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Client Alert Commentary

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Green Shoots for the Commercialisation of Cannabis-Based Medicinal Products in the UK?

Recent legal and regulatory developments pave the way for an increased commercialisation opportunity in cannabis-based medicines, but complex rules require careful navigation.

The National Institute for Health and Care Excellence (NICE) recommended the reimbursement of two plant-derived cannabis products for the first time on 10 November 2019. This follows Epidyolex becoming the first cannabis-derived medicine to be granted a marketing authorisation by the European Commission when it was approved for the treatment of two rare forms of epilepsy on 23 September 2019.[1] In addition, recent changes to UK law loosen some of the restrictions on cannabis-based products for medicinal use. However, the regulatory regime for medicines containing cannabis-derived ingredients remains complex and nuanced.

What is cannabis and what substances derive from it?

Cannabis is a generic term used to denote the several preparations of the plant *Cannabis sativa*. The plant contains a number of substances called cannabinoids, which are chemical compounds that act on cannabinoid receptors or the endocannabinoid system in cells. THC, or tetrahydrocannabinol, is the main active ingredient in cannabis and is responsible for the psychoactive response or "highs". Cannabinol is another psychoactive substance found in cannabis, although in much smaller quantities than THC. CBD or cannabidiol is the second most prevalent cannabinoid found in cannabis, but, unlike THC, CBD is non-psychoactive. In other words, it does not cause a high.

Are cannabis-based products illegal?

Cannabis, cannabis resin, cannabinol, and cannabinol derivatives, including THC, (not being dronabinol or its stereoisomers) are all Class B drugs under the Misuse of Drugs Act 1971 (the Act), Schedule 1 substances under the Misuse of Drugs Regulations 2001 (the 2001 Regulations) and designated under the Misuse of Drugs (Designation) (England, Wales, and Scotland) Order 2015 (the 2015 Order). The cumulative effect of this Act and these regulations mean that it is unlawful to import, export, possess, supply, or produce any of these substances, except under certain carefully limited conditions.

CBD or cannabidiol, however, is not a controlled substance and is not subject to such stringent restrictions.

When can a cannabis-based product be marketed as a medicine in the UK?

If a medicinal product derived from cannabis does not contain any controlled substances then it can be marketed after obtaining a marketing authorisation from the MHRA or, if applicable, the European Commission. For example, if the product is based on an isolated, pure form of CBD (*i.e.*, which does not contain any cannabis, cannabis resin, cannabinol or cannabinol derivatives (including THC)) or if it is an "exempt product" under the 2001 Regulations (*i.e.*, the product meets all three limbs of the test in the 2001 regulations), it may be marketed after obtaining a marketing authorisation.

The 2001 regulations set out the following criteria for an exempt product:

"a preparation or other product consisting of one or more component parts, any of which contains a controlled drug, where—

(a) the preparation or other product is not designed for administration of the controlled drug to a human being or animal;

(b) the controlled drug in any component part is packaged in such a form, or in combination with other active or inert substances in such a manner, that it cannot be recovered by readily applicable means or in a yield which constitutes a risk to health; and

(c) no one component part of the product or preparation contains more than one milligram of the controlled drug or one microgram in the case of lysergide or any other N -alkyl derivative of lysergamide;"

Unlike other controlled drugs under the Act, an exempt product is not subject to the restrictions on possession, production, supply, import, or export.

If a cannabis-based medicinal product contains controlled substances and does not come within the definition of exempt product, it must fulfil the requirements of the amended 2001 Regulations in addition to the requirements for marketing authorisation and other restrictions.

In November 2018, the 2001 Regulations were amended[2] to introduce a definition of "cannabis-based product for medicinal use in humans" (CBPM) and to reschedule such products into Schedule 2 from Schedule 1. These products were also removed from designation under the 2015 Order. A CBPM, for the purpose of the 2001 Regulations, is essentially a medicinal product or an ingredient of a medicinal product that contains cannabis, cannabis resin, cannabinol, or a cannabinol derivative (not being dronabinol or its stereoisomers). The effect of this amendment and rescheduling is that the restrictions applicable to CBPMs have been eased and now permit CBPMs to be prescribed in particular circumstances, provided that certain restrictions are complied with.

What restrictions apply to medicines made from cannabis?

Under the amended 2001 Regulations, a CBPM can be ordered or supplied if it satisfies any of the below conditions:

a) Has a marketing authorisation

b) Is an investigational medicinal product for use in a clinical trial

c) Is a special medicinal product for use in accordance with a prescription or direction of a specialist medical practitioner[3]

The difficulty with obtaining a marketing authorisation, as acknowledged by the House of Commons Health and Social Care Committee in their June 2019 report on medicinal cannabis, is that restrictions on accessing cannabis products affect the ability to conduct robust clinical trials. "*Without a thorough research base products remain unlicensed and may only be prescribed if the individual prescribing doctor is satisfied that there is sufficient evidence for the product's safety and efficacy for the individual patient*".[4]

Currently, only one cannabis-derived product, Sativex Oromucosal Spray, which contains both THC and CBD, has received a national marketing authorisation in the UK for treatment of MS-related muscle spasticity[5] (approved in 2010). Another product, Epidyolex, which is a purified CBD product, has received a marketing authorisation from the European Commission for treatment of children and adults with epilepsy through the centrally authorised procedure, which means that its marketing authorisation applies throughout all countries in the EU.[6] In addition, there is one synthetic cannabinoid (*i.e.*, a substance that is not derived from cannabis, but which acts in a similar manner to cannabinoids), Nabilone, which was approved for marketing in the UK for treatment of chemotherapy patients in January 2017.[7]

In the absence of a marketing authorisation, CBPMs, like other medicines, can only be provided to patients under the restrictive "specials" regime or as part of a clinical trial. The specials or named-patient regime provides an exemption from the need for a marketing authorisation for a medicinal product that:

- Is supplied in response to an unsolicited order
- Is manufactured and assembled in accordance with the specification of a doctor, dentist, nurse independent prescriber, pharmacist independent prescriber, or supplementary prescriber
- Is for use by a patient for whose treatment that person is directly responsible in order to fulfil the special needs of that patient
- Complies a number of further strict conditions including with regard to supply, use, supervision, manufacture, advertising, and records[8]

Even if a CBPM or other cannabis-derived product (including exempt products) obtains a marketing authorisation, certain restrictions will apply over and above those applicable to other medicines. These restrictions include Section 285 of the Human Medicines Regulations 2012,[9] which prohibits the publication of any advertisements relating to medicinal products containing products listed in Schedule I, II, or IV of the Single Convention on Narcotic Drugs (which includes cannabis, cannabis resin, and extracts and tinctures of cannabis), except as part of an approved vaccination campaign. This advertising regime is notably more restrictive than that applicable to other medicinal products, which permits advertising of authorised non-prescription medicines to the public and advertising of prescription-only medicines to healthcare professionals in certain circumstances. The provision of samples of medicinal products containing scheduled products is also prohibited under Section 298 of the Human Medicines Regulations 2012, which is again more restrictive than the position on other medicinal products.

Is it possible to secure NHS reimbursement for cannabis-derived medicines?

Like many other novel or innovative medicines, even if a cannabis-derived medicine is successful in obtaining a marketing authorisation, it can be difficult to secure reimbursement through the public health system. In order for a product to be reimbursed through the NHS, it must undergo a technology appraisal in which NICE will review the clinical evidence and economic evidence and make a recommendation on the cost-effectiveness of the treatment.

On 10 November 2019, NICE recommended the reimbursement from NHS England of Epidyolex (as an adjunctive therapy for seizures associated with Lennox Gastaut syndrome or Dravet syndrome) and Sativex (as a treatment of spasticity due to multiple sclerosis), which was the first time plant-derived cannabis products have been recommended as cost-effective treatments in the UK. Prior to this, Sativex had been subject to a "do not offer" recommendation from NICE, on the basis that it is not a cost-effective treatment.

How can you cultivate/produce cannabis-based products in the UK?

In addition to the above regulatory requirements for placing cannabis-based products on the market, a licence from the Home Office is also required in order to possess, manufacture, produce, or supply a controlled substance.

In order to cultivate cannabis plants in the UK for industrial purposes or to obtain seeds which will then be pressed for their oil, it is possible to obtain an Industrial Hemp Licence. The Home Office requires the applicant to have a defined commercial end use for the plants and will only issue licences for cultivation of plants from approved seed types with a THC content not exceeding 0.2%. For other controlled substances (including those with a THC content exceeding 0.2%) or for other purposes, a Controlled Drug Licence from the Home Office is required.

It is also necessary to obtain a Home Office Controlled Drug Import Licence to import any cannabis plants or products containing THC or other controlled cannabinoids into the UK.

Likely future developments

In the UK and elsewhere, recent trends point to an exploration of the benefits of cannabis-based medicinal products and an increased openness to making such products available, particularly for patients with unmet needs.

The House of Commons Health and Social Care Committee published its report on medicinal cannabis on 18 June 2019.[10] The Committee made a number of recommendations, including calling on NICE, the National Institute of Health Research (NIHR), and the Department of Health and Social Care to encourage and progress research to develop the evidence base for CBPMs with a "sense of urgency". The Committee supports robust, randomised, controlled clinical trials, in particular calling on the NIHR to make resources available for clinical trials for the treatment of intractable epilepsy. These concerns were echoed by an NHS England report on barriers to accessing CBPMs, which noted that since the change the 2001 Regulations, there has been an increase in the prescribing of CBD products, but no increase in NHS prescriptions of products containing THC.[11]

A clear sense of the general impact of the recent developments in approvals and reimbursement decisions on the UK CBPM market is several months away, but green shoots for the commercialisation of CBPMs in the UK are growing, albeit subject to compliance with a complex legal and regulatory regime, which will require careful navigation.

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Endnotes

[1] Lennox-Gastaut syndrome and Dravet syndrome.

[2] The Misuse of Drugs (Amendments) (Cannabis and Licence Fees) (England, Wales and Scotland) Regulations 2018 and http://www.legislation.gov.uk/uksi/2018/1055/pdfs/uksiem_20181055_en.pdf.

[3] Regulation 16A of the 2001 Regulations.

[4] https://publications.parliament.uk/pa/cm201719/cmselect/cmhealth/1821/1821.pdf.

[5] Sativex Oromucosal Spray https://www.medicines.org.uk/emc/product/602/smpc.

[6] Epidyolex - https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3141339.

[7] Nabilone - http://www.mhra.gov.uk/spc-pil/?subsName=NABILONE&pageID=SecondLevel.

[8] Regulation 167 of the Human Medicines Regulations 2012.

[9] http://www.legislation.gov.uk/uksi/2012/1916/regulation/285/made.

[10] https://publications.parliament.uk/pa/cm201719/cmselect/cmhealth/1821/1821.pdf.

[11] https://www.england.nhs.uk/wp-content/uploads/2019/08/barriers-accessing-cannabis-based-products-nhs-prescription.pdf.