substances> for further information on the registration process, changes to registration, annual compliance reports, termination of registration, fees and payments.¹⁰

5 Manufacture and assembly in the UK

The manufacturer or assembler of “specials” must hold a Manufacturer’s (Specials) Licence granted by the Licensing Authority and in most cases, a Home Office Licence. The licence should be applied for in the usual way (subject to the usual application procedures and conditions, see MHRA Guidance Note 5, Notes for applicants and holders of Manufacturer’s Licences). The manufacturing/assembly site and its operations will be inspected for compliance with GMP and the conditions of the licence. These require that manufacture or assembly is carried out under the supervision of appropriately qualified staff, including a named quality controller and production manager, who are acceptable to the Licensing Authority. However, a Qualified Person (QP) is not required to be named on a Manufacturer’s (Specials) Licence for release of a finished unlicensed product.

Release of “specials” should be by the quality controller or a nominated deputy.

Unlicensed CBPMs

- *Adequate precautions should be taken to ensure that the product is of the quality required for its intended purpose and that it complies with any standards described in relevant pharmacopoeial monographs.*
- *The product should, in particular, comply with the requirements of the British Pharmacopoeia (BP) monographs on Pharmaceutical Preparations and Substances for Pharmaceutical Use.*
- *The BP monograph on Pharmaceutical Preparations encompasses the requirements of the specific monographs concerning active substances, excipients, general monographs (e.g.*

¹⁰ MHRA Guidance on Medicines: register to manufacture, import or distribute active substances – <https://www.gov.uk/guidance/medicines-register-to-manufacture-import-or-distributor-active-substances>

residual solvents) and the general monographs covering dosage forms, herbal drugs, herbal drug preparations, herbal extracts and herbal medicinal products.

- *Specifications applied to CBPMs and their active substances should take account of all relevant pharmacopoeial monographs and current guidelines on herbal drugs, herbal drug preparations and herbal medicinal products. Suitable validated analytical methods should be applied in line with current guidelines; major cannabinoids, in particular, THC/CBD should be quantitatively determined, as appropriate.*

Written records of manufacture/assembly and supply must be kept for five years and be made available to the Licensing Authority on request.

When inspecting a “specials” manufacturing site, in addition to confirming compliance with GMP and the Human Medicines Regulations 2012, an Inspector will also take account of product specifications, labelling, stability data and justification for expiry dating. Where appropriate, evidence to support compliance with GACP (Good Agricultural and Collection Practice) of the cannabis plant material must be demonstrated; in line with current guidelines.

Decontamination of the cannabis plant material using ethylene oxide is not permitted in accordance with the BP monograph on Herbal Drugs. Use of gamma irradiation to reduce microbial bioburden is permitted provided it does not affect the quality of the material; such treatment should be documented and records should be available for inspection.

The licence holder must demonstrate compliance with the European Commission’s ‘Notes for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products’ and future updates, in accordance with The Unlicensed Medicinal Products for Human Use (Transmissible Spongiform Encephalopathies) (Safety) Regulations 2003 [SI 2003/1680]. See MHRA’s guidance: Minimising the risk of Transmission of Transmissible Spongiform Encephalopathies via Unlicensed Medicinal Products for Human Use, available from MHRA’s website www.mhra.gov.uk

A holder of a Manufacturer’s (Specials) Licence may also be a registered pharmacy supplying unlicensed medicinal products prepared under the exemption provided by regulation 4 of The Human Medicines Regulations 2012. Under these circumstances, the labelling of products prepared under regulation 4, and any documentation associated with them, should not make reference to the Manufacturer’s (Specials) Licence or number.

For guidance on labelling of unlicensed medicinal products manufactured by the holder of a Manufacturer’s Special Licence, reference should be made to the relevant monographs of the BP.¹¹

In addition, labelling should take account of current guidelines on declaration of herbal substances and herbal preparations in herbal medicinal products; content of THC/ CBD (and ratio of THC/CBD where relevant), as appropriate.

¹¹ British Pharmacopoeia Volume III – Formulated Preparations: General Monographs Unlicensed Medicines
British Pharmacopoeia Volume V – Supplementary Chapters – SC V Unlicensed Medicines SC V Unlicensed Medicines

6 Importation into the UK

The Specialist Importer of an unlicensed CBPM into the UK must hold either a Wholesale Dealer's Licence (WDA (H)) if the product is to be imported from an EEA member state i.e. the EU plus Norway, Iceland and Liechtenstein, or a Manufacturer's (Specials) Licence if the product is to be imported from a third country i.e. a non-EEA country; and,

The Specialist Importer must notify the MHRA at least 28 days before the date of the intended import stating:

- (a) The name of the product, which may be the brand name, common name or scientific name under which it is to be sold or supplied.
- (b) Any trademark or name of the manufacturer.
- (c) The International Non-proprietary Name (INN), British Approved Name (BAN) or other monograph, scientific name or description of the true nature of each of the constituents.
- (d) The quantity to be imported which may be 25 individual doses or a quantity that must not exceed that required for 25 courses of treatment of no more than 3 months.
- (e) The name and address of the manufacturer or assembler of the medical product, or the name and address of the supplier if not the manufacturer or assembler.

Unlicensed CBPMs

*For unlicensed CBPMs, in addition to the general requirements, the MHRA will require the following with **each** notification:*

1. *The content/ratio of THC/CBD is declared, and appears on the label, as appropriate;*
2. *A Certificate of Analysis is provided to support the batch specification;*
3. *A valid GMP certificate is provided for the site of manufacture;*
4. *A justification for special clinical need by a doctor registered on the GMC Specialist Register, which may take the form of a prescription or a prescriber's letter.*

The unlicensed CBPM must not be imported if the MHRA issues an objection to import within 28 days of their acknowledgment of the notification of intent to import.

The MHRA may choose to permit import before 28 days from the date of its acknowledgment. This is usually only used in the case of immediate import of medicines for life threatening or immediately injurious clinical emergencies.

Records required in addition to other provisions of licences are:

- (a) The batch number of the product supplied.
- (b) Details of any adverse reactions to the product supplied of which the licence holder becomes aware.

Requirements from the Specialist Importer:

- o *The Specialist Importer must not import more than the quantity notified to the Licensing Authority.*

- *The Specialist Importer must also apply to the Home Office for an appropriate Home Office licence.*
- *Notifications to MHRA and applications to the Home Office can be submitted in parallel.*
- *The Specialist Importer should send a copy of the Home Office licence to the manufacturer/exporter of unlicensed CBPM in the source country.*
- *UK customs check will be carried out. The product will be placed in quarantine at Specialist Importer's warehouse until routine checks are carried out.*
- *The products will then be supplied to pharmacy/dispensing doctor for dispensing/administering the product to the patient.*
- *The Specialist Importer must inform the MHRA immediately of any matter coming to their attention which may mean that an unlicensed medicine they have imported may not be safe or of adequate quality for administration to humans.*
- *The Specialist Importer must cease import or supply of the unlicensed CBPM from a specified date if so instructed by the MHRA.*
- *The Specialist Importer shall take all reasonable precautions and exercise all due diligence to ensure that any information he provides to the MHRA which is relevant to an evaluation of the safety, quality or efficacy of the unlicensed CBPMs which he imports from a third country, handles, stores or distributes is not false or misleading in a material particular.*

If the product contains substances of animal origin, the Specialist Importer must demonstrate compliance with the European Commission's 'Notes for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products' and future updates, in accordance with, The Unlicensed Medicinal Products for Human Use (Transmissible Spongiform Encephalopathies) (Safety) Regulations 2003 [SI 2003/1680]. See MHRA's guidance: Minimising the risk of Transmission of Transmissible Spongiform Encephalopathies via Unlicensed Medicinal Products for Human Use, available from MHRA's website www.mhra.gov.uk

7 Record keeping

Any person who sells or supplies the unlicensed CBPM in the UK must maintain for at least five years a record showing:

- The name of the product, brand/supplier; cannabis strain and content of THC/CBD (and ratio of THC/CBD where relevant), as appropriate.
- The source from which and the date on which the person obtained the product;
- The person to whom and the date on which the sale or supply was made;
- The quantity of the sale or supply;
- The batch number of the batch of that product from which the sale or supply was made; and
- Details of any suspected adverse reaction to the product so sold or supplied of which the person is aware or subsequently becomes aware. For further guidance on ADR reporting see below.

The person must make the records available for inspection by the MHRA on request. The person must notify the licensing authority of any suspected adverse reaction to the medicinal product which is a serious adverse reaction.

Persons will also need to comply with the record keeping requirements set out in the Misuse of Drugs Regulations 2001.

8 Distribution

Distribution by wholesale dealing must be through licensed wholesale dealers, subject to the usual application procedures and conditions, and appropriate records must be kept.

Directive 2001/83/EC defines wholesale distribution of medicinal products as: 'All activities consisting of procuring, holding, supplying or exporting medicinal products, apart from supplying medicinal products to the public. Such activities are carried out with manufacturers or their depositories, importers, other wholesale distributors or with pharmacists and persons authorized or entitled to supply medicinal products to the public in the Member State concerned.'

The holder of a Wholesale Dealer's Licence (WDA(H)), must only supply unlicensed medicinal products to:

- The holder of a Wholesale Dealer's Licence relating to those products;
- The holder of an authorisation granted by the competent authority of another EEA State authorising the supply of those products by way of wholesale dealing;
- Any person who may lawfully supply medicinal products in circumstances corresponding to retail sale, or
- Any person who may lawfully administer those products.

The holder of a Manufacturer's (Specials) Licence must comply with these requirements in order to distribute the unlicensed medicines that they have manufactured or imported as if they were the holder of a Wholesale Dealer's Licence.

Wholesale dealer's will also require a Home Office licence to lawfully possess and supply these substances.

9 Storage requirements for controlled drugs

The storage requirements for unlicensed CBPM will be the same as for other Schedule 2 controlled drugs (CD).

- They will be subject to the Misuse of Drugs (Safe Custody) Regulations 1973¹² and so should be stored in a locked receptacle, usually in an appropriate CD cabinet or approved safe, which can only be opened by the person in lawful possession of the CD or a person authorised by that person.
- A register must be kept for Schedule 2 CDs and this register must comply with the relevant regulations.
- The destruction of CDs in Schedule 2 must be appropriately authorised and the person witnessing the destruction must be authorised to do so.

10 Labelling

Unlicensed CBPM manufactured in the UK should be labelled in accordance with BP.

¹² The Misuse of Drugs (Safe Custody) Regulations 1973 - <http://www.legislation.gov.uk/uksi/1973/798/contents/made>

The BP general monograph of “Unlicensed Medicines” contains the following advice for labelling (including warnings). It cross refers to the MHRA guidance:

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. The requirements were previously included as guidance in Supplementary Chapter V of the British Pharmacopoeia 2007.

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, 2012).¹³ 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).

The following would be considered the minimum information:

- 1. The name of the product and declaration of active herbal ingredient, as appropriate for herbal medicinal products.**
- 2. A statement of the content/ratio of THC/CBD as appropriate.**
- 3. Route of administration.**
- 4. Instructions for use, including any special warnings.**
5. The pharmaceutical form.
6. The contents of the container by weight, volume as appropriate.
7. Excipients of known effect. For injectable, topical (including inhalation products) and ophthalmic medicines, all excipients.
8. ‘Keep out of reach and sight of children’. [Note 1]
9. The expiry date expressed in unambiguous terms (dd/mm/yy).
10. Any special storage precautions.
11. The manufacturer’s MS number, where appropriate.
12. The manufacturer’s name and address.
13. The batch number.

Labelling should take account of current guidelines on declaration of herbal substances and herbal preparations in herbal medicinal products; content of THC/CBD (and ratio of THC/CBD where relevant) should be stated, as appropriate.

Specials’ manufacturers and pharmacists ordering unlicensed CBPMs should ensure that the labelling provisions above are complied with as a minimum.

Separately when the product is dispensed the pharmacist should ensure that the usual dispensing label provisions are applied. These are set out in Schedule 25 of Human Medicines Regulations 2012 and apply to any medicine supplied on prescription regardless of legal category. (See Appendix 3).

The products will also need to comply with the marking requirements set out in the Misuse of Drugs Regulations 2001.

¹³ BEST PRACTICE GUIDANCE ON THE LABELLING AND PACKAGING OF MEDICINES – https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/474366/Best_practice_guidance_labelling_and_packaging_of_medicines.pdf

Special label warnings for Driving

Unlicensed CBPMs may impair a person's ability to drive safely, and patients should be advised of the risks. The label should include the following information:

- 'WARNING' This medicine may make you feel sleepy. If this happens do not drive or use tools or machinery. Do not drink alcohol
- Do not drive while taking this medicine until you know how it affects you
- Do not drive if you feel sleepy, dizzy, unable to concentrate or make decisions, or if you have blurred or double vision

Further information is available on the Department for Transport website [here](#), which includes information on statutory medical defence.

11 Advertising

A "specials" manufacturer, importer or wholesaler may advertise the service he provides but particular "specials" must not be advertised as provided by condition B of regulation 167 of the Human Medicines Regulations 2012. He may, however, provide factual responses to requests for information on specific "specials" or the range of products he is able to supply.

"Advertisement" is defined in regulation 7 of the Human Medicines Regulations 2012 as "anything designed to promote the prescription, supply, sale or use" of a "special" and includes, in particular, the following activities—

- door-to-door canvassing;
- visits by medical sales representatives to persons qualified to prescribe or supply medicinal products;
- the supply of samples;
- the provision of inducements to prescribe or supply medicinal products by the gift, offer or promise of any benefit or bonus, whether in money or in kind, except where the intrinsic value of such inducements is minimal;
- the sponsorship of promotional meetings attended by persons qualified to prescribe or supply medicinal products; and
- the sponsorship of scientific congresses attended by persons qualified to prescribe or supply medicinal products, including the payment of their travelling and accommodation expenses in that connection.

"Advertisement" does not include reference material and announcements of a factual and informative nature, including—

- material relating to changes to a medicinal product's package or package leaflet,
 - adverse reaction warnings,
 - trade catalogues, and
 - price lists,
- provided that no product claim is made.

Paragraphs 22(7) and 40 of Schedule 4 of the Human Medicines Regulations 2012 preclude a "specials" manufacturer, importer or wholesaler from publishing a catalogue or circular. However, provided no product claim is made, a trade catalogue or circular can be sent to an authorised healthcare professional where it is relevant to respond to an unsolicited request for information on the range of products supplied.

Additionally, a “specials” manufacturer, importer or wholesaler may issue a price list to authorised healthcare professionals to whom the price of “specials” may be relevant, such as potential customers and budget managers. Price lists can be sent out at reasonable intervals or in response to an enquiry.

A price list would typically consist of a basic line listing providing the following information:

- reference number;
- drug name (British Approved Name or equivalent);
- dosage form;
- strength;
- pack size; and
- price.

No product claims may be included.

This advice takes into account the decision of the European Court of Justice in *Ref: C-143/06 Ludwigs-Apotheke München Internationale Apotheke v Juers Pharma Import-Export GmbH* (see Section 10 in Guidance note 14).

The advertising of unlicensed medicinal products, including CBPMs, to members of the public is prohibited. For further advice on the prohibition of advertising unlicensed medicines see Section 4.2 of the Blue Guide ‘Advertising and Promotion of Medicines in the UK. This is available at the following link:

<http://www.mhra.gov.uk/Howweregulate/Medicines/Advertisingofmedicines/BlueGuide/index.htm>

12 Pharmacovigilance and reporting of Adverse Drug Reactions (ADR)

As for all unlicensed medicines manufacturers should report the suspected ADR immediately and in no case later than 15 calendar days from receipt, stating that the product is unlicensed. It is a mandatory requirement to electronically report suspected ADRs. The ICH-E2B international standard electronic report should be used and the report should be electronically submitted via the EudraVigilance European Gateway (see MHRA or EMA websites for more details).

Prescribers or pharmacists supplying the “special” should report using the electronic Yellow Card (found at <http://www.mhra.gov.uk/yellowcard>), the Yellow Card app or using a paper form stating the manufacturer and indicating that the product is unlicensed. Wholesalers supplying unlicensed CBPMs are under an obligation to keep records of any adverse reaction of which they become aware and report any serious adverse reaction to the MHRA; this should be done by submission of a ‘Yellow Card’ report.

For CBPMs the MHRA requires reporting of ALL suspected adverse reactions (serious and non-serious, whether the product is licensed or unlicensed), including reports of failure of efficacy. Given the limited safety data that is currently available on the products, the MHRA will be conducting enhanced vigilance activities to support their safe use.

These obligations are placed on any person selling or supplying “specials”, not only manufacturers, importers and distributors but also the Specialist doctor prescribing the unlicensed CBPMs where appropriate. An adverse reaction means a response to a medicinal product which is noxious and unintended.

Pharmacovigilance involves:

- Monitoring the use of medicines in everyday practice to identify previously unrecognised adverse effects or changes in the patterns of adverse effects
- Assessing the risks and benefits of medicines in order to determine what action, if any, is necessary to improve their safe use
- Providing information to healthcare professionals and patients to optimise safe and effective use of medicines
- Monitoring the impact of any action taken

Persons involved in the supply, manufacture, importation and distribution of unlicensed CBPMs should refer to below guidelines¹⁴ to ensure good practice and compliance with the requirements. Further information on reporting procedures can be found on links below:

- [Guidance on adverse drug reactions](#)
- [Contribution of Yellow Cards to identifying safety issues](#)
- [Pharmacovigilance – how MHRA monitors the safety of medicines](#)
- [What to include in your Yellow Card of an adverse drug reaction](#)
- [Specific areas of interest for adverse drug reactions reporting](#)
- [Send and receive information on adverse drug reactions \(ADRs\)](#)

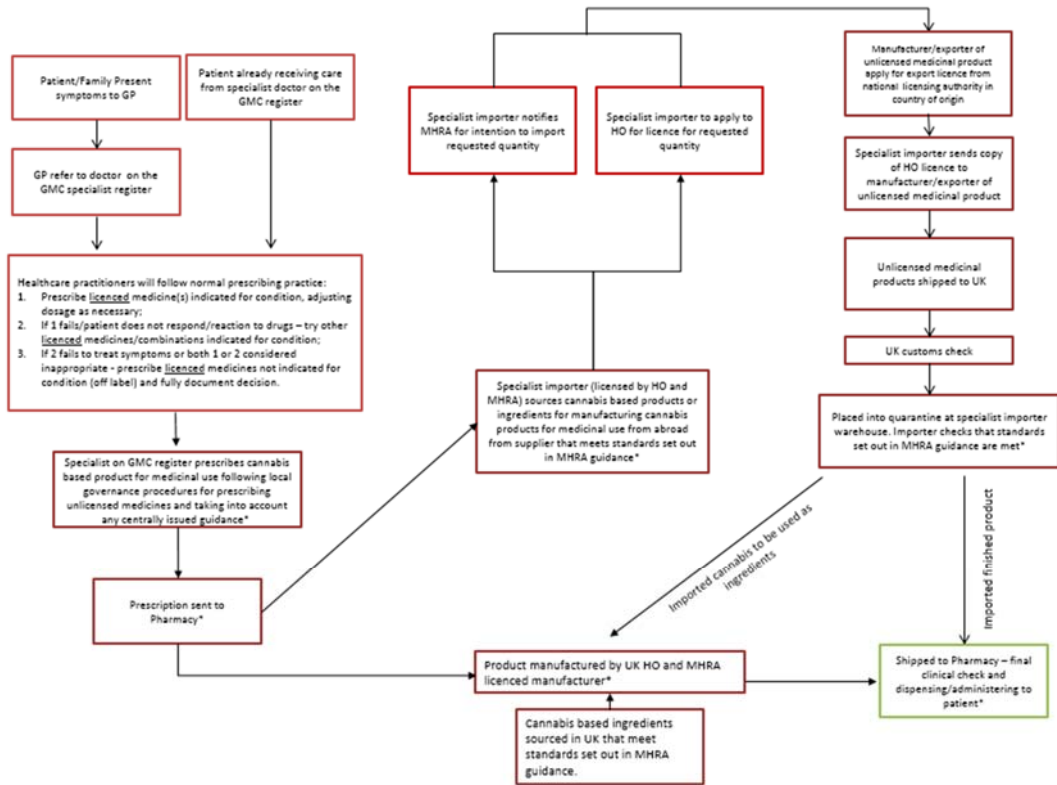
Additional information can be found on NICE guidelines on Clinical Knowledge Summaries- Adverse drug reactions.¹⁵

¹⁴ The Yellow Card Scheme: guidance for healthcare professionals 2017 - <https://www.gov.uk/guidance/the-yellow-card-scheme-guidance-for-healthcare-professionals#what-to-report>

¹⁵ NICE – Clinical Knowledge Summaries ADR - <https://cks.nice.org.uk/adverse-drug-reactions#!scenario>.

APPENDIX 1 – Flowchart

Process for prescribing, supplying & importing unlicensed cannabis-based medicinal products



Notes:
 * Refer to the Quality Checklist in this guidance which details what checks should be made at each stage to ensure that the prescription/direction of the specialist doctor is fulfilled.
 This is a summary only and in no way seeks to supersede the legal effect of The Misuse of Drugs Act 1971; Misuse of Drugs Regulations 2001 or Misuse of Drugs (Licence Fees) Regulations 2010.

APPENDIX 2 - Guidance on the hierarchy for the use of unlicensed medicines

This hierarchy is provided for guidance only and each case should be considered on its individual merit.

1. An unlicensed product should not be used where a product available and licensed within the UK could be used to meet the patient's special need.
2. Although MHRA does not recommend "off label" (outside of the licensed indications) use of products, if the UK licensed product can meet the special clinical need, even "off-label", it should be used instead of an unlicensed product. Licensed products available in the UK have been assessed for quality, safety and efficacy. If used "off-label" some of this assessment may not apply, but much will still be valid. This is better than the use of an un-assessed, unlicensed product. The fact that the intended use is outside of the licensed indications is therefore not a reason to use an unlicensed product. It should be understood that the prescriber's responsibility and potential liability are increased when prescribing off-label medicines.
3. If the UK product cannot meet the special need, then another (imported) medicinal product should be considered, which is licensed in the country of origin.
4. If none of these options meet the special clinical need, then a completely unlicensed product may have to be used, for example, UK manufactured "specials", which are made in GMP inspected facilities, but which are otherwise un-assessed (GMP inspection of "specials" manufacturers is not product specific). There may also be other products available which are unlicensed in the country of origin.
5. The least acceptable products are those that are unlicensed in the country of origin, and which are not classed as medicines in the country of origin (but are in the UK). For example, the use of products from countries where they are classed as supplements, not pharmaceuticals, and may not be made to expected standards of pharmaceutical GMP. These should be avoided whenever possible.

APPENDIX 3 - Packaging requirements: specific provisions for the dispensing label

SCHEDULE 25 Regulation 258 - Packaging requirements: specific provisions

PART 1: Medicines on prescription

1. Where the product is to be administered to a particular individual, the name of that individual.
2. The name and address of the person who sells or supplies the product.
3. The date on which the product is sold or supplied.
4. Unless paragraph 5, applies, such of the following particulars as the appropriate practitioner who prescribed the product may specify—
 - (a) the name of the product or its common name;
 - (b) directions for use of the product; and
 - (c) precautions relating to the use of the product.
5. This paragraph applies if the pharmacist, in the exercise of professional skill and judgement, is of the opinion that the inclusion of one or more of the particulars mentioned in paragraph 4 is inappropriate.
6. Where paragraph 5 applies, the pharmacist may include such particulars, of the same kind as those mentioned in paragraph 4, as the pharmacist thinks appropriate.

APPENDIX 4 - Supply Chain Checklist

This checklist is to be used only as guidance for importers and pharmacists carrying out the final clinical check and dispensing/administering the unlicensed CBPMs to the patient.

The pharmacist and importer should satisfy themselves of the following with respect to the product being prescribed/dispensed:

Specialist doctor registration check:

- ✓ there is an unsolicited order from a Specialist doctor;
- ✓ the decision to prescribe is made by a doctor registered on the GMC Specialist Register;

Prescription validation check:

- ✓ the product is specified by brand/supplier; cannabis strain and content of THC/CBD (and ratio of THC/CBD where relevant), as appropriate.
- ✓ route of administration and dosage instructions are stated on the prescription;
- ✓ the quantity is specified;
- ✓ the pharmacist should ensure before the product is ordered and administered that the prescriber is fully aware of the unlicensed status of the product; and
- ✓ the product is for use by a patient for whose treatment that person is directly responsible in order to fulfil the special needs of that patient that cannot be met by existing licensed medicines.

Verification of Importers/Manufacturers

- ✓ the importer has a valid Home Office Licence for the relevant activities which will include possession, supply and possibly production and schedules;
- ✓ the importer has a valid MHRA Wholesaler Dealer's or Manufacturer's (Specials) licence for possession and supply of unlicensed CBPMs;
- ✓ a valid GMP certificate is available for the site of manufacture/from the importer;
- ✓ a valid Certificate of Analysis (CoA) including parameters appropriate to define product quality and to support batch specification is available from manufacturer/wholesaler;
- ✓ that the product to be imported is labelled with the that the content/ratio of THC/CBD, as appropriate.
- ✓ A holder of a Manufacturer's (Specials) Licence may also be a registered pharmacy supplying unlicensed medicinal products prepared under the exemption provided by regulation 4 of The Human Medicines Regulations 2012. Under these circumstances, the labelling of products prepared under regulation 4, and any documentation associated with them, should not make reference to the Manufacturer's (Specials) Licence or number.

Dispensing label checklist

- ✓ The pharmacist should ensure that the usual dispensing label provisions are applied. These are set out in Schedule 25 of Human Medicines Regulations 2012 and apply to any medicine supplied on prescription regardless of legal category. (See Appendix 3)
- ✓ Special label warnings for Driving should appear on the dispensing label.

Record keeping

Any person who sells or supplies the unlicensed CBPM in the UK must maintain for at least five years a record showing:

- ✓ The name of the product, brand/supplier; cannabis strain and content of THC/CBD (and ratio of THC/CBD where relevant), as appropriate.
- ✓ The source from which, and the date on which, the person obtained the product;
- ✓ The person to whom, and the date on which, the sale or supply was made;
- ✓ The quantity of the sale or supply;

- ✓ The batch number of the batch of that product from which the sale or supply was made; and
- ✓ Details of any suspected adverse reaction to the product sold or supplied of which the person is aware or subsequently becomes aware.
- ✓ Pharmacists and importers should remember these products are classified as Schedule 2 Controlled Drugs and record keeping and storage provisions apply as for any other Schedule 2 CD.

Reporting of ADR and pharmacovigilance checklist

- ✓ For cannabis-based products the MHRA requires reporting of ALL suspected adverse reactions (serious and non-serious, whether the product is licensed or unlicensed), including reports of failure of efficacy. Pharmacists supplying the “special” should report using the electronic Yellow Card (found at <http://www.mhra.gov.uk/yellowcard>), the Yellow Card app or using a paper form stating the manufacturer and indicating that the product is unlicensed.