Specialist Pharmacy Service

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NHS Pharmaceutical Quality Assurance Committee

Advice to Chief Pharmacists: Assessing the quality of Cannabis-Based Products for Medicinal Use (CBPM) and cannabis-based food supplements available in the UK (September 2022 - updated)

Summary

This document provides an overview of the quality assurance issues to consider when procuring and supplying cannabis products for medicinal use.

1. With the exception of Sativex, cannabis-based products available in the UK fall into 3 categories

- Unlicensed cannabis-based products for medicinal use (CBPM)
- (Licensed) cannabidiol (CBD)-only medicinal products. Epidyolex is currently the only product in this category.
- Cannabis-based products marketed as food supplements.

2. Specific guidance about the quality of unlicensed cannabis-based products for medicinal use in humans is set out in MHRA Guidance[2]

3. Currently none of the CBPM available as unlicensed medicines in the UK are licensed anywhere else in the world. They are therefore supplied as Specials made either in the UK under a Manufacturer's Specials (MS) Licence or made overseas and imported via an MS licence. If it is possible to obtain robust evidence of manufacture to GMP standards products quality may be assessed in the same way as for other batch-manufactured medicines. Patients may present for NHS care whilst receiving treatment with cannabis-based products which they have sourced for themselves from outside the UK.

4. If no evidence of manufacture to GMP standards is available, product quality can't be assessed against traditional pharmaceutical criteria and there must be a local assessment of the quality, taking into consideration all available information including the UK supplier's status, whether or not they have had a positive NHS PQA audit for example, the product specification and compliance with a suitable specification indicated in a batch-specific certificate of analysis.

5. Based on such an assessment and in discussion with the patient or carer, the (Chief) Pharmacist and the responsible clinician must make an informed judgement about how best to support continuation of treatment whilst the patient is under their care. This judgment will need to take into account how further supplies of CBPM can be sourced if necessary and how storage and administration will be managed during an inpatient stay.

Background

On 1 November 2018 legislation was introduced moving cannabis products from Schedule 1 to Schedule 2 of the Misuse of Drugs Regulations 2001. Cannabis-based products for medicinal use (CBPM) are defined and controlled under the Misuse of Drugs Act as schedule 2 CDs. This allows CBPM to be prescribed but restricts routes of access and limits the prescribing of these products to specialist doctors on the GMC's Specialist Register.

There are currently only two licenced cannabis based products in the UK; Epidyolex® (isolated CBD) as a treatment for two rare childhood-onset epilepsy disorders and Sativex® which contains two extracts providing tetrahydrocannabinol THC and cannabidiol. All other products meeting the definition for CBPM are unlicensed medicines and must be prescribed and supplied in line with local unlicensed medicines and controlled drug (CD) policies as well as the MHRA guidance for the prescribing and supply of CBPM and with other relevant professional guidance for prescription of unlicensed medicines.

It is unlikely that cannabis-based products would be eligible for registration under the Directive on Traditional Herbal Medicinal Products (2004/24/EC (the EU Herbal Directive[4]) as, depending on levels of THC and proposed clinical indications, they are unlikely to fulfil the requirements of the Directive.

Product categories and QA considerations

With the exception of Sativex (see above), the products largely fall into three distinct categories

1. Unlicensed cannabis-based products for medicinal use (CBPM)

2. Cannabidiol (CBD)-only* medicinal products

3. Cannabis-based products marketed as food supplements.

**Random testing of Epidyolex® showed that THC levels marginally exceeded the defined limit for exemption from control as a CBPM. From 1 October 2019, Epidyolex® has therefore been classified as*

a Schedule 2 controlled drug (CD) in the UK rather than being exempt from scheduling (an 'Exempt Product').

1. Unlicensed cannabis-based products for medicinal use (CBPM)

There are three broad requirements that a product should satisfy:

- The product is or contains cannabis, cannabis resin, cannabinol or a cannabinol derivative; and
- It is produced for medicinal use in humans; and
- It is a product that is regulated as a medicinal product, or an ingredient of a medicinal product.

Currently none of the unlicensed CBPM available in the UK are licensed elsewhere in the world. They are therefore supplied as Specials made either in the UK under a Manufacturer's Specials (MS) Licence or made overseas and imported via an MS licence. There must be a local assessment of the quality, taking into consideration the supplier's status, for example whether or not they have had a positive NHS PQA audit, the product specification and compliance with a suitable specification indicated in a batch specific certificate of analysis. For both these groups of products the NHS Pharmaceutical Quality Assurance *Committee Standards Quality Assessment of Unlicensed Medicines*[1] should be followed.

If products become licensed within the EU or in a country with a Mutual Recognition Agreement (MRA) but not in UK, then this licence (Marketing Authorisation) would be suitable as an assurance of quality. Issues such as pack readability, over-labelling in English etc. will, however, need to be assessed and approved locally.

Specific guidance covering the quality of unlicensed cannabis-based products for medicinal use in humans is set out in MHRA Guidance[2]. For example:

- Although there are no specific British Pharmacopoeial specifications for 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. 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[3]. Suitable validated analytical methods should be applied in line with current guidelines; major cannabinoids, in particular, THC/CBD should be quantitatively determined, as appropriate.

- In accordance with the BP monograph on Herbal Drugs, decontamination of the cannabis plant material using ethylene oxide is not permitted. 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.

- In addition to the general requirements listed above, MHRA will require evidence that:

    1. The content/ratio of THC/CBD is declared, and appears on the label, as appropriate
    2. A Certificate of Analysis is available to support the batch specification
    3. A valid GMP certificate is available for the site of manufacture

The purchaser's product specification should include the acceptable concentration ranges for all stated constituents and other information such as details of acceptable preservatives and other excipients. Once the product has been approved for use within an organisation each batch will need to be assessed for compliance with the specification and approved for use based on this assessment and the certificate of analysis.

Whether the specification of any particular product will meet the clinical needs of the patient will need to be assessed locally. There are many variations of CBPM with very different proportions and concentrations of THC and CBD, and sometimes also include other cannabinoids and cannabinoid derivatives, not all of which may be recognised as being present and/or of having a pharmacological effect.

Cannabis is not on the list of traditional herbal remedies to which Directive 2004/24/EC (the EU Herbal Directive[2]) applies, hence, no cannabis based products are or are ever likely to be authorised as Traditional Herbal Medicinal Products.

2. Cannabidiol (CBD)-based medicinal products (eg Epidyolex®)

Although Epidyolex® is claimed to contain only isolated cannabidiol, random testing showed that THC levels marginally exceeded the defined limit for exemption from control as a CBPM. *From 1*

October 2019, Epidyolex® has therefore been classified as a Schedule 2 controlled drug (CD) in the UK rather than being exempt from scheduling (an 'Exempt Product').

3. Cannabis-based products marketed as food supplements.

Products marketed as *bona fide* food supplements would not usually be expected to be prescribed although they can be legally bought in the UK and hence patients may be seen who are using them. There is the potential for all of these products to interact with prescribed medication and hence it is important that they are understood.

Cannabis-based products which are not medicinal products are marketed as *food supplements* and no claims of therapeutic benefit can be made for these products which contain CBD only. There have been recent reports that approximately half of commercially available CBD oil products tested were found to contain measurable levels of THC (above 0.04%) which would make them illegal in the UK.[5]

A wide range of products is available. Because food supplements are regulated under food law and not subjected to the strict controls of medicinal products, it is difficult to be able to assess their quality in pharmaceutical terms. Sometimes certificates of analysis can be obtained from manufacturers, but the products cannot be expected to have been made to full GMP. Within the EU these cannabis based food supplements are controlled by the general EU food legislation Regulation 178/2002 and through the Novel Food Regulation 2015/2283[6] in force since 1st January 2018. The Novel food Catalogue[7] includes entries for Cannabis sativa (due to historic use not subject to the Novel Food Regulation) and cannabinoids (which do require a safety assessment under the regulation before they can be marketed as a food or food ingredient).

The European Food Standards Authority (EFSA) is currently discussing the permitted types of botanical ingredients and how their safety should be assessed. EFSA is also discussing which health claims should be permitted and on which levels and types of evidence they should be based[8]. There is currently a large backlog of work to be done and no agreement in place as to how this should be progressed or how the assessments should be done. Until recently most cannabis-based food supplements had not been included in this assessment, although some hemp oil (the fatty oil extracted from hemp seeds and not relevant in this context) preparations were. If these products made any claims and any claims to treat, prevent or cure a medical condition they would be classified and controlled as medicines.

References:

1. Quality Assessment of Unlicensed Medicines 1st Edition November 2016, NHS Pharmaceutical Quality Assurance Committee https://www.sps.nhs.uk/articles/quality-assessment-of-unlicensed-medicines/ (registration needed)

2. MHRA: The supply, manufacture, importation and distribution of unlicensed cannabis-based products for medicinal use in humans 'specials'
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/752796/Cannabis_Guidance unlicensed_CBPMs -_Final_311018.pdf
https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-herbal-medicinal-products#Quality

3. Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products

https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0085:0090:en:PDF

4. RPS asks Home Office for guidance on THC in CBD oil, Pharm journal, July 2019, vol. 303, P11

https://www.pharmaceutical-journal.com/news-and-analysis/news/rps-asks-home-office-for-guidance-on-thc-levels-in-cannabidiol-oil/20206419.article?firstPass=false

5. Regulation (EU) 2015/2283 on novel foods
https://ec.europa.eu/food/safety/novel_food/legislation_en

6. The EU Novel foods catalogue https://ec.europa.eu/food/safety/novel_food/catalogue_en

7. EU Regulations on food supplements, health foods and herbal medicines
https://www.export.gov/article?id=EU-Regulations-on-Food-Supplements-Health-Foods-Herbal-Medicines1

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