CONSERVATIVE
DRUG POLICY
REFORM GROUP

THE UK REVIEW OF MEDICINAL CANNABIS

The needs of a nation

PART A: THE CURRENT LANDSCAPE

A review of pathways and barriers to access of cannabis-based products for medicinal use in the UK

PRESENTED BY

Dave King
Amber Moore

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Suite 15.17, Citibase, Millbank Tower,
21-24 Millbank, London, SW1P 4QP, ENGLAND

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FOREWORD

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The global Coronavirus crisis has pushed the demand for policy based on evidence and an intense interest in all emerging evidence. That approach has been largely absent from global drugs policy since 1961, yet the impact every year of a failing drugs policy around the world is of a similar order of magnitude in human misery. It is secured more on a moral code now over 50 years old than on evidence of outcomes. One of its effects has been to delay research into the potential health benefits of drugs stained with the most public opprobrium. Chief among these was cannabis, directed into the most restricted research category of all, less on evidence and more on the racial prejudice towards its main consumers by 1950s US law enforcement, black Americans. The world followed.

It has taken a long time to start to catch up and the UK began this process in 2018 after the Chief Medical Officer was invited to pronounce on the potential efficacy of medicine based on cannabis. It took her no time at all to return a positive answer with a rapid review of the available evidence. Progress since has been painful and difficult.

I am proud to present the results of our investigation into current routes of access to cannabis for medicinal purposes in the UK. Its objective is to review the full extent of the relationship between the movement of cannabis based products from Schedule 1 to Schedule 2 in November 2018, and its overt political sanction, against the actual health and social issues which now arise in relation to accessing it. It defines seven different routes of access in the UK today to medicinal use of cannabis and reveals that the current policy framework by any test is not working.

I hope that these findings can serve as a foundation document for those seeking a fuller understanding of the use of cannabis-based products for medicinal purposes in the UK, whether from a personal or professional perspective. The analysis presented here has been peer reviewed by some of our distinguished if unrenumerated Policy Council and other academics and policy experts. Its analysis will be updated as the legal and regulatory environment evolves, as it must. We will keep those proactively engaged with the work of CDPRG abreast of the implications of developing policy, and the accompanying guidelines, regulations and licenses.

The complexity surrounding the lawful and unlawful routes of access to medical cannabis set out in this “Part A: The Current Landscape” reflects, and, in reality, stems from the complex nature of the plant itself. An initial object to the 2018 rescheduling voiced in 1999 was that permitting the use of raw cannabis as a medicine would “blur the distinction between misuse and therapeutic use,” a statement which acknowledges the existence of such a distinction. Marked differences characterising the use of cannabis-based products for medicinal purposes are underscored by each line of enquiry in this report — the development of each of the unlawful routes of access to medical cannabis set out in the second chapter, including otherwise law-abiding citizens growing their own plants while living “in fear of a knock at the door,” is revealed to be motivated by desires to source products akin to licensed cannabis preparations in quality, and to avoid tangling with the illicit criminal market; being, this report finds, especially vulnerable to potential exploitation.

The demand for medical-grade cannabis-based products is growing in step with a global awareness of the evidence of treatment potential. Significant pharmaceutical investment continues to be available reflecting the growing global evidence base for the safety, efficacy, and cost-effectiveness of cannabis- based treatments. Countries that are leading the way in terms of developing and supplying licensed cannabis-based medicines include Israel, Uruguay, Canada, the Netherlands, Germany, and the Czech Republic. The UK has an illustrious history of translating naturally occurring substances into pivotal treatments — kick-starting the era of antibiotics by conducting follow-up research on Alexander Fleming’s 1928 discovery of mould-derived penicillin — but we have been

comparatively slow on the uptake when it comes to cannabis.

Eighteen months on from the November 2018 rescheduling of cannabis-based products, which was intended to enable and open the doors to research, only three products are licensed as medicines, recommended to treat four conditions, predicted to be prescribed to just 5,000 people by 2024. Due to prohibitive costs, unlicensed medicines, which are now in theory importable, were prescribed in just 204 instances and to only a few dozen individuals in the year following the rescheduling. While the UK's provision of legal, cannabis-based medicinal products lags behind other countries, the awareness and treatment needs of the British public do not. Their desperation to access the cannabis-based products that are licensed abroad for their particular conditions sees some travelling overseas for prescriptions, smuggling the granted products back across the UK's border, risking having these seized at customs.

I first became involved in the debate around widening access to medical cannabis in the UK in 2018, in relation to the case of Alfie Dingley, a child with severe epilepsy whose family had moved to the Netherlands to enable his access to the life-changing THC-containing product that reduced his seizures. I asked the Urgent Question to the Home Secretary. While his individual case has been addressed, the urgency remains current to all those still in the situation highlighted by his case, which the change of law was meant to help. It is entirely appropriate that we commissioned a follow-up to the initial policy change in the form of this report.

The result is an unprecedentedly penetrating review of how the rescheduling of cannabis-based products from Schedule 1 to Schedule 2 relates to both licit and illicit modes of accessing medical cannabis — revealing the rescheduling on its own to be wholly insufficient to manage the challenge. The result of the research and analysis of the current position is enabling us to examine why. It includes the multiple different perspectives that inform it — from the specialists who are unwilling to prescribe it due to a lack of familiarity with the endocannabinoid system and corresponding lack of of education on cannabis in medical schools, to the police who are "very reluctant" to make arrests where cannabis is being used for medicinal purposes. It is only by reckoning with the landscape as a whole that the problems produced by the disjunctions between its different groups, guidelines, legislative and regulatory bodies can be clearly seen, and subsequently addressed.

Acknowledgements

This report is substantially the work of Dave King and Amber Moore, two of our brilliant researchers, whose meticulous work in has resulted in this comprehensive overview of access to medical cannabis in the UK. The CDPRG gratefully acknowledges every set of insights shared with us in the service of rendering the most complete possible picture of the landscape. This includes patients and their families, policymakers and physicians, licensing authorities and law enforcement professionals, support services and leading academics from relevant fields. In this regard, we are grateful for input from the clinical cannabinoid medicine physician specialist Dr Dani Gordon and human rights and drug policy specialist Dr Melissa Bone from the University of Leicester. I am proud to feature both on our Policy Council.

Evidence-based policy is at the heart of every endeavour undertaken by the CDPRG — to this last, I would like to thank every reader who comes to the information in this report ready to think critically to explore how we can manage this exciting opportunity for medicine, science and public benefit better consistent with the available evidence.

Crispin Blunt MP

Chairman of the Conservative Drug Policy Reform Group (CDPRG)

EXECUTIVE SUMMARY

Almost exactly twenty years after a House of Lords committee recommended moving cannabis to Schedule 2, HMG rescheduled cannabis-based products for medicinal use (CBPM) to allow specialist doctors to prescribe them as unlicensed medicines and to reduce the obstacles to clinical research. This comprehensive report documents the ways in which this policy change, enacted on 01 November 2018, has shaped the emergence of medicinal cannabis in the UK.

The findings provide a stark outline of the current landscape of medicinal cannabis supply and demand in the UK. They evidence the obstacles to safe, legal access encountered by the people who seek cannabis products for medical reasons. The interviews with stakeholders from relevant sectors and population groups in the body of the proceeding report explain how reasonable patient demand for access to medicinal cannabis is not being met under current regulation and legislation.

This report identifies and investigates seven routes by which cannabis-based products for medicinal use are being accessed, reviewing the distinct operational characteristics, rates of access, and challenges associated with each route. The evidence collated in this report explains UK citizens' disproportionate dependence on illicit routes of access. Our findings identify a complex network of medical, research, and crime issues linked to medicinal cannabis policy, and the population groups that would benefit the most from a recasting of current regulations.

There is a wide range of cannabis-based products: this report finds and defines 17 categories, distinct in terms of form, contents, use, and legal control. The variety of cannabis-based products relates directly to the complexity of cannabis itself, which is known to contain at least 540 phytochemicals, with 144 known cannabinoids, more than 200 terpenes, and 20 flavonoids identified to date. Different plant-based products may contain different compounds and combinations and may have distinct effects in humans. The wide range of purported and proven medicinal applications of cannabis are rooted in this polypharmacy.

CHAPTER 1: LAWFUL ROUTES OF ACCESS

A review of four lawful routes of access to medicinal cannabis reveals the paucity of currently available licensed medicines; the ways in which the process of prescribing licensed and unlicensed cannabis-based medicines raises bureaucratic barriers for both doctors and patients; the impact of current policies on clinical research and drug development; and the costs and processes of production, importation and supply of unlicensed CBPM in the UK. The key findings in Chapter 1 thereby explain the bottleneck on the provision of medicinal cannabis in the UK. A result of these conditions is the emergence of a "two-tier" system, in which only those with the means to secure private prescriptions can lawfully access unlicensed cannabis-based medicinal products.

INTRODUCTION

FOI requests were sent to every Acute NHS Trust in the country to assess the volume of prescriptions for cannabis-based products that were dispensed within hospitals. Adding this data to publicly available information on dispensing from community pharmacies, we identified a total of 6,923 known prescriptions for cannabis-based products from November 2018 to October 2019 (*see Fig. A*). Licensed cannabis-based medicinal products (L-CBM) Sativex and Nabilone account for 92% of prescriptions. Epidyolex, which was licensed in late 2019, accounts for 5%, while just 3% of prescriptions were for unlicensed cannabis-based products for medicinal use (CBPM).

ROUTE 1: LICENSED CANNABIS-BASED MEDICINES (L-CBM)

L-CBM are products which have market authorisation in the UK. Product licenses determine the medical conditions and patient groups for which a medicinal product can be prescribed, and for which medical claims may be made. Licensing decisions are based on rigorous standards of evidence on safety, quality, and efficacy. As of December 2019, three cannabis-based products have achieved status as a licensed medicine for use in the UK: Sativex, Epidyolex, and the synthetic cannabinoid medicine Nabilone. They are licensed, respectively, for use in spasticity in multiple sclerosis (MS); the

Figure A. Prescriptions of L-CBM & U-CBPM from Nov 18 - Oct 19

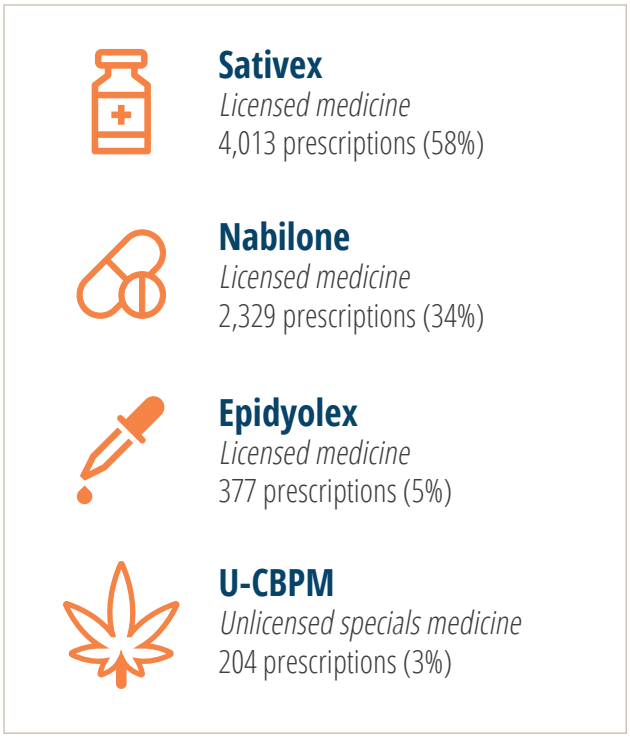
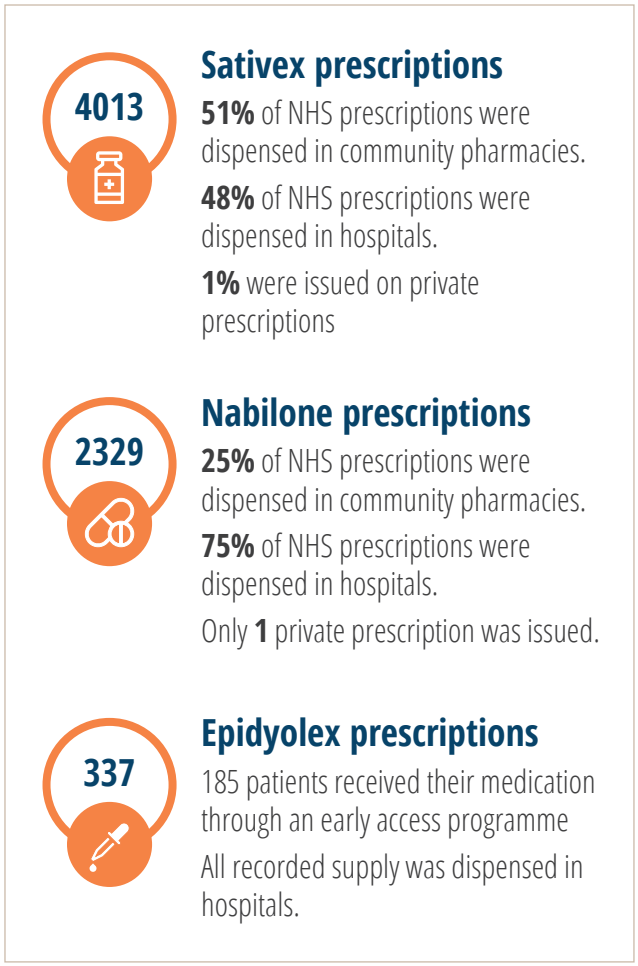


Figure B. Prescriptions of L-CBM from Nov 18 - Oct 19



treatment of seizures in patients with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS); and the treatment of chemotherapy-induced nausea and vomiting (CINV).

However, numbers of people receiving and likely to receive licensed L-CBM are low for several reasons:

1. These drugs are only licensed for the treatment of conditions and patient populations in which there is strong clinical evidence of safety, efficacy, and cost-effectiveness.

2. Guidelines published by NICE and by specialist clinical organisations only recommend treatment with L-CBM for people whose symptoms are not adequately controlled by conventional interventions.

3. Following reasons (1) and (2); licensed indications represent small clinical populations.

4. Funding for some L-CBM is still not routinely provided by local NHS Trusts or Clinical Commissioning Groups (CCGs), and CCGs may be open to legal challenges from patients.

Despite achieving regulatory approval and demonstrating cost-effectiveness, the total number of patients expected to receive either Epidyolex or Sativex on the NHS by 2024 is only around 5,000 – far fewer than the numbers of patients estimated to be unlawfully using CBP with medicinal intent in the UK today (*see Chapter 2*).

ROUTE 2: UNLICENSED CANNABIS-BASED 'SPECIALS' MEDICINES (U-CBPM)

Schedule 2 unlicensed cannabis-based medicinal products (U-CBPM) can only be prescribed by a specialist doctor, or at the direction of a specialist. In the first year after the rescheduling, there were 204 known prescriptions issued for U-CBPMs, of

which 85% were issued on private prescription. 9% were issued on NHS prescriptions dispensed in community pharmacies and just 5% were dispensed on the NHS in hospitals. In 2019, 242 MHRA notifications to import U-CBPM were received, and 452 Home Office import licenses were issued for shipments containing cannabis or cannabinoids. Obstacles to accessing unlicensed cannabis-based products include:

1. **The unwillingness of specialists to prescribe.** This is based on limited evidence on safety, quality, and efficacy; the fact that clinical guidelines do not recommend use; special medicines being considered as a last resort; and the fact that they cannot lawfully be solicited by the patient.

2. **Medical education on cannabinoids is limited.** Almost 1/2 (44%) of medical schools provide no preclinical training on cannabis, cannabinoids or the endocannabinoid system. Almost 2/3 (62.5%) of medical schools provide no preclinical training on the endocannabinoid system.

3. **U-CBPMs have been difficult to fund.** The NHS does not routinely commission U-CBPM and applying for funding requires a complex approvals process. The average cost of U-CBPM to the NHS was £2,789.21 per prescription. The total NHS cost in the first year totalled £52,995. Private prescriptions, correspondingly, are unsustainably costly.

4. **Furthermore, supply has been unreliable.** Until March 2020, bulk importation of U-CBPM was not allowed by UK licensing authorities and INCB import quotas for THC were restrictively low. The UK INCB assessment for THC has now been raised from 20g/year to 1,120g/year. There is no established UK production, and there is limited transparency regarding the issuing of Home Office licenses needed for cultivation, production, importation and supply.

    - 362 Schedule 1 possession licenses were issued in 2019

    - 33 low-THC cultivation licenses were issued in 2019 (an increase of 370% since 2014)

    - 20 high-THC cultivation licenses were issued in 2019 (an increase of 300% since 2014)

ROUTE 3: CANNABIS-BASED INVESTIGATIONAL MEDICINAL PRODUCTS (IMP)

There have been 77 clinical trials in cannabis-based IMP at UK sites since 2001. Of these, 56 were completed trials, with this report finding a total of just 4,560 participants receiving a study drug over the past 20 years. There are 5 currently active trials. Three quarters of all trials relating to cannabis-based medicines in the UK sponsored by GW Pharmaceuticals. **Only 10 distinct cannabis-based IMP have been tested in clinical trials in humans in the UK.**

The NIHR Clinical Research Network has historically supported 14 commercial clinical trials in cannabis products and are supporting a further 2 in set up. At least 3 more are being assessed. NIHR themed calls for cannabis medicines had a total of 5 applications across the first and second call for submissions: the Efficacy & Mechanism Evaluation programme received 5 applications, while the Health Technology Assessment programme received 0 applications. No applications were awarded funding.

ROUTE 4: NON-CONTROLLED CANNABIS BASED WELLNESS PRODUCTS

The British CBD market may be worth £300 million/year, according to the Centre for Medicinal Cannabis (CMC). Polling consistently shows about 9% of UK adults have used CBD products, mostly for health & wellness reasons. There is a wide range in terms of quality, legality and accuracy of labeling of products on the market; only 4 UK manufacturers have API registration for CBD.

CBD products are regulated according to their intended use. The VMD requires all products for animals to have market authorization as veterinary medicines and the MHRA requires all products for medicinal use in humans to have market authorization as medicines. Cosmetics cannot lawfully contain CBD derived from cannabis flowers. The Food Standards Agency (FSA) has given a deadline of 31 March 2021 for suppliers to submit novel foods applications for products for human consumption. Due to

common misconceptions about cannabis law, many CBD products currently on the market are controlled drugs under the Misuse of Drugs Act 1971 and subsequent regulations. Home Office hemp cultivation licenses do not permit growers to use or sell the flowers.

CHAPTER 2: UNLAWFUL ROUTES OF ACCESS

Many of the findings discussed in Chapter 1 factor heavily in explaining the dependency of approximately 1.4 million people in the UK on unlawful routes of access to cannabis-based products for medicinal reasons. Chapter 2 considers three unlawful routes of access to cannabis-based products, revealing that the most common route of unlawful access (and the most common route of access overall) is through the illicit criminal market, which also presents the greatest threat to patients' health.

ROUTE 5: IMPORTED CANNABIS-BASED MEDICINES

A small fraction of those sourcing medical cannabis unlawfully do so by acquiring prescriptions overseas, from countries such as the Netherlands, and importing the medicines back into the UK on their person. Without a Home Office license, this is unlawful for individuals habitually resident in the UK, even if the patient has a valid prescription. It is not surprising that this route is relatively uncommon compared to other routes of unlawful access, due to the costs required to travel overseas, the cost of the medication itself, and the risks of criminal penalties and seizure of medication. However, the route has been and continues to be a life-line for some patients, particularly the parents of children with intractable epilepsy who are not prepared to risk using unregulated cannabis-based products sourced from other unlawful routes (i.e. the criminal market or through self-cultivation).

Some patients and parents claim that it has been necessary for them to import products unlawfully, because licensed medicines, including Epidyolex, have not controlled symptoms adequately, and unlicensed products have not been affordably available in the UK. It is hoped that the high costs and long lead times of private prescriptions may reduce under the new bulk import model, once more affordable international supply chains are available. For now, however, lawful routes of supply are failing to meet the needs of many children whose stories were so fundamental to the decision to reschedule CBPM in 2018.

ROUTE 6: SMALL-SCALE CULTIVATION FOR PERSONAL USE, CO-OPERATIVE BASED CULTIVATION GROUPS AND "CANNABIS SOCIAL CLUBS"

A remarkable proportion of individuals who grow cannabis at home are doing so for medicinal purposes. A 2014 survey of 418 small-scale cannabis cultivators in the UK found that half cited medicinal use as their reason for growing the plant, with subsequent analysis of the results indicating that the findings 'reflect a genuine belief in medical benefit' among these individuals, rather than an attempt to justify their cannabis consumption. These growers risk up to 14 years in prison – a significantly more serious sentence than cannabis possession alone. This report finds that self-cultivation for medical purposes is demarcated by multiple characteristics which differentiate it from the illicit market. As well as generally being employed and uninvolved in other criminal activities, those who cultivate cannabis for personal use tend to detach from the criminal market in that they are not buying or supplying illicit products, nor profiting from the plants they cultivate. We estimate that there are tens of thousands of people growing cannabis in the UK for medicinal reasons.

Quality control is a significant motivator for growing cannabis for medicinal purposes. The belief that the cannabis they can grow is "healthier" than what is available to buy on the illicit market incentivises the majority of self-cultivators. Growing plants themselves allows people who use cannabis for medicinal reasons to try a much wider range of products than could otherwise be accessed, either through the black market or lawfully through prescription. Many claim that the self-cultivation of cannabis has allowed them to identify and select plants which best meet their individual needs, accentuating the therapeutic benefits over time. Cannabis Social Clubs (CSCs) are found to offer those medicating with cannabis the scope to develop products that meet their unique needs, while avoiding contact with street dealers and funding

criminal activities associated with the illicit market. While small-scale self-cultivation of cannabis for medical purposes is a safer route of access than the illicit market, it is estimated that around 1 in 10 medicinally-motivated users source cannabis in this way. Self-cultivation requires initial investment in equipment and seeds (which are legal to buy), an appropriate and secure space to grow, continued management, as well as physical capacity. It also carries the risk of greater criminal penalties than simple possession.

Policing and prosecution relating to cannabis cultivation for medicinal purposes is highly variable. This leads to a confusing and unjust distribution of risk of penalties for offending, which has resulted in claims of *de facto* decriminalisation of cannabis cultivation in the UK and a postcode lottery. The situation has also created public uncertainty regarding the legal status of cultivation, particularly where the product is grown for personal use with medicinal intent. Awareness and acceptance of the potential therapeutic uses of cannabis have become increasingly recognised, both among the public and within the political and medical sectors, but lawful access is still limited by operational challenges, regardless of whether or not the treatment might be appropriate for the patient. People who grow their own cannabis for medicinal use tend to reject the image of being a criminal perpetrator because they are detached from the 'criminal market'. Irrespective of this position, they live in constant fear of the 'knock at the door' and detection by law enforcement.

ROUTE 7: THE ILLICIT MARKET IN CANNABIS AND CANNABIS-BASED PRODUCTS

Avoidance of the illicit market is a key motivation for using unlawful Routes 5 and 6 to source cannabis-based products for medicinal use. The heightened risks of legal persecution involved in Routes 5 and 6 (including the seizure of products) contributes to a reliance on the illicit market for the large majority of self-medicating users, despite the reduced control over the range and quality of products associated with that route.

The most recent UK estimates, based on a nationally represented survey of the British public conducted by YouGov and commissioned by the CMC, suggest that more than 1 million people with chronic health conditions are self-medicating with cannabis-based products from the illicit market, exposing themselves to higher risks of harm and fueling the criminal market, while forgoing the attendant health benefits which safe, lawful access to a cannabis-based product suited to their needs could provide. Based on the findings from the CMC survey, which indicated average spending of £162 per month on the illicit market among those who used cannabis for medicinal reasons, £2 billion a year in revenue could potentially be going to organised crime groups from self-medicating consumers alone.

CONCLUSIONS

Understanding the current supply chains of cannabis for medical purposes in the UK is key to working out how to deliver a successful legal and regulatory framework that supports better access to evidence-based, cost-effective treatments, while clearly identifying what remains in the realm of crime and law enforcement. The evidence collated in this report indicates the scope for improvements to public health which should result from addressing the complex challenges of medicinal cannabis policy. Future UK developments could seek to protect patients by improving safe and legal access to CBPM, while giving much greater clarity to law enforcement charged with sustaining HMG's clear policy against recreational use.

INTRODUCTION

This report is Part A of a two-part series reviewing medicinal cannabis policy in the UK. Part A provides a descriptive review of the present situation, while Part B evaluates regulatory options for the road ahead. We do not examine or make recommendations concerning the use or supply of cannabis-based products for non-medicinal use, nor do we make assessments of the current evidence-base on either the benefits or the risks of using cannabis-based products.

Part A provides a comprehensive overview of seven routes by which cannabis-based products are presently being accessed for medicinal reasons by people in the UK. In order to deliver a picture of the current situation that is as complete and accurate as is possible, we address both lawful and unlawful routes of access. We describe the legal and regulatory landscapes, pathways and processes, volumes of access, and challenges associated with each route. The seven routes we consider are as follows:

1. Licensed cannabis-based medicines (CBM) accessed on prescription;

2. Unlicensed cannabis-based products for medicinal use (U-CBPM) accessed on prescription as 'specials' medicines;

3. Cannabis-based investigational medicinal products (IMP) prescribed in a clinical trial;

4. Non-medicinal cannabis-based products (CBP) on the health and wellness markets;

5. Medicinal CBP prescribed overseas and unlawfully imported on person;

6. Cannabis cultivated unlawfully without a license for personal medicinal use; and

7. Cannabis and CBP accessed unlawfully on the black market for medicinal use.

Part B assesses policy goals, challenges and possibilities for the road ahead. Taking into account the findings of Part A regarding obstacles to safe access, we compare the current UK situation with models of medical access that have been implemented in other countries, review outcomes, and evaluate options for the UK against three policy goals:

1. To improve **safe access** to medicinal cannabis-based products where clinically appropriate;

2. To ensure the development of an **evidence-base** to assess product safety and effectiveness; and

3. To minimise existing and potential **risks and harms** to society, public health and the individual.

To inform this report, the authors have consulted with a wide range of stakeholders in the UK and other jurisdictions, including: patients and their families; patient advocacy groups; campaigners; physicians; pharmacists; medical scientists; specialist medical organisations; importers and manufacturers of specials medicines; small- and large-scale cultivators of cannabis; pharmaceutical companies with cannabis-based product lines; NHS-England and NHS-Improvement; NICE; licensing authorities and regulators; members of Parliament; Government ministers; law-enforcement personnel; lawyers; policy analysts; criminologists; and a range of academics from other relevant fields. In addition to the testimonies of these stakeholders, we have regularly reviewed the available academic and grey literature on this policy area.

This introductory chapter to Part A begins with a brief background to the 'legalisation of medicinal cannabis' in 2018. 'Medicinal cannabis,' and related terms, are used rather vaguely by some commentators in this policy area to refer to a multitude of products, but there are distinct categories of 'medicinal cannabis-based products' available in the UK with important differences between them. In this introduction, we provide a brief overview of the differences between licensed and unlicensed medicines, so that we may go on to define four terms used regularly in this report to denote different types of product (*see Box 1*).

0.1. THE RESCHEDULING OF CANNABIS-BASED PRODUCTS FOR MEDICINAL USE (CBPM)

The regulatory status of cannabis for medicinal and scientific use has been raised and debated in Parliament since the late 1990s. On November 4, 1998, the Science and Technology Committee

Box 1. Definitions

LICENSED CANNABIS-BASED MEDICINES (L-CBM)	Products with market authorisation from the MHRA for use as a medicine in the UK. This category now includes Nabilone, Sativex, and Epydiolex.
UNLICENSED CANNABIS-BASED PRODUCTS FOR MEDICINAL USE IN HUMANS (U-CBPM)	Products that do not have market authorisation from the MHRA, but which meet the definition of a CBPM in the Misuse of Drugs Regulations 2001 (MDRegs 2001), as amended, and can be prescribed in the UK as 'specials' medicines. All CBPM are Schedule 2 controlled drugs, unless individually rescheduled. While Epidyolex falls within the definition of a CBPM, we will refer to it as a L-CBM in this report in respect of its EU market authorisation. It is highly probable that Epidyolex will be individually rescheduled in early 2020.
CANNABIS-BASED PRODUCTS (CBP)	Although this term in its broadest sense covers all types of product, we primarily use it in this report to denote products which do not have market authorisation and are not prescribed as specials medicines. These include a number of distinct subcategories, including: hemp products; synthetic cannabinoids; black market cannabis products for recreational use; and a variety of products that are not authorised for medicinal use but which are used with medicinal intent. Some CBP are controlled as Schedule 1 drugs, while others are not controlled at all.
MEDICINAL CANNABIS OR CANNABIS-BASED PRODUCTS	An umbrella term for any cannabis-based product used with medicinal intent to meet an unmet clinical need, i.e. any L-CBM, U-CBPM or CBP used for medicinal purposes.

of the House of Lords published *Cannabis: The Scientific and Medical Evidence,* in which evidence was provided that the licensing system and policy associated with the Schedule 1 status of cannabis had impeded clinical research into potential therapeutic benefits. It recommended that the Government should move cannabis and cannabis resin from Schedule 1 of the Misuse of Drugs Regulations 2001 (MDRegs 2001) to Schedule 2, to allow doctors to prescribe unlicensed cannabis-based medicines on a named patient basis.[1] Two weeks later, the Government responded that cannabis should not be available for prescription until there was sufficient evidence on safety, quality and efficacy to award market authorisation to cannabis as a medicinal product.[2] The full response, published in March 1999, clarified that the Government was unwilling to allow cannabis to be prescribed as an unlicensed medicine, stating that "allowing raw cannabis... as a medicine would seriously blur the distinction between misuse and therapeutic use."[3]

Almost exactly twenty years after the publication of the House of Lords Committee's report, on November 1, 2018, the Government decided to take a new approach. The MDRegs 2001 were amended to move CBPM from Schedule 1 to Schedule 2 and allow them to be prescribed as unlicensed medicines by specialist physicians. This move has been described by some outlets, somewhat inaccurately, as the 'legalisation of medical cannabis.'[4][5][6] The decision to reschedule came in response to mounting pressure on ministers to permit medical access to cannabis-based products for young children with severe forms of epilepsy. Several high-profile and emotional stories of young children dramatically increased the urgency and visibility of the two-decade old debate.

Traction had been gaining in Parliament for a change in policy since at least 2015. The All-Party Parliamentary Group on Drug Policy Reform (APPG-DPR) commissioned expert reviews on medicinal cannabis in 2015 and 2016; the former summarising policy options for regulating the medicinal use of CBP and the latter reviewing the evidence for the medicinal use of CBP.[7][8][9] The second review was accompanied by an APPG Inquiry Report calling for a change in the

Events Leading to the Rescheduling of CBPM in 2018

2015

Jun — APPG for Drug Policy Reform publish *Regulating Cannabis for Medical Use in the UK*

2016

May — APPG for Drug Policy Reform publish *Cannabis: The Evidence for Medical Use*

2017

Oct

10th — Paul Flynn MP introduces *Legalisation of Cannabis (Medicinal Purposes) Bill*

2018

Feb

20th — Crispin Blunt MP asks Urgent Question regarding Alfie Dingley

Mar

19th — Alfie's mother, Hannah Deacon, meets the Prime Minister Theresa May

Jun

11th — UK customs officials seize Billy Caldwell's cannabis oil
15th — Billy Caldwell is admitted to hospital
15th — Crispin Blunt MP writes to Home Office and Department of Health Ministers
16th — An emergency Schedule 1 license is issued to return Billy's oil for treatment
18th — Tonia Antoniazzi MP asks Urgent Question regarding Billy Caldwell
18th — Nick Hurd MP announces creation of Expert Panel on cannabis prescription
19th — A Schedule 1 license is issued to allow ongoing treatment for Alfie
19th — Sajid Javid MP announces a two-part review on the rescheduling of CBPM
25th — Professor Dame Sally Davies publishes part 1 of the review
27th — Expert Panel on cannabis-related medicinal products is established

Jul

3rd — Home Office commissions the ACMD to undertake part 2 of the review
18th — APPG on Medical Cannabis Under Prescription is formed
19th — ACMD publishes short-term advice under part 2 of the review
26th — Sajid Javid MP announces the rescheduling of CBPM

Sep

11th — ACMD publishes further advice under part 2 of the review
21st — Sajid Javid MP accepts the recommendations of the ACMD

Nov

1st — CBPM are rescheduled to Schedule 2 under the MDRegs 2001

law to permit medical prescription.[10] The report reviewed a range of policy models and noted that rescheduling with no other reform would leave the majority of patients who might benefit with a number of problems. The following predictions were made:

- rescheduling alone would not improve availability in the short term;
- many patients would be unable to afford private prescriptions;
- there would be few or no new L-CBM that achieve both market authorisation from the MHRA and a recommendation for use in clinical practice from NICE; and that
- existing L-CBM may be unsuitable or inadequate options for many patients.

The APPG's predictions were broadly prescient of the current situation (*see Chapter 1: Routes 1 and 2*).

In October 2017, the late Labour MP for Newport West, Paul Flynn, introduced a private Member's bill for debate in Parliament with the support of 11 MPs from across five political parties. It was titled the *Legalisation of Cannabis (Medicinal Purposes) Bill* (HC Bill 108) and known informally as the 'Elizabeth Price Bill,' in honour of a campaigner for medical cannabis of that name. If it had passed, the bill would have rescheduled all forms of 'Cannabis' and 'cannabis resin' to Schedule 2, but unexpected delays prevented a second reading of the bill before the Parliamentary session ended and it made no further progress.

The debate on medicinal cannabis rapidly gained momentum in the first half of 2018, spurred by a BBC interview in February with Hannah Deacon, whose son, Alfie Dingley, is one of only nine boys worldwide known to have PCDH19 epilepsy. Alfie's rare and serious condition had been causing clusters of seizures on a weekly basis, each time requiring hospitalisation and treatment with intravenous steroids. In desperation, his family turned toward cannabis-based oils. Alfie was ineligible for recruitment into clinical trials in Epidyolex and with no suitable products legally available for prescription in the UK, his family moved to the Netherlands. There, Alfie was given a full-extract oil containing cannabidiol (CBD) and other cannabinoids, supplemented with a second oil containing tetrahydrocannabinol (THC). He went without seizures for 40 days. However, struggling with the costs and difficulty of living abroad, the family returned to the UK in February 2018, determined to find a way to legally continue Alfie's prescriptions.[444]

On February 20, an Urgent Question (UQ) was submitted by the present Chairman of the Conservative Drug Policy Reform Group, Crispin Blunt MP, requesting a statement on Alfie's case from the then-Home Secretary, Amber Rudd. One month later, on March 19, Mrs Deacon met with the then-Prime Minister Theresa May to appeal for legal access. In response, the Prime Minister gave her approval for Alfie's doctors to apply for a Schedule 1 licence to prescribe the cannabis oil in the UK. Since there was no precedent for a Schedule 1 license being issued for use outside research, Alfie's NHS neurologist Prof Mike Barnes worked with Nick Hurd, the minister responsible for drug policy, and his Home Office team to create the application. This process later helped inform the creation of an expert panel of clinicians to advise the Government on individual license applications.

Billy Caldwell, a young child diagnosed with autism and a severe form of epilepsy, had been receiving a CBP on prescription in Northern Ireland to manage his seizures for a year, until the Home Office advised that these prescriptions were unlawful and should cease in April 2018. On June 11, 2018, UK customs officials at Heathrow Airport seized a small supply of medicinal cannabis oil from Billy's mother, Charlotte, as she returned from Canada, where the oil had been prescribed. This seizure was not accidental: Charlotte Caldwell declared the oil at customs and reporters were present throughout the incident.

With no available cannabis-based treatments, Billy was admitted to hospital on the 15th with life-threatening seizures. As public pressure mounted on the Government to return the oil, Mr Blunt wrote to Ministers at the Home Office and Department of Health and Social Care to recommend that the Government commission an urgent review of the legal status of CBP for medicinal use and introduce immediate steps to provide early access in exceptional cases.

What Did the 2018 Amendment Amend?

The Misuse of Drugs Act 1971 lists controlled drugs in three classes and defines criminal offences relating to their cultivation, production, supply, movement or possession (see Annex A for a detailed description of the legal controls on cannabis and cannabis-related products). Cannabis and cannabis products are listed under Class B of the 1971 Act.

Section 7(3) of the 1971 Act requires the Secretary of State (i.e. the Home Secretary) to make regulations to permit the authorised medical use of controlled drugs. The secondary legislation associated with Section 7(3), the Misuse of Drugs Regulations 2001, stipulate the conditions under which the professional use of controlled drugs can lawfully occur. Excepting Sativex and Nabilone, cannabis and cannabis products were wholly listed under Schedule 1 of the 2001 regulations prior to November 2018.

Section 7(4) of the 1971 Act grants the Home Secretary power to designate certain drugs as being exempt from Section 7(3) if "it is in the public interest" to do so. Section 7 (4) provides that, under such circumstances, the "production, supply and possession of that drug to be either wholly unlawful or unlawful except for purposes of research or other special purposes." The Misuse of Drugs Designation Order 2015 lists drugs to which this Section applies, and which may not be used lawfully except under a license or other authority issued by the Home Office. Prior to the 2018 amendment, all cannabis products other than Sativex and Nabilone were designated under Part 1 of the 2015 Order.

Under powers permitted by the 1971 Act, the 2018 amendment moved CBPM, as defined below, from Schedule 1 to Schedule 2 of the 2001 Regulations and from Part 1 to Part 2 of the 2015 Order, permitting their use for medicinal and scientific purposes without a Schedule 1 domestic license.

The definition of a CBPM is as follows: "a preparation or other product," (not being Sativex) "which -

a. is or contains cannabis, cannabis resin, cannabinol or a cannabinol derivative" (not being synthetic dronabinol) "which;
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."

Regulation 16A of the 2001 Regulations, as amended, provides that a CBPM may be ordered and supplied if the product is –

a. "a special medicinal product that –
    i. is not also an investigational medicinal product, but
    ii. is for use in accordance with a prescription or direction of a specialist medical practitioner;
b. an investigational medicinal product without a market authorisation that is for use in a clinical trial; or
c. a medicinal product with a marketing authorisation."

This definition is not limited to unlicensed medicinal products (U-CBPM), which may be supplied as 'specials' medicines, but also includes products that meet the definition and have a market authorisation, unless or until they are individually rescheduled and exempted from the definition. The regulations do not state that the definition of a CBPM is dependent on there being in existence an 'order' or 'prescription' for that product.

The next day, in an unprecedented move, the Home Secretary Sajid Javid issued an emergency licence under s. 7(4) of the Misuse of Drugs Act 1971 to allow Billy to receive treatment at the Chelsea and Westminster Hospital. On the 18th, Tonia Antoniazzi MP submitted an UQ to the Home Office in which she highlighted the cases of constituents who faced similar challenges to Billy's family, and requested clarification from the Government on future licensing policy. In response, Nick Hurd, Home Office Drugs Minister, announced the creation of the aforementioned expert clinical panel to advise on licensing decisions. The panel, which was formally formed on June 27, was chaired by Dr Michael McBride, Chief Medical Officer (CMO) of Northern Ireland. Matt Hancock, the incumbent Health Secretary at the time of writing this report, has since claimed that a "few dozen" special licenses were issued.[11]

On June 19, Alfie Dingley's doctors received a Schedule 1 license to enable the ongoing prescription of an unlicensed cannabis product - the first of its kind in the UK. Under this licence, medical cannabis oil was legally brought into the country for the first time on July 10. On the same day that Alfie's license was awarded, the Home Secretary announced that Professor Dame Sally Davies, CMO for England, and the Advisory Council on the Misuse of Drugs (ACMD) had been commissioned for a two-part review on the rescheduling of cannabis and cannabis related products. The CMO's report, published under Part 1 of the review on the 25th of that month, found "conclusive evidence of the therapeutic benefit of cannabis based medicinal products for certain medical conditions and reasonable evidence of therapeutic benefit in several other medical conditions."[12] It recommended that CBPM, including synthetic cannabinoids, should be moved out of Schedule 1.

On July 19, the day after the launch of the APPG for Medicinal Cannabis under Prescription, the ACMD published their short-term advice under Part 2 of the review.[13] The advice contained four recommendations and three conclusions, in effect suggesting that a narrowly defined category of CBPM should be moved into Schedule 2, but that all CBP falling outside that category, including synthetic cannabinoids, should remain in Schedule 1. On the basis of these reviews, the Home Secretary formally announced the rescheduling of CBPM from Schedule 1 to Schedule 2 on July 26.[14]

Further recommendations on the design and implementation of the proposed change in law were offered over the following months in correspondence between the ACMD and the Home Office.[15] On November 1, CBPM were officially defined and rescheduled by Statutory Instrument 2018/1055, a piece of secondary legislation issued by the Home Office to amend the Misuse of Drugs Regulations 2001, referred to throughout this paper as the '2018 amendment.'[16] On the same day that the amendment came into effect, Alfie Dingley received the first legal NHS prescription to be issued for an U-CBPM without a Schedule 1 license.

This amendment did not affect the scheduling status of L-CBM, namely Sativex and Nabilone, which had already been individually rescheduled shortly after receiving market authorisation in the UK (*see Chapter 1: Route 1*). The following subsection provides a brief overview of the important differences between licensed and unlicensed medicines.

0.2. UNDERSTANDING LICENSED AND UNLICENSED MEDICINES

Medicinal products require a marketing authorisation (or 'product license') from the Medicines and Healthcare products Regulatory Agency (MHRA) or the European Medicines Agency (EMA) before they can be marketed in the UK (*see Annex A: Human Medicines Regulations 2012 for the legal definition of 'medicinal product'*).[17] This license determines the medical conditions and patient groups for which the product can be prescribed. New medicinal products must meet rigorous standards of evidence on safety, quality and efficacy to achieve a product licence, and consequently it is only licensed products on which medical claims can lawfully be made.

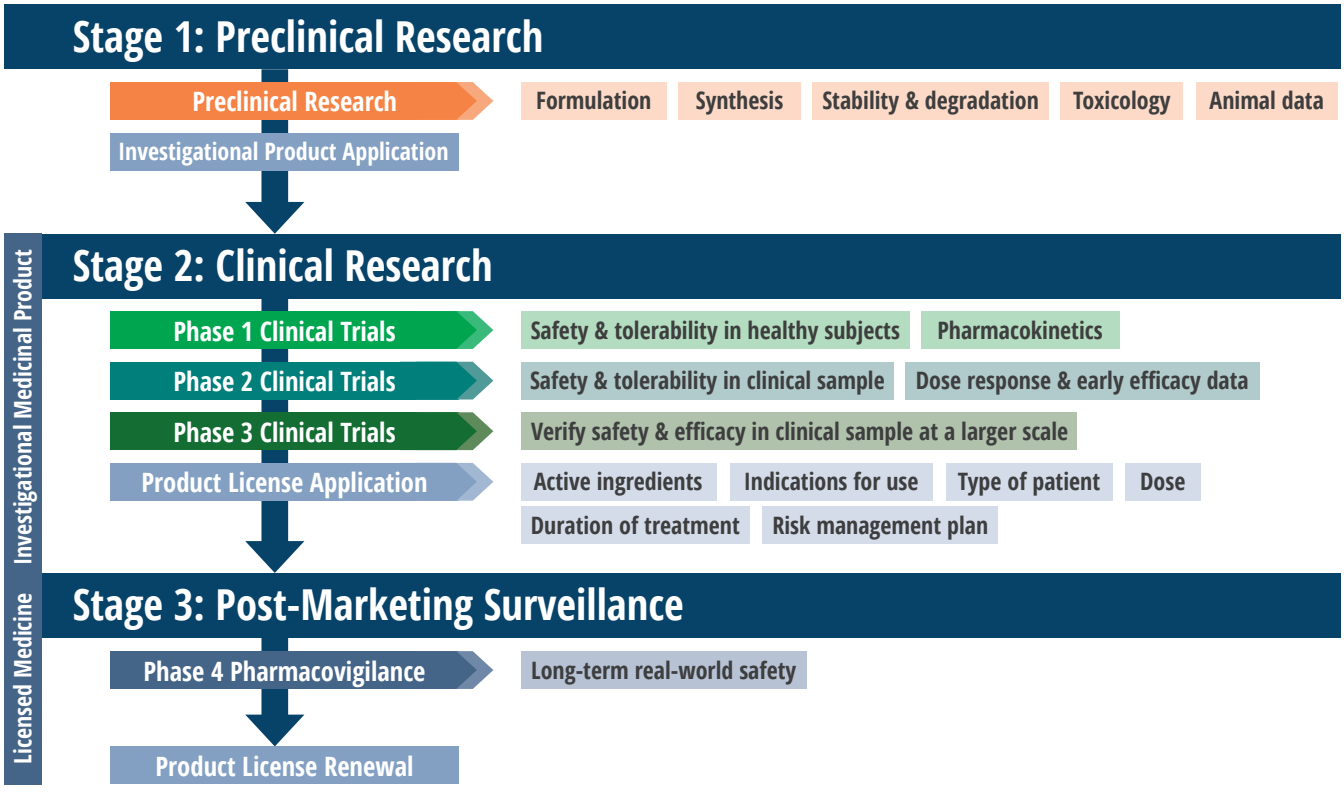
Licence applications evaluate the safety, efficacy and quality of the medicinal product. The product must perform significantly better than placebo in treating the disease or condition of interest, but it does not need to be more effective than existing treatments. The assessment of a product's safety takes into consideration both the potential risks associated with the medical condition for which the treatment is intended

and the risk profile of other treatments licensed for that medical condition. Quality evaluation is intended to ensure that the product can be reliably manufactured to consistent standards and retains that quality standard over the duration of its shelf life. Applications for a medicinal product license must provide a risk management plan including existing safety data, missing safety data (e.g. patient populations not included in the clinical trials to date), additional pharmacovigilance research required to inform potential product harms after marketing authorisation, and a risk minimisation strategy to limit potential harms.[18]

The gold-standard methodology for assessing the safety, efficacy and quality of a medicinal product is through large-scale, multi-site randomised double/triple-blind controlled trials. It is typically expected that medicinal product applications are supported by data from these types of study. In randomised controlled trials (RCTs), a number of people are randomly assigned to groups in order to test the effects of a specific intervention. People in the 'study group' receive the drug or intervention being tested and those in the 'control group' receive either a placebo treatment or an existing treatment known to be effective in the treatment of the indication in question. Well-controlled studies are 'blinded,' meaning that neither the study participants nor the administering clinicians know who has been assigned to which group, reducing potential biases that may affect results. The statistical robustness of the findings of a trial increases with larger study sample sizes and minimisation of compounding factors.

Study drugs must be registered as 'investigational medicinal products' (IMPs) for use in clinical trials in humans. The application process requires the submission of an IMP dossier containing information on quality and manufacture of a product, including any non-clinical or pre-clinical data. Clinical research on IMPs typically follows a three-phase process. Phase 1 clinical trials are 'first-in-human' studies, testing the safety, side-effects, activity and metabolism of the drug in humans. These studies are often unblinded 'open-label' studies, meaning that participants are aware that they are receiving the active drug. Phase 2 studies are usually randomised and placebo-controlled, designed to investigate the safety and tolerability of the drug in a small sample of patients with the disease or medical condition for which it is intended that the treatment is to be used. These studies are not designed to produce high-quality data on the

Figure 1. Stages of Drug Development



effectiveness of the drug, but in the absence of any evidence of efficacy at this stage it is unlikely that the drug sponsor will pursue further clinical research. Phase 3 studies are large scale RCTs, often involving hundreds of patients, typically conducted at a number of different sites to improve the quality of sampling. These studies are designed to provide evidence to verify the safety and efficacy in patient populations.

Product licenses determine how a product can be used, but do not limit what the medicine can be prescribed for, or to whom, on an 'off-label' basis. Off-label use refers to the use of a licensed medicine outside the remit of its product licence, for instance in an age group or medicinal condition which is not described in the terms of its market authorisation.

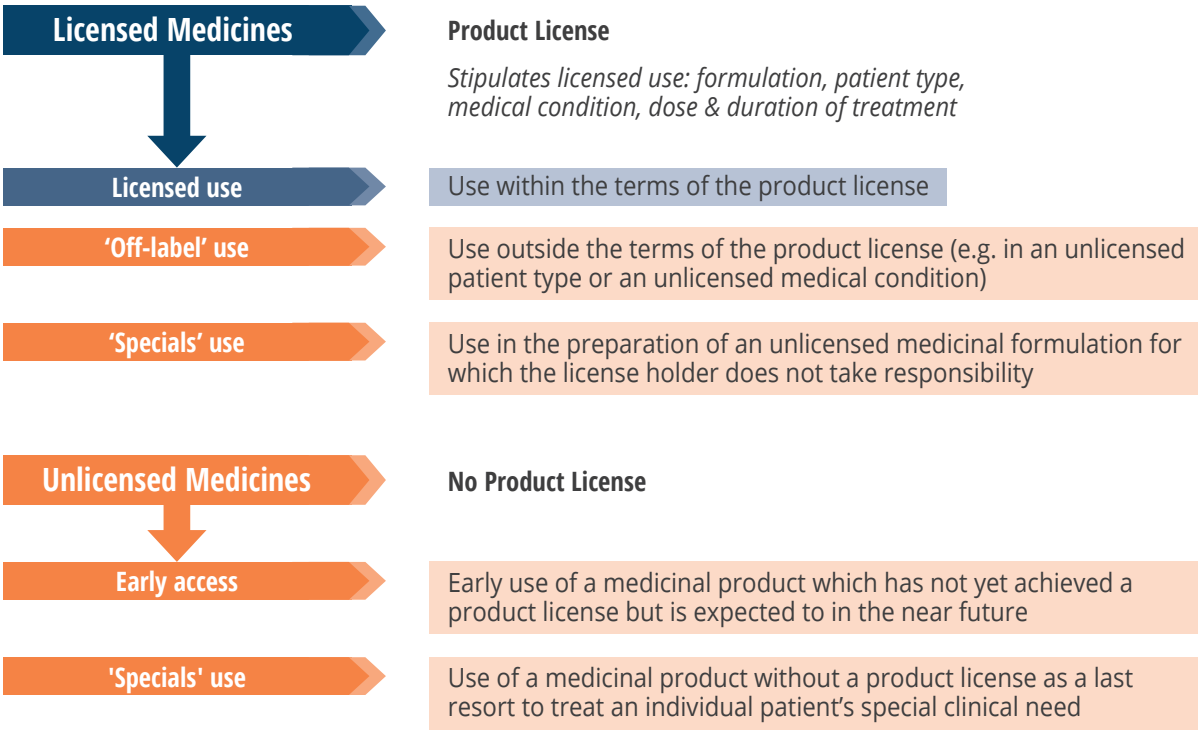
A licensed medicine can also be used in the preparation of a 'specials' medicine - a product for medicinal use that has no license but for which an individual patient has a special clinical need. For instance, a patient with a naso-gastric tube may require a liquid formulation of a medicine only licensed in solid forms; or a child may require a specially prepared pill containing a medicine that is only licensed in larger dose sizes for adult use. When a medicine is used either off-label or as part of a specials medicine, it is commonly referred to as an unlicensed medicine.

The term 'unlicensed medicine' can also refer to medicinal products with no product licenses at all, regardless of formulation, patient type or medical condition, that may nonetheless be prescribed as 'specials' (i.e. to meet the special clinical needs of an individual patient for whom no other treatments have been adequate). Specials medicines may be imported from a country in which they do have licenses for medicinal use, or may be unlicensed both in the UK and in the country of production.

In some instances, an IMP that is already supported by an adequate evidence base on safety, quality and efficacy, and which is in the process of applying for market authorisation, may be prescribed as an unlicensed medicine as part of an 'early access scheme.'

There are a range of distinct cannabis-based medicinal products that fall into each of these categories mentioned above and it is important to be specific when using terms such as 'medicinal cannabis,' 'cannabis-based medicine' (L-CBM), 'cannabis based product for medicinal use' (CBPM), or 'cannabis-based product' (CBP), since there are significant differences between the products available.

Figure 2. Medicinal Product Licenses



Box 2. Licenses

At various points in this report we refer to products, places and people as being 'licensed.' There are distinct types of license relevant to cannabis policy, issued by different authorities for different purposes, and confusion awaits the reader who does not bear this in mind.

For instance, a cannabis plant may be grown under a Home Office high-THC cultivation license; the flowers of that plant may be held and processed at a site under Home Office Schedule 1 possession and manufacture licenses; and may be transported as ingredients to a specials manufacturer for the production of a CBPM under Home Office Schedule 1 or 2 licenses, an MHRA Wholesaler Dealer's License, and an MHRA Manufacturer's (Specials) License. If a manufacturer imports a cannabis-based product from abroad they require a Home Office Schedule 1 or 2 import license in addition to domestic Home Office licenses and MHRA licenses.

However, if the medicinal product that emerged from this fully licensed supply chain did not have market authorisation for use in the UK, it would be an unlicensed medicinal product.

0.3. THE RANGE OF CANNABIS-BASED PRODUCTS IN THE UK

On the basis of the laws and regulations described in Annex A, we have identified 17 categories of cannabis-based products, distinct from one another in terms of form, quality, potential harms and therapeutic value, intended use, and/or regulatory control:

1. Cannabis or cannabis resin (unless exempt and in Categories 4, 5, 6, or 16)
2. Controlled cannabinoids and -containing products (unless exempt and in Categories 4, 5, or 6)
3. Synthetic cannabinoids (unless exempt and in Categories 7 or 8)
4. CBPM 'specials' containing Category 1 or 2 items
5. API containing Category 1 or 2 items
6. IMP containing Category 1 or 2 items
7. Synthetic L-CBM with market authorisation
8. Synthetic CBM without market authorisation in the UK
9. Plant-derived L-CBM with market authorisation (Schedule 4)
10. Plant-derived L-CBM with market authorisation (Schedule under review)
11. Pure non-controlled cannabinoids
12. Non-medical, non-controlled products containing Category 11 items
13. Non-controlled API containing Category 11 items
14. Non-controlled 'specials' medicines containing Category 11 items
15. Non-controlled IMP containing Category 11 items
16. Non-controlled parts of the cannabis plant after separation
17. Commercial products derived from Category 16 items

These categories, which are defined and explained in detail in Annex B, can be sorted into three parent categories, as follows:

0.3.1. LICENSED CANNABIS-BASED MEDICINES (L-CBM)

There are three CBM currently licensed for use in the UK: Nabilone (Cat. 7), Sativex (Cat. 9), and Epidyolex (Cat. 10) (*see Table 1 and Annex*

B for more details). L-CBM are covered in detail in Chapter 1, Route 1. These products have a robust evidence-base on safety, quality and efficacy and can be prescribed in the UK under the terms of their license, used off-label as unlicensed medicines, or used as ingredients in the production of unlicensed CBPM (U-CBPM).

GW Pharmaceuticals, the company that brought both Sativex and Epidyolex to market, have reported that their clinical trials have involved almost 6,000 patients globally and that more than 80,000 years of human safety data have been collected.[19]

Table 1. Licensed cannabis-based medicines (L-CBM)

			Legislative Classification					Regulatory Controls	
#	Category Description	Example	MDA 1971 (as amended), Class	MDRegs 2001 (as amended), Schedule	Rescheduled by SI 2018/1055?	MHRA Market Authorisation	May be prescribed (outside of research)	Circumstances under which authorizedactions may occur (MDRegs, 2001)	Criminal penalties for unauthorized actions (MDA, 1971)
7	Synthetic L-CBM with market authorisation	*Nabilone* (THC-type)	B	2	✗	✓	✓	May be procured and prescribed, subject to terms of licensing, Schedule 2 controls.	Unauthorized actions (i.e. production, importation, exportation, supply, or possession without authorisation, or provision of premises for unauthorized actions)may incur penalties including up to 14 years imprisonment.
9	Plant-derived L-CBM with market authorisation	*Sativex* (CBD:THC)	B	4	✗	✓	✓	May be procured and prescribed, subject to terms of licensing & Schedule 4 controls.	
10	Plant-derived L-CBM with market authorisation	*Epidyolex* (CBD) Contains trace levels of THC.	B	?	✗	✓	✓	May be procured and prescribed, subject to terms of licensing, Reg 16A & Schedule 2 controls. The scheduling status of Epidyolex is currently under review.	

0.3.2. UNLICENSED CANNABIS-BASED PRODUCTS FOR MEDICINAL USE (U-CBPM)

We distinguish between seven categories of U-CBPM (*see Table 2 and Annex B for further details*). These include three categories rescheduled by the 2018 amendment: U-CBPM for use as 'specials' medicines (Cat. 4), IMP for use in a clinical trial (Cat. 6), and ingredients for the production of either of the above (Cat. 5). Regulation 16A of the 2001 Regulations limits the lawful supply of U-CBPM to that which is in accordance with the prescription or direction of a specialist doctor. U-CBPM are covered in detail in Chapter 1, Route 2.

In addition, we identify constituents of cannabis which are not controlled by the 1971 Act or the 2001 Regulations (though some may be covered under the Psychoactive Substances Act 2016). Medicinal products that contain no controlled drugs can also be prescribed as specials medicines (Cat. 14), used in the preparations of medicinal products (Cat. 13) or used in a clinical trial (Cat. 15), but are not subject to the statutory requirements that limit the order and supply of Cat. 4 U-CBPM to the direction of specialist doctors.

Dronabinol (Cat. 8), a synthetic form of THC, is licensed as a medicine in the US, Canada,

Germany, Australia and New Zealand, but does not have market authorisation from the MHRA or the EMA. It is technically not a CBPM under the MDRegs 2001 definition, but since it is under Schedule 2 and without market authorisation for use in the UK, we include it in this parent category. Dronabinol has a robust evidence base on safety, quality and efficacy. It can be prescribed as a specials medicine by any authorised prescriber according to ordinary specials regulations, or used in the production of a Cat. 4 medicinal product. In this context, 'Dronabinol' refers to a synthetic THC formulation, although the term is also used sometimes to refer to plant-derived THC (e.g. the British National Formulary lists the ingredients of Sativex as 'dronabinol' and 'cannabidiol').

Table 2. Unlicensed cannabis-based products for medicinal use (U-CBPM)

			Legislative Classification					Regulatory Controls	
#	Category Description	Example	MDA 1971 (as amended), Class	MDRegs 2001 (as amended), Schedule	Rescheduled by SI 2018/1055?	MHRA Market Authorisation	May be prescribed (outside of research)	Circumstances under which authorizedactions may occur (MDRegs, 2001)	Criminal penalties for unauthorized actions (MDA, 1971)
4	CBPM 'specials' containing Category 1 or 2 items	GMP-grade product ranges by Bedrocan, Tilray, Aurora, etc.	B	2	✓	✗	✓	May be produced, procured and prescribed as 'specials medicines,' subject to Schedule 2 & specials regulations with statutory restrictions.	Unauthorized actions (i.e. production, importation, exportation, supply, or possession without authorisation, or provision of premises for unauthorized actions)may incur penal-ties including up to 14 years imprison-ment.
5	API containing Category 1 or 2 items	GMP-grade product ranges by Bedrocan, Tilray, Aurora, etc.	B	2	✓	✗	✗	May be produced, procured and used in the manufacture of a Category 4 item, subject to Schedule 1 or 2 regulations with statutory restrictions.	
6	IMP containing Category 1 or 2 items	Approved IMP administered in an authorized clinical trial	B	2	✓	✗	✗	May be produced, procured and prescribed as 'specials medicines,' subject to Schedule 2 & specials regulations with statutory restrictions. Must have an IMP dossier & Clinical Trials Authorisation (CTA).	
8	Synthetic CBM without market authorisation in the UK	Dronabinol (THC)	B	2	✗	✗	✓	May be procured and prescribed as a 'specials medicine,' subject to Schedule 2 and specials regulations.	
13	Non-controlled API containing pure non-controlled cannabinoids (Category 11)	Isolates of Category 11 items for use in the preparation of a medicinal product	✗	✗	✗	✗	✗	May be produced, procured and used in the manufacture of a Category 14 item, subject to Specials regulations.	
14	Non-controlled 'specials' medicines containing Category 11 items.	GMP-grade product ranges manufactured from Category 13 items	✗	✗	✗	✗	✓	May be prescribed as 'specials' medicines, subject to specials regulations.	
15	Non-controlled IMP containing Category 11 items	Approved IMP administered inan authorized clinical trial.	✗	✗	✗	✗	✗	May be produced, procured and administered as part of a clinical trial. Must have an IMP dossier & Clinical Trials Authorisation (CTA).	

0.3.3. CANNABIS-BASED PRODUCTS NOT AUTHORISED FOR MEDICINAL USE (CBP)

We identify seven categories of CBP which are not authorised for medicinal use (*see Table 3 and Annex B for further details*). Products include raw cannabis and cannabis resin, such as living plants or black-market products (Cat. 1); controlled cannabinoids (Cat. 2); new psychoactive substances containing synthetic cannabinoids (Cat. 3); non-controlled cannabinoids, such as CBD (Cat. 11); cannabinoid-based food supplements sold on the 'wellness market' (Cat. 12); seeds and stalk from plants after separation (Cat. 16); and products made from the seeds and stalk, such as hemp rope or hemp flour (Cat. 17). Only some of the products in this parent category are controlled under the Misuse of Drugs Act 1971 and the Misuse of Drugs Regulations 2001.

Table 3. Cannabis-based products not authorised for medicinal use (CBP)

			Legislative Classification					Regulatory Controls	
#	Category Description	Example	MDA 1971 (as amended), Class	MDRegs 2001 (as amended), Schedule	Rescheduled by SI 2018/1052?	MHRA Market Authorisation	May be prescribed (outside of research)	Circumstances under which authorizedactions may occur (MDRegs, 2001)	Criminal penalties for unauthorized actions (MDA, 1971)
1	Cannabis or cannabis resin (unless exempt and in Categories 4, 5, 6, or 16)	Cannabis items not authorized for medical use	B	1	✗	✗	✗	May be produced with a Home Office high-THC cultivation license. May be used for research purposes with a Home Office Schedule 1 license.	Unauthorized actions (i.e. production, importation, exportation, supply, or possession without authorisation, or provision of premises for unauthorized actions)may incur penal-ties including up to 14 years imprison-ment.
2	Controlled cannabinoids and -containing products (unless exempt and in Categories 4, 5, or 6)	CBN-type compounds, including THC-type compounds (e.g. THCV)	B	1	✗	✗	✗	May be used for research purposes with a Home Office Schedule 1 license.	
3	Synthetic cannabinoids (unless exempt and in Categories 7 or 8)	JWH-018, AM-2201, UR-144, XLR-11, PB-22, 5F-PB-22, APICA	B	1	✗	✗	✗	May be used for research purposes with a Home Office Schedule 1 license.	
11	Pure non-controlled cannabinoids	CBG-, CBC-, CBD-, CBF-, CBDL-, CBL-, CBT- and CBE-type compounds	✗	✗	✗	✗	✗	May be prepared, supplied and possessed without a license. No medical claims can be made. Must meet all three limbs of an exempt product under MDRegs 2001.	
12	Non-medical, non-controlled products containing Category 11 items	CBD-containing products on the 'wellness market'	✗	✗	✗	✗	✗	May be prepared, supplied and possessed without a license. No medical claims can be made. Must meet all three limbs of an exempt product under MDRegs 2001. Consumables must have Novel Foods authorisation.	
16	Non-controlled parts of the Cannabis plant after separation.	Seeds, mature stalk and stalk fibre	✗	✗	✗	✗	✗	May be removed from plants cultivated or imported under a Home Office license. May be supplied and possessed within the UK without a license.	
17	Commercial products derived from Category 16 items.	Hemp seed oil, hemp flour, animal feed	✗	✗	✗	✗	✗	May be prepared and supplied from Category 16 items, subject to food regulations. May be supplied and possessed without a license.	

CHAPTER 1

Lawful Routes of Access to Cannabis-Based Products

There are three routes via which eligible patients can access cannabis-based medicinal products legally in the UK:

1. a prescription for cannabis-based medicines with product licenses (L-CBM);

2. a prescription for unlicensed cannabis-based 'specials' medicines (U-CBPM) on:
    a. the NHS; or
    b. private healthcare;

3. provision of a cannabis-based investigational medicinal product (IMP) as part of a clinical trial.

An additional route to legally access U-CBPM exists but will not affect most UK patients. It is lawful for individuals to import controlled drugs on their person into the UK, but only if the product has been lawfully prescribed in the individual's country of habitual residence. If an individual wishes to import more than a three month supply, they are required to apply for a personal controlled drug license from the Home Office.[20] This policy does not apply to individuals habitually resident in the UK. Since this exemption is likely to only affect overseas residents staying in the UK for a short period, it is not addressed further as a route of access. Unlawful importation of U-CBPM is covered briefly in Chapter 2.

There is also a rather ambiguous, but rapidly developing, market in non-controlled, non-medicinal CBP, such as CBD oils:

4. non-controlled cannabis-based products available to consumers in the health and wellness sector.

These products are non-medicinal, meaning that they do not have market authorisation for medicinal use, are not prescribed through the specials route, and suppliers cannot make claims of medicinal benefit. Nonetheless, consumers report using these products with medicinal intent. A poll conducted by Dynata in 2019, for the Centre for Medicinal Cannabis (CMC), revealed that consumers were using CBD products for overall health and wellbeing (54%), sleep (54%), pain management (42%) and anxiety management (38%).[21] The market is ambiguous because, despite substantial public popularity, there is confusion over the legal and regulatory framework controlling the market. Many widely available products are, technically, controlled drugs under the Misuse of Drugs Act 1971 and the Misuse of Drugs Regulations 2001, and are, therefore, unlawful to supply or possess without Home Office licenses. Other products on the market contain lower concentrations of CBD than advertised, and some have been found to contain none at all. Access to these products is discussed in Route 4.

At present, there are few individuals successfully achieving access through routes 1 – 3. The Impact Assessment attached to the 2018 amendment foresaw low levels of access to U-CBPM in the first year, predicting that a maximum of 757 patients could expect to receive a prescription (0.25% of the total central estimate of case volume after ten years).[22] This figure assumed that 100% of cases were considered cost-effective. Considering that guidelines published by NICE make no recommendations for the cost-effectiveness or use of U-CBPM, the low rates of prescription observed in the first year were in line with predictions.

Although low rates of prescribing were predicted, poor communication to the public about what the amendment would mean in practice led to various unintended outcomes, including raised expectations among patients and their families, increased requests for cannabis-based medicines, and a negative impact on patient-doctor relationships. Some clinicians have since reported that up to 80% of their clinic time is now taken up explaining to patients that U-CBPM are not yet freely available on the NHS.[23] We have been informed by a member of the ACMD that the decision to change the law quickly and let the NHS work out the details in practice was an active choice, intended to improve immediate access for those in most need. The alternative choice was to work with NHS and other stakeholders to design access models in advance of rescheduling, but this would have delayed the change in the law.

An overview of prescribing rates for L-CBM and U-CBPM in the year following the 2018 amendment is provided in Tables 4 and 6. NICE did not recommend the use of Sativex until guidelines were updated in November 2019; nonetheless, rates of prescription

for both Sativex and Nabilone substantially exceeded rates of prescription for unlicensed cannabis-based specials medicines. This is in accordance with MHRA prescribing guidelines, which recommend the use of licensed and off-label treatments before considering a specials medicine.[24]

The total number of prescriptions known to have been issued between November 2018 – October 2019 amounts to **6,926**, accounting for products with and without market authorisation, prescribed either on the NHS or in the private sector, and dispensed by either community or hospital pharmacies. Sativex and Nabilone accounted for **92%** of total prescriptions.

Table 4. Prescribing rates for licensed and unlicensed CBPM in the year following the 2018 amendment

	Total number of prescriptions known to have been issued from Nov '18 – Oct '19
Nabilone	2,329
Sativex	4,016
Epydiolex	377
Unlicensed CBPM	204
Total	6,926

U-CBPM, excluding Epidyolex, which was unlicensed for most of the time period, accounted for only **3%** of prescriptions.

185 patients received Epidyolex on prescription through an early access programme which closed in September 2019. The total numbers of patients who have received other L-CBM or CBPM is unknown. Department of Health minister, Jo Churchill, has said: "The NHS Business Services Authority does not hold information on the number of patients able to access medicinal cannabis on the National Health Service, and therefore this information is not held centrally." [27] However, the numbers of people in receipt of a prescription for a medicinal product per month will not exceed the total number of prescriptions issued for that product each month.

The total quantities of product associated with 18 NHS prescriptions for U-CBPM known to have been dispensed in the community between November 2018 and September 2019 are provided in Table 5.[28]

Prescribing data from the private sector covers only England (NHSBSA ePACT2), while NHS community data covers England and Wales (NHSBSA Prescription Cost Analysis, Copyright 2019). The values provided represent the number of times a product appears on a prescription form, not the quantity prescribed.

Table 5. The total quantities of product associated with 18 NHS prescriptions for U-CBPM known to have been dispensed in the community between November 2018 and September 2019

PRODUCT NAME	MANUFACTURER	TOTAL QUANTITY (ML)	CONTENTS
Bedrolite 10%	Bedrocan	1,270	CBD: 10% / THC: <0.01%
Bedica 2%	Bedrocan	70	THC: 2% / CBD: <0.1%

This data was provided in a response to an FOI available at: https://apps.nhsbsa.nhs.uk/FOIrequests/requests/FOI_Request_(08823).csv Copyright NHSBSA 2019.

Table 6. Prescribing rates for licensed and unlicensed CBPM in the year following the 2018 amendment

	NHS								PRIVATE PRACTICE			
	Community pharmacies				Hospital pharmacies				Community pharmacies			
	Nabilone	Sativex	Epidyolex	U-CBPM	Nabilone	Sativex	Epidyolex	U-CBPM	Nabilone	Sativex	Epidyolex	U-CBPM
Nov-18	46†	175†	n.d.	2§	143±	177±	15±	0±	0‡	1‡	0‡	0§
Dec-18	49†	181†	n.d.	1§	135±	146±	13±	0±	0‡	6‡	0‡	0§
Jan-19	44†	167†	n.d.	2§	149±	169±	12±	0±	0‡	5‡	0‡	4§
Feb-19	36†	159†	n.d.	1§	145±	166±	15±	0±	0‡	3‡	1‡	2§
Mar-19	51†	171†	n.d.	2§	163±	148±	20±	0±	0‡	3‡	0‡	6§
Apr-19	49†	156†	n.d.	2§	144±	180±	20±	0±	1‡	2‡	0‡	13§
May-19	49†	176†	n.d.	2§	146±	173±	31±	0±	0‡	2‡	0‡	13§
Jun-19	57†	187†	n.d.	2§	129±	208±	27±	0±	0‡	3‡	0‡	22§
Jul-19	54†	158†	n.d.	2§	154±	159±	28±	0±	0‡	2‡	0‡	26§
Aug-19	46†	174†	n.d	1§	137±	161±	45±	0±	0‡	3‡	0‡	27§
Sep-19	58†	179†	0°	1§	141±	167±	35±	9±	0‡	4‡	0‡	28§
Oct-19	46†	173†	0°	1°	n.d.	n.d.	n.d.	n.d.	0*	1*	0*	33*
Unspecified month (Nov 18-Oct 19)	-	-	-	-	157±	71±	115±	2±	-	-	-	-
Subtotal	585	2,056	0	19	1,743	1,925	376	11	1	35	1	174

n.d. = No data available.

† *Data from NHSBSA Prescription Cost Analysis (PCA) data, available at: https://www.nhsbsa.nhs.uk/prescription-data/dispensing-data/prescription-cost-analysis-pca-data. Information is copyright NHSBSA PCA 2018/19.*

‡ *Data from FOI available at: https://apps.nhsbsa.nhs.uk/FOI/foiRequestDetail.do?bo_id=8823. Information is copyright NHSBSA ePACT2 2019.*

§ *Data from FOI available at: https://apps.nhsbsa.nhs.uk/FOI/foiRequestDetail.do?bo_id=8823.Information is copyright NHSBSA 2019.*

* *Cannabis: Medical Treatments. (HC Deb 30 January 2020 c 6669W) https://www.parliament.uk/business/publications/written-questions-answers-statements/written-question/Commons/2020-01-22/6669/*

° *Cannabis: Medical Treatments. (HC Deb 23 January 2020 c 3830W) https://www.parliament.uk/business/publications/written-questions-answers-statements/written-question/Commons/2020-01-15/3830/*

± *Data compiled from FOI requests sent by the CDPRG to every UK hospital trust.*

Data from NHSBSA does not include prescriptions for cannabis-based medicines issued and dispensed in hospitals, and, at present, there is no central prescription level data system for hospitals in the UK. To build a more complete picture of NHS prescribing, we sent FOI requests to every acute NHS Trust in the country to request the number of prescriptions issued and dispensed within hospitals between November 2018 and September 2019. Of the 134 Trusts that acknowledged receipt of the request, 127 provided prescribing data. Four Trusts withheld data, either on grounds of confidentiality or because they did not record prescription numbers, and three Trusts did not provide data before the publication of this report.

Some Trusts withheld complete data on the basis that only a few prescriptions had been issued in that time and that information could not be provided without compromising patient confidentiality. In some cases, prescribing data for a given drug in a given month was provided as "<5." In these instances, we entered the data as "1,' as the minimum verifiable number. Data on the number of prescriptions was not held by all Trusts and we were occasionally provided data on the number of packs issued instead. We entered this data as the minimum verifiable number of prescriptions. For these reasons, our hospital prescribing data may underestimate the true figure.

Although some Trusts also provided data for October and November 2019, most did not. As we knew our data for those months would be incomplete, we have not included them in this report. It is also worth noting that some Trusts included prescribing data from clinical trials and early access programmes, while other Trusts excluded these data. Therefore, the numbers provided should only be considered a rough estimate of total prescriptions in the UK. Prescriptions of Epidyolex issued prior to market authorisation appear in the column for that drug and are not included in the figures for U-CBPM.
The following sections provide detailed reviews of access to L-CBM and U-CBPM in the 12 months following the 2018 amendment. We provide a breakdown of the processes involved in prescribing and the major challenges facing access on each route.

1.1. ROUTE 1: LICENSED CANNABIS-BASED MEDICINES (L-CBM)

As of December 2019, three CBPM have achieved status as a licensed medicine for use in the UK: the plant-derived medicines Sativex and Epidyolex, and the synthetic cannabinoid medicine Nabilone. The scheduling statuses of Sativex and Nabilone under the MDRegs 2001 were not affected by the 2018 amendment, since Nabilone had been individually rescheduled to Schedule 2 in 2009,[29] and Sativex rescheduled to Schedule 4 in 2013.[30]

Epidyolex contains mostly CBD, which has never been controlled by the MDA 1971 or the MDRegs 2001, but it also contains trace levels of THC as an impurity (limited to <0.1% w/w).[31] It was granted a product license by the EMA in late 2019. NHS England report that prior to licensing, Epidyolex was considered an 'exempt product' under the MDRegs 2001 and, accordingly, was not a controlled drug.[32] However, guidance from individual NHS Trusts indicates that Epidyolex was treated as a Schedule 2 drug in some parts of the country.[33] Now that Epidyolex has received market authorisation, NHS England and the Home Office report that Epidyolex is controlled under Schedule 2 as a cannabis-based product for medicinal use under the MDRegs, as defined by the 2018 amendment. [34]

The manufacturer of Epidyolex, GW Pharmaceuticals, have been in discussions with the Home Office concerning rescheduling to a lower level of control since market authorisation was granted. The MDA 1971 requires the Home Office to consult the Advisory Council on the Misuse of Drugs (ACMD) before scheduling decisions are made and an ACMD dossier on Epidyolex has been submitted to the Home Office, followed by a letter on 29 January 2020.[35] The letter advised that Epidyolex "has a low risk of abuse potential, low risk of dependency and low risk of diversion." Until the Home Office make a final decision, its scheduling status is presently unclear – but we would predict that it will be relisted under Schedule 5 in 2020, as per the recommendations of the ACMD. The definition proposed by the Council was as follows:
"A liquid formulation -

1. containing cannabidiol obtained by extraction and purification from Cannabis;

Table 7. Cannabis-based medicines with market authorisation in the UK

	SATIVEX	EPIDYOLEX	NABILONE
Product type	Plant-based medicine	Plant-based medicine	Synthetic medicine
Formulation	Oromucosal spray	Oral solution	Capsule
Cannabinoid profile	1:1 ratio THC:CBD	CBD	Synthetic THC-type
Licensed indications	Severe-to-moderate spasticity in Multiple Sclerosis (MS)	Seizures in Lennox-Gastaut syndrome and Dravet syndrome	Chemotherapy-induced nausea and vomiting
NICE recommendation	Guidelines: Offer a trial to adults who have not responded adequately to conventional treatment	Technology appraisal: Offer as an add-on treatment to people two years old and above who have not responded adequately to conventional treatment	Guidelines: Offer as an add-on treatment in people who have not responded adequately to conventional treatment
MDA Classification	Class B	Class B	Class B
MDRegs Schedule	Schedule 4	Under review	Schedule 2
Prescriptions issued: Nov 18 – Oct 19	4,016	377	2,329

2. where the concentration of—
   i. delta-9-tetrahydrocannabinol is not more than 0.1 milligram per millilitre; and
   ii. cannabidiol is 95 - 105 milligrams per millilitre; and
3. which is presented in a bottle, as an oral solution for oral administration; and

which was approved for marketing by the European Commission on 19th September 2019."

1.1.1. PRESCRIBING, PROCURING AND DISPENSING LICENSED CANNABIS-BASED MEDICINES

Sativex (Bayer Plc), an oromucosal spray containing THC and CBD in a 1:1 ratio, is licenced for symptom management in multiple sclerosis (MS). Until November 2019, Sativex was not considered a cost-effective treatment by NICE and thus not recommended for routine clinical use in England, though its use was recommended by the All Wales Medicines Strategy Group. Since November 2019, NICE have recommended offering a 4-week trial of Sativex to treat moderate to severe spasticity in adults with MS if other treatments have not been effective and if the company provides the product according to a pay-for-responders scheme (by which 3 x 10ml vials are funded by the company if there is an agreement for continued funding for patients who respond to treatment, as defined by a 20% or greater reduction in symptoms on a patient-reported scale).[36]

Epidyolex (GW Pharmaceuticals), an oral solution containing CBD, was granted Orphan Drug Designation by the European Medicines Agency (EMA) on 23 September, 2019. This decision is valid in all 28 countries of the European Union. It is licensed for adjunctive use in conjunction with

clobazam in the treatment of seizures in patients with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) – making it the first plant-derived cannabis-based medicine to achieve approval by the EMA.[37] GW had previously been granted Orphan Drug Designation for CBD for the treatment of perinatal asphyxia in July 2015.[38] NICE Technology Appraisal guidance published 18 December, 2019, recommended the use of Epidyolex with clobazam in the treatment of LGS and DS, if seizures have not been adequately controlled with at least two antiepileptic drugs. An early access programme facilitated NHS prescriptions of Epidyolex prior to the EMA's decision and, according to the Department of Health and Social Care (DHSC), 185 patients had achieved access by this means as of early September, 2019.[39]

Nabilone (Brown & Burk UK Ltd), a capsule containing a synthetic THC-type cannabinoid, is licensed for the treatment of nausea and vomiting induced by chemotherapy. NICE recommend that Nabilone should be considered as an add-on treatment for adults where conventional therapies have failed to meet the patient's clinical need.

Since all published guidelines on the supply of specials medicines - including those issued by the MHRA, the Royal Pharmaceutical Society, and the General Medical Council - recommend the off-label use of licensed treatments over the use of unlicensed, it would have been reasonable to expect the surge in patient demand for U-CBPM, as was reported by prescribers following the 2018 rescheduling amendment, to lead to higher rates of prescriptions for L-CBM. However, there is no data to indicate that the 2018 amendment caused an increase in prescription rates of L-CBM. In the period January 2018 to October 2018, inclusive, there were averages of 48 prescriptions for Nabilone and 166 prescriptions for Sativex issued per month on the NHS and dispensed in community pharmacies, compared to averages of 49 and 171 respectively in the 11 months following rescheduling.

Rates of prescribing for Sativex are likely to increase in England, since its use is now recommended for treatment-resistant spasticity, as per the updated NICE guidelines published in November 2019. Numerous acute NHS Trusts have informed us that they are updating their local guidelines in accordance with these recommendations. However, at the time of writing, no data is yet available for this time period.

1.1.2. CHALLENGES IN ACCESSING LICENSED CANNABIS-BASED MEDICINES

Medicines may not be widely used in UK clinical practice despite receiving market authorisation from the MHRA. For the majority of the year following the 2018 amendment, L-CBM were not recommended for use by the National Institute for Health and Care Excellence (NICE) and were not routinely commissioned on the NHS. Even in situations where medicines are both licensed and recommended for use, the patient populations indicated may be limited in size. This is presently the case for L-CBM; despite achieving regulatory approval and demonstrating cost-effectiveness, the total number of patients expected to receive either Epidyolex or Sativex on the NHS by 2024 is only around 5,000 – far fewer than the numbers of patients estimated to be unlawfully using CBP with medicinal intent in the UK today.[40] L-CBM are also still controlled drugs under the 2001 Regulations and their medical use must be in compliance with controlled drugs guidance. These obstacles to the availability of L-CBM are described in detail in the following subsections.

1.1.2.1. EVIDENCE BASE & CLINICAL GUIDELINES

Licensed medicines are not always considered cost-effective treatments

NHS England is responsible for distributing resources to Clinical Commissioning Groups (CCGs) across the country; clinically-led NHS bodies who plan and commission local services. Since 2012, CCGs have had statutory responsibility for commissioning the majority of NHS health care services and making local policy decisions on funding medicines.[41] Local commissioning decisions are shaped by the recommendations of NICE, who produce evidence-based guidance, quality standards, and information services for commissioners, health and social care practitioners and managers across the NHS. NICE clinical guidelines and health technology appraisals assess the efficacy and cost-effectiveness of treatments and provide recommendations concerning use.

Whether NICE guidance is binding or merely advisory depends on the type of document and the nature of the recommendation. A recommendation that a treatment *should not* be used does not prevent medical practitioners from prescribing that treatment, where funding is available. However, recommendations that a treatment *should* be used are, in some instances, binding. Where NICE technology appraisal guidance recommends the use of an intervention, NHS funding must be made available for that intervention within 3 months of the date the appraisal was published.This is in accordance with the NHS Constitution, which states that service users "have the right to drugs and treatments that have been recommended by NICE for use in the NHS," if the prescribing doctor believes that they are clinically appropriate for the patient.[42] However, where recommendations are made for the use of an intervention in NICE guidelines, which are distinct from technology appraisal guidance, there is no fixed timescale for funding.[43]

Sativex received a product license from the MHRA in 2010 for its use as a treatment for spasticity in MS. In 2014, NICE published clinical guidelines on the treatment of MS in which they recommended that Sativex should not be offered by NHS England to treat spasticity because the committee concluded that it was not a cost-effective treatment. There was no economic analysis produced by NICE at this time to assess the cost-effectiveness of Sativex. Instead, their conclusion was based primarily on an existing analysis that estimated the incremental cost-effectiveness ratio (ICER), expressed as cost per quality-adjusted life year (QALY), at £49,238. Probabilistic sensitivity analysis found that there was only a 10.2% chance that adding Sativex to ordinary care would meet the cost-effectiveness threshold of £30,000 per QALY, unless: (a) the price dropped by 40%; (b) the difference in utilities was 60% higher than the base case; or (c) the same benefits for patients could be produced with 4 sprays daily as seen with 8 sprays daily.[44]

Following the rescheduling of U-CBPM in 2018, NICE chose to develop a *de novo* economic model to examine the cost-effectiveness of cannabis-based medicinal products in patients with spasticity who had not responded adequately to conventional treatment. It found that adding Sativex to ordinary care was associated with an ICER of £19,512 per QALY over a 5-year time horizon. Probabilistic sensitivity analysis found a 66% probability that Sativex plus standard care would fall within with the threshold of cost-effectiveness: an ICER of £30,000 / QALY or better. The model assumed a 'Pay for Responder' discount scheme, in which the drug sponsor provides the first 270 doses for free in return for an agreement that NHS will reimburse the costs of future treatment for patients who respond.

In November 2019, NICE published clinical guidelines on the use of cannabis-based medicinal products in the treatment of a range of medical conditions. On the basis of NICE's *de novo* economic model, and two other analyses identified by a literature review (one analysis on which the 2014 guidelines were based on and a 2016 analysis commissioned by GW Pharmaceuticals), the guidelines recommended the use of Sativex in the treatment of MS. These guidelines updated the 2014 guidelines.

The use of Nabilone in the treatment of intractable chemotherapy-induced nausea and vomiting (CINV) was also evaluated in the guidelines published in November 2019. The committee's literature review retrieved no economic studies modelling the cost-effectiveness of Nabilone and no novel modelling was undertaken. Research recommendations were made for robust studies exploring the clinical and cost effectiveness of cannabis medicines as an adjunct to optimal therapy in adults with persistent nausea and vomiting. Despite the paucity of data on cost effectiveness, the committee recommended the use of Nabilone on the basis that the patient population is likely to be relatively small, and the treatment period relatively short, meaning that the overall resource burden of treatment per patient was likely to be lower than for other indications covered by the guidelines. It was observed that more clinically appropriate drugs for CINV had been licensed and incorporated into current practice in the years since Nabilone achieved market authorisation. The NICE resource impact report attached to the guidelines predicted that "the level of prescribing will not change significantly" as a result of the recommendation.

On December 18, 2019, NICE published health technology appraisal guidance on the use of cannabidiol (Epidyolex) with clobazam for

treating seizures associated with Lennox-Gastaut syndrome and Dravet syndrome. To evaluate the cost effectiveness of CBD, the HTA guidance on Lennox-Gaustaut syndrome used an economic model produced by the sponsor company and adjusted according to recommendations from the committee, resulting in an incremental ICER of £33,721 per QALY. The HTA guidance on Dravet syndrome reported broadly similar findings, with an incremental ICER of £32,471 per QALY. Taking into account uncertainties that may have increased the ICER figures (had data been available to address them) and additional factors affecting overall quality of life for siblings of young children with Lennox-Gastaut and Dravet syndromes, NICE concluded that treatment with CBD represents "a good use of NHS resources" and recommended its use for both conditions. For patients that fulfil the criteria, funding has been fast-tracked and has been in place from 6th January 2020.[45]

NHS organisations are expected to take the recommendations of clinical guidelines into account but are not compelled to follow them by either the NHS Constitution or by legislation. Some case law, such as R (Elizabeth Rose) -v- Thanet Clinical Commissioning Group (2014), has held that health and social care professionals are not able to choose not to follow a NICE guidelines recommendation for the use of a treatment simply because they disagree with it.[47] Noting that "NICE guidelines have always been less black and white [than technology appraisals]," NICE summarised the 2014 court judgement to mean that commissioners and providers "could be open to challenge" if they choose not to put clinical guidelines into practice.[48]

Therefore, while the NICE technology appraisal guidance recommendations on the use of Epidyolex require funding to be made available, the clinical guideline recommendations on the use of Sativex and Nabilone do not require commissioners to allocate funding within a fixed timescale, although they could potentially be taken to court by service users for refusing to fund those medicines when a doctor believes they would be clinically appropriate.

Feedback received by the authors from physicians and from NHS Trusts has indicated that funding is not being made available by some local commissioners for Sativex, despite NICE guidelines recommending its use under certain conditions. One NHS source told us that Sativex was still blacklisted by their local CCG and consequently could not be prescribed in that area, even after the publication of the updated guidelines by NICE. In response to an FOI request to all NHS Trusts requesting the number of prescriptions issued for Sativex, Nabilone, Epidyolex and U-CBPM, several trusts replied to say that the FOI request was not applicable since they "do not use any of the above drugs" or were "not commissioned to do so." While commissioners can lawfully make policies not to fund certain treatments, they are not permitted to impose "blanket bans" and are obliged to consider exceptional cases submitted as Individual Funding Requests.[49] If local commissioning policies continue to prevent access where clinically appropriate, CCGs may face legal challenges from patients in 2020.

Product licenses and clinical guidelines cover limited patient populations

Product licenses determine the medical conditions and patient groups for which a

Table 8. Costs of L-CBM in the UK

DRUG NAME	INGREDIENTS	PACK SIZE	PRICE (COUNTRY)*	COST PER DAY (£)*
Sativex	CBD 2.5mg & THC 2.7mg/ dose	270 doses	£300 (UK)	1.39 to 16.67
Nabilone	Synthetic THC 1mg/ capsule	20 capsules	£196 (UK)	19.60 to 58.80
Epidyolex	CBD 100mg/ mL	100 mL	$1,235 (US)	10.84 to 43.38

** Costs of licensed CBPM products as provided in NICE Evidence review C* [46]

The cost of Epidyolex to the NHS was due to be confidential until January 2020, but the drug does not appear in the March 2020 Drug Tariff and the cost is still not publicly available at the time of writing this report.

medicinal product can be prescribed, and for which medical claims may be made. Licensing decisions are based on rigorous standards of evidence on safety, quality and efficacy. Clinical guidelines published by NICE and by specialist professional bodies make recommendations for the circumstances under which medicines should be offered. Even when a medicine is licensed and recommended as cost-effective, the size of the clinical populations that might benefit from treatment is often limited. This applies to all licensed L-CBM.

The numbers of people receiving and likely to receive licensed L-CBM are low for several reasons:

1. These drugs are only licensed for the treatment of conditions and patient populations in which there is strong clinical evidence of safety, efficacy and cost-effectiveness.

2. Guidelines published by NICE and by specialist clinical organisations only recommend treatment with L-CBM for people whose symptoms are not adequately controlled by conventional interventions.

3. Following (1) and (2); licensed indications represent small clinical populations.

The only medical conditions for which there are licensed and recommended cannabis-based treatments available in the UK are multiple sclerosis (MS), chemotherapy-induced nausea and vomiting (CINV), Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS).

The Impact Assessment for the rescheduling of cannabis-based products for medicinal use, published by the Home Office in October 2018, estimated the maximum number of people potentially receiving a cannabis-based medicine per year at just over 1 million (after ten years, assuming 100% of cases were recommended as cost-effective). The central estimate for the number of people receiving cannabis-based medicine was approximately 300,000. [50]

The overwhelming majority (99%) of these cases were for chronic pain in adults. Although the Chief Medical Officer's 2018 review on the therapeutic and medicinal benefits of cannabis-based products found 'conclusive or substantial evidence' that cannabis or cannabinoids are effective for the treatment of chronic pain, there are no L-CBM licensed or recommended for this indication in the UK. In guidance published by the Royal College of Physicians and the Royal College of Radiologists (RCP/RCR), the use of cannabis-based medicines for chronic and palliative pain was not recommended.[51] NICE guidelines also state cannabis-based medicines should not be used as a treatment for chronic pain.[52]

MS, CINV, DS and LGS were associated with a maximum number of 11,650 people estimated by the Home Office to receive treatment per year. The central estimate for the total number of people who could receive L-CBM for these conditions was only 2,980 people.

Resource impact assessments published alongside NICE guidelines on the use of cannabis-based medicines estimate that by financial year 2024/25, 3,271 people will receive Sativex on the NHS for the treatment of spasticity in MS, while 1,806 people will receive Epidyolex for the treatment of seizures in LGS (*see Table 9*).[53] The numbers of people likely to receive Nabilone for CINV, and Epidyolex for DS, were too low to have a significant impact on resources. Accordingly, no numbers were provided.

Sativex: indications & restrictions

Sativex is only licensed and recommended for the treatment of moderate to severe spasticity in MS. Although the total prevalence of MS in England is approximately 90,000 people, NICE estimate that fewer than 4,000 are eligible for Sativex. Almost three-quarters of adults with MS do not report spasticity symptoms rated as moderate or severe, leaving only around 24,000 patients with symptoms for which Sativex is indicated. Of these patients, only one-fifth (4,800) do not adequately respond to the conventional treatments which NICE recommend should be used in advance of L-CBM.

NICE guidelines recommend that a 4-week trial of Sativex should only be offered if other pharmacological treatments have not been effective, and that treatment should continue only if the person shows a 20% or greater reduction in symptoms. Only 3,600 of those with treatment-resistant, severe-to-moderate

Table 9. NICE projections on rates of prescription for Sativex and Epidyolex

		Estimated number of people receiving treatment by financial year						
Drug	**Condition**	**2018/19**	**2019/20**	**2020/21**	**2021/22**	**2022/23**	**2023/24**	**2024/25**
Sativex	*MS*	800	981	2,453	3,271	3,271	3,271	3,271
Epidyolex	*LGS*	-	-	493	1,210	1,528	1,727	1,806

spasticity are predicted to respond to Sativex and thus be eligible for ongoing treatment.

Epidyolex: indications & restrictions

The British Paediatric Neurological Association (BPNA) found high quality evidence for the efficacy and short-term safety of pure CBD (i.e. Epidyolex) in the treatment of LGS and DS.[54] Epidyolex has since received market authorisation for these disorders. The BPNA also reported some low-quality evidence, from open-label studies and animal studies, that CBD may have an anti-epileptic effect in other forms of epilepsy. However, guidelines from the Association of British Neurologists (ABN) advise "extreme caution" in the consideration of medicinal CBD products in epilepsies other than LGS and DS on the basis of "no or very little evidence for benefit."[55]

BPNA recommend that Epidyolex should only be considered as a treatment of last resort for children who:

1. have epilepsies that have proven resistant to conventional licensed drugs;

2. have not responded to the ketogenic diet (where appropriate); and

3. are not candidates for epileptic surgery.

It is worth mentioning that the BPNA issued these recommendations prior to the MHRA granting market authorisation to Epidyolex. NICE guidelines currently recommend that Epidyolex should be offered as an add-on to clobazam only if seizures are not well controlled after treatment with two or more antiepileptic drugs, and that treatment should be stopped if the frequency of seizures has not fallen by 30% compared to the 6 months prior to treatment. They estimate that fewer than 2,000 patients with Lennox-Gastaut syndrome will receive Epidyolex by 2024.

Nabilone: indications & restrictions

Nabilone is listed as a prescription-only medicine (POM). Any doctor can prescribe Nabilone for its licensed indication, chemotherapy-induced nausea and vomiting, though the British National Formulary states that prescribing should preferably occur in a hospital setting under close medical supervision.[56]

RCP/RCR guidance recommends that it should not be used as first-line treatment on the basis of a high side-effect profile and lower efficacy than other medications. NICE guidelines recommend that it should be offered as an add-on treatment if symptoms persist with optimized conventional antiemetics. The total numbers of people likely to benefit from treatment with Nabilone was estimated to be too low to have a significant impact on NHS resources.

Nabilone was used in the NHS as an adjunct treatment for pain in the 1990s, without much success. It is still in use for the treatment of CINV, but there are now new treatments that are more effective, better tolerated by patients, and in much wider use, such as the serotonin antagonist ondansetron. NHS sources have told us that there is little confidence in Nabilone as a useful drug in the UK.

1.1.2.2. REGULATORY RESTRICTIONS

L-CBM are subject to controlled drugs guidelines and regulations

All existing L-CBM are Class B controlled drugs under the MDA 1971. Nabilone is currently listed under Schedule 2 of the MDRegs 2001 and Sativex is listed under Schedule 4. Epidyolex currently

meets the definition of a Schedule 2 CBPM, but its scheduling status is under review and it will likely be moved to Schedule 5 in early 2020. The supply, prescription, storage, destruction and record keeping of these medicines are, accordingly, subject to the MDRegs 2001 and the Misuse of Drugs (Safe Custody) Regulations 1973 (MD(SC) Regs 1973), as well as professional guidance on controlled drugs for health practitioners.[57 58 59]

As per Regulation 15 of the 2001 Regulations, and professional guidance, prescriptions for Schedule 2 drugs must be written in indelible ink, or be machine-written, and must include the:

- handwritten signature of the prescriber (advanced electronic signatures are acceptable where the Electronic Prescription Service is used);
- date of signing;
- address of the prescriber and, if issued on a private prescription form, the prescriber's identification number;
- name and address of the patients;
- form and strength of the preparation
- total volume or number of doses; and the
- clearly defined dose.

Regulation 16 of the 2001 Regulations states that Schedule 2 controlled drugs may only be supplied if all legally required information is on the prescription. Pharmacists may amend the prescription in indelible ink only if it contains minor typographical errors or specifies the total quantity only in words or in figures. Amendments must be clearly attributable to the pharmacist and must state the name and date of amendment alongside the pharmacist's signature and registration number. As per Regulation 16 (1.e), prescriptions are only valid for 28 days.

All Schedule 2 drugs must be stored in a locked metal cabinet or safe fixed to the wall or floor of an authorised site. Each site must nominate a designated person as responsible for the storage of controlled drugs and appoint authorised holders of the key to the cabinet or safe. All sites storing or supplying controlled drugs must keep a controlled drugs register, keeping records for at least two years; invoices for controlled drugs should be kept for six years and records of the destruction of controlled drugs are kept for at least seven years. Regular stock checks should be undertaken and all discrepancies must be recorded, investigated and reported to the local controlled drugs accountable officer.[60 61]

NICE guidelines on controlled drugs advise that prescribers should consider the risks of dependency, overdose and diversion. Documentation in the person's care record should state clearly the indication, regimen for use, and justification for not following any local or national guidelines on prescribing. Except under exceptional circumstances, prescriptions for controlled drugs should not exceed 30 days.[62]

Schedule 4 drugs are not subject to controlled drug prescription requirements and are not subject to safe custody requirements. Sativex is the only Schedule 4 drug for which records must be kept in a controlled drugs register.[63]

Schedule 5 drugs are exempt from most of the requirements pertaining to controlled drugs.

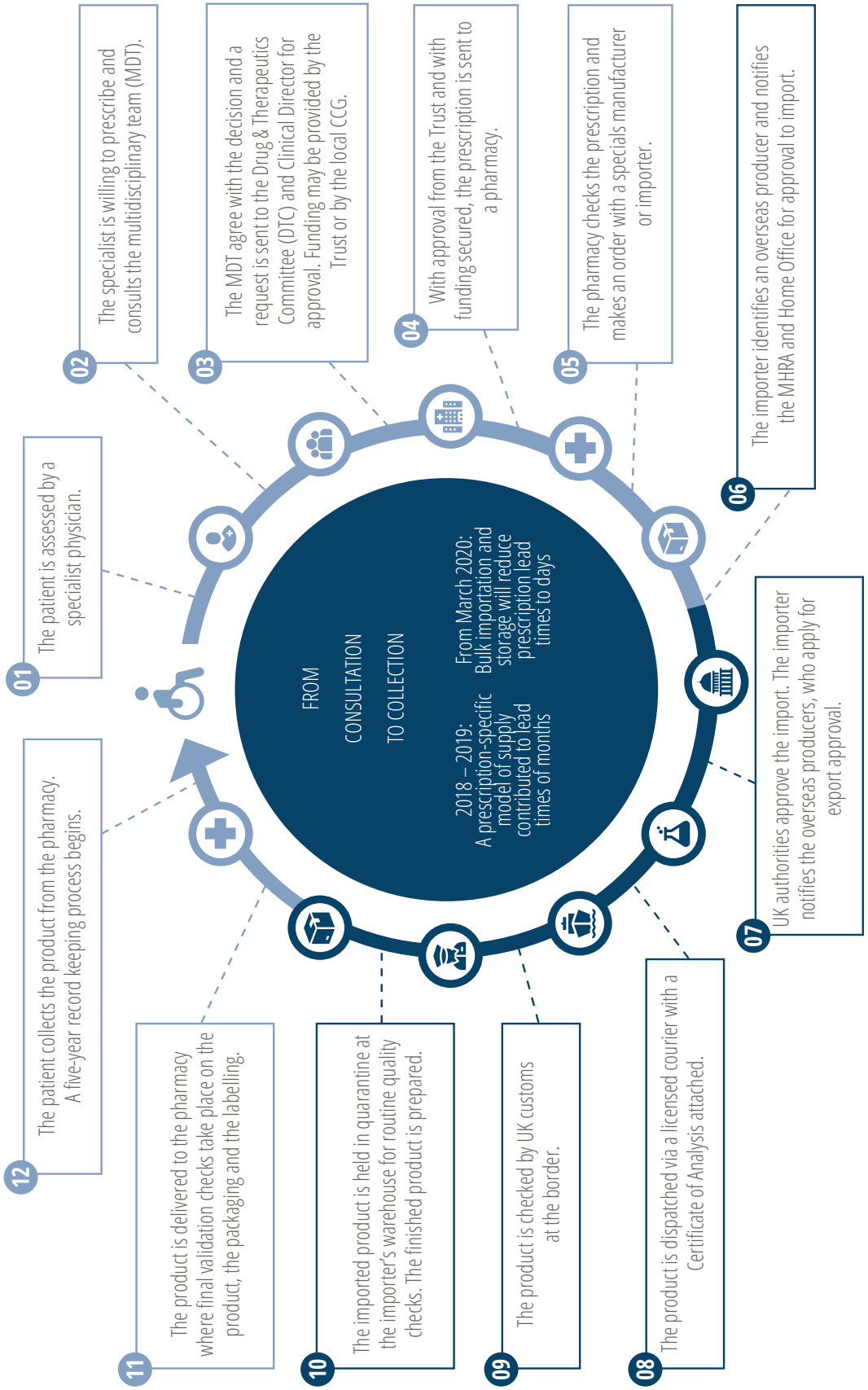
1.2. ROUTE 2: UNLICENSED CANNABIS-BASED 'SPECIALS' MEDICINES (U-CBPM)

The first part of this section outlines the complex process of supplying U-CBPM as 'specials' medicines on the NHS and in private practice, from consultation to collection. Secondly, we explore a number of obstacles, encountered by patients, prescribers and suppliers, which have severely restricted access in the year following the 2018 amendment.

The broadest definition of 'unlicensed cannabis-based medicinal product' contains a number of distinct subcategories, including:

- U-CBPM available as 'specials' medicines and controlled under Schedule 2 of the 2001 Regulations (e.g. Bedrocan).
- IMP controlled under Schedule 2 of the 2001 Regulations and prescribed in a registered clinical trial. This route of access is described under Route 3.

Figure 3. The process of accessing unlicensed CBPM on the NHS



- Unlicensed medicinal products derived from cannabis that do not contain any controlled products under the 2001 Regulations (e.g. pure encapsulated CBDV). While this category of product exists theoretically, there were no known instances in which such products were prescribed as specials, or otherwise, in the year following the 2018 amendment.

- Ingredients for the manufacture of U-CBPM. These products are addressed briefly in the following subsections on production and importation.

- Medicinal products with market authorisation overseas but not in the UK (i.e. Dronabinol). Such products are not known to have been used widely in the UK.

Off-label use of licensed L-CBM in the UK (e.g. Sativex) is not addressed in this section, nor do we include the early access use of Epidyolex prior to its market authorisation. Other than for the first subcategory listed above, there is little or no available data regarding use in the UK. Accordingly, the following section only considers the use and supply of Schedule 2 U-CBPM specials medicines, as defined in the 2018 amendment.

1.2.1. PRESCRIBING, PROCURING AND DISPENSING UNLICENSED CANNABIS-BASED 'SPECIALS' MEDICINES

1.2.1.1. THE PATIENT IS ASSESSED BY A SPECIALIST

Under Regulation 16A of the MDRegs 2001, prescriptions for U-CBPM can only be initiated by physicians on the General Medical Council Specialist Register. Guidance from NHS England states that prescribing decisions should only be made by specialists who have clinical competency in the condition of interest and in the patient group (e.g. prescriptions for CBPM for children with intractable epilepsy should be made by tertiary care consultants specialising in paediatric neurology – not by consultants specialising in adult neurology or in any other specialty).[64] The specialist register lists the specialties that the physician is qualified in and the date of registration for each specialty. Physicians on this register are eligible for appointment as NHS consultants. There are no restrictions on the medical conditions for which a specialist can decide to prescribe a CBPM.

General Practitioners (GPs) are not typically qualified in specialties, are thus not listed on the Specialist Register, and are not permitted to initiate a prescription for U-CBPM. The legislation permits GPs to issue repeat prescriptions under a Shared Care Agreement and, although the initial guidance from NHS England "expect[ed] specialist prescribing only," the latest NICE guidance supports the use of such arrangements to improve access for patients once treatment has been initiated by a specialist.[65] Therefore, the initial step for a patient who may be eligible for a CBPM prescription is assessment at a specialist secondary or tertiary care unit, either directly or through referral via primary care.

Theoretically, medicinal products containing only non-controlled cannabinoids would not be subject to the statutory restrictions on prescribing under Regulation 16A and could be prescribed by any authorised prescriber according to the ordinary protocol for specials medicines. This possibility was recognised as early as 1998.[66] However, no guidance has yet been published to suggest that prescribing in this way is either prevalent or recommended.

1.2.1.2. THE SPECIALIST IS WILLING TO PRESCRIBE U-CBPM

A specialist physician may issue a prescription for U-CBPM on the basis of GMC and MHRA guidelines on unlicensed medicinal products; clinical guidelines issued by NICE and by specialist medical bodies; assessment of cost-effectiveness; and assessment of the individual patient and the relative benefit to risk ratio to the patient conferred by the product. The order to prescribe a specials medicine must not be solicited by the patient or other parties; the initiative must come from the doctor, as per restrictions laid out in section 167 of the Human Medicines Regulations 2012 (HMRegs 2012).

Clinical guidelines do not presently support the routine use of U-CBPM in clinical practice, but nor are they intended to prohibit their use. Whether U-CBPM should be prescribed to meet the special needs of the patient is ultimately a matter for the prescribing specialist. However, prescribers of any unlicensed medicine are responsible and professionally accountable for their decisions

and may be called upon to justify their actions.[67] The decision must then be discussed with the multidisciplinary team (MDT) responsible for that patient's care and authorised by the medical director of the clinic or hospital.

1.2.1.3. THE PRESCRIPTION IS WRITTEN AND SENT TO A SPECIALS PHARMACY

If the specialist is willing to prescribe U-CBPM to a patient and the MDT has agreed, the prescription is written and delivered to a registered pharmacy. This prescription should state details of the product being prescribed (the name of the product or its common name; the manufacturer; the type of formulation – e.g. oil, tincture, whole flower or capsules; the content of THC and CBD in the product; directions for use; and quantity), and details of the patient (name, address). Though not required by legislation, GMC Best Practice Guidance limits prescriptions to a one-month supply.

NHS prescriptions for CBPM specials are issued by hospital consultants in liaison with the in-house hospital pharmacy.Hospital Trusts are expected to meet any costs of specials medicines and, depending on local procedure, the consultant would ordinarily send a request to the Drug and Therapeutics Committee, who will make an approval decision. This may result in the adding of a CBPM to the hospital formulary, or, if the drug is deemed to be high-cost, an Individual Funding Request may be submitted to the local Clinical Commissioning Group (CCG).[68] Funding decisions are made on the basis of evidence of efficacy, patient safety and cost-effectiveness. To date, funding requests for U-CBPM have not been routinely approved. The cost to the patient of CBPM prescriptions on the NHS will be the standard prescription charge per item (currently £9.00).[69]

Private prescriptions are issued to patients on pink FP10(PCD) forms and may be processed by any community pharmacy with a Home Office Domestic License. Since CBPM specials are unlicensed, the pharmacy will not have the medicine in stock and will be required to place an order. If the pharmacy is also in possession of an MHRA Wholesaler Dealer's Licence they are permitted to make an order directly with an overseas manufacturer from an EEA member state, and if they possess an MHRA Manufacturer's (Specials) License they may import from non-EEA states. However, few community pharmacies possess these licenses, which are difficult to acquire due to strict requirements, and in most cases the pharmacy will place an order with a licensed specialist importer. The cost to the patient of a private prescription for U-CBPM can be substantial.

The pharmacist is required to check that the order is unsolicited, that the prescription includes all the required information, that the decision to prescribe has been made by a doctor registered on the GMC Specialist Register, and that the prescriber is fully aware of the unlicensed status of the product. Moreover, since the pharmacist shares with the prescriber accountability for supplying a special to a patient, it is typical for the prescriber and pharmacist to work together to establish the optimal treatment for the patient and identify a preparation and a supplier. Pharmacists will also advise patients and carers regarding continuity of supply, shelf life, the likely timescales of the supply and who to contact if they run out of medicine. The Royal Pharmaceutical Society provide Professional Guidance for the Procurement and Supply of Specials to support pharmacists in this regard.[70]

The responsibility for identifying and prescribing a product which meets the patient's special clinical need lies with the prescribing physician, but the pharmacist is responsible for ensuring that the product that is ordered fulfils the requirements of the prescription. Suppliers and manufacturers of specials medicines are responsible for providing products that comply with the product specification.[71] In collaboration with both the prescriber and the supplier, the pharmacist will identify a product that is appropriate for the patient and is either in stock or available for manufacture or importation.

If the supply chain is reliant on importation, as it has been for the first year following the 2018 amendment, see step 4. If the U-CBPM is being manufactured in the UK, see step 6.

1.2.1.4. THE ORDER IS SENT TO AN OVERSEAS MANUFACTURER VIA A LICENSED SPECIALS IMPORTER

Specialist Importers (SI) must have an MHRA Wholesaler Dealer's License or an MHRA

Manufacturer's (Specials) License if they are importing CBPM from an EEA or non-EEA member state, respectively. If the SI is trading raw materials or importing ingredients from outside the EU, they must also have Active Substance registration. The intention to import an unlicensed medicine must be notified to the MHRA at least 28 days in advance, stating:

a) the name of the product under which it is to be sold or supplied;

b) the name of the overseas manufacturer;

c) the name and address of the manufacturer or assembler of the final medical product, or the name and address of the supplier;

d) the monograph, scientific name or description of the constituents of the medicine; and

e) the quantity to be imported.

Additionally, the MHRA require evidence that the content of THC/CBD is declared and appears on the product label; that the site of manufacture is GMP-certified; and that a batch-specific Certificate of Analysis (CoA) is available, detailing tests of quality that have been performed, required results, actual results and the laboratory that issued the certificate. The Department of Health and Social Care have reported that 242 notifications were received by the MHRA in 2019.[72]

In the instance that the MHRA object to importation, for reasons such as patient safety concerns or the known availability of a licensed medicine in the UK, the medicine must not be imported. In the instance that the MHRA do not issue an objection within 28 days from the date of its acknowledgement, or if they choose to permit import before 28 days, the SI is permitted to proceed with the order. Importers must also apply for a Home Office license to import controlled drugs and this must be approved before the MHRA consider an import notification for U-CBPM. Applications to the MHRA and Home Office may be submitted in parallel.

Once the MHRA and the Home Office have approved an order, the SI is required to send a copy of their Home Office Licence to the overseas manufacturer. If the manufacturer has a license to export from their domestic licensing authority, the overseas manufacturer may then ship the product to the UK via a specialist courier. However, only the Netherlands presently export U-CBPM within the EEA and SIs have reported that stock from Dutch suppliers is limited. Exports from additional EEA countries, such as Germany and Malta, are expected to develop in 2020. Supply from non-EEA states is possible, though complicated by requirements to achieve EU Good Manufacturing Practice (GMP) certification. In some cases, importers have reported that overseas manufacturers have refused to supply certain products to the UK despite having permission to export.

1.2.1.5. THE CANNABIS PREPARATION IS IMPORTED INTO THE UK

Once an order has gone through the aforementioned checks and approvals, the overseas manufacturer ships the product to the UK, via a specialist courier, where it is subject to customs checks at the border and delivered to the importer's warehouse site to be placed in quarantine for routine checks. These checks include confirming that the contents match the purchase order, that the packaging meets quality standards and has not been damaged, and that there have been no temperature excursions during shipment of sensitive products. If the imported product is an active pharmaceutical ingredient (API), such as raw cannabis material for use in the manufacture of a medicinal product, the product may be independently tested to confirm the results in the attached CoA.

If the imported material is a finished product, see step 7. If the imported material is API, see step 6.

1.2.1.6. THE MEDICINE IS MANUFACTURED AT A LICENSED SITE

Authorised license holders may manufacture and assemble cannabis-based specials medicines from API, or other active substances, sourced either by importation or from domestic production. Manufacturers must hold a Manufacturer's (Specials) License from the MHRA and, in most cases, a Home Office License. Under 2019 Home Office and MHRA

policy, importers required Schedule 1 licenses to import ingredients containing THC. As of March 2020, bulk volumes of finished product and ingredients can be imported under Schedule 2 licenses.

Under certain circumstances, pharmacies may manufacture unlicensed medicines without the need for a manufacturing licence, under exemptions listed in Section 10 of the Medicines Act 1968.Pharmacies may prepare unlicensed medicines for individual patients either in accordance with a prescription or for the purposes of preparing stock in anticipation of prescriptions, though it is presently unclear whether or not additional restrictions would be imposed by Licensing Authorities in regard to CBPM.[73]

Any company manufacturing, importing or distributing API in the UK must have Active Substance registration with the MHRA.[74] The manufacturing site of license holders will be inspected by licensing authorities for compliance with GMP and, where appropriate, Good Agricultural Practice (GACP). Production must be supervised by a named quality controller and production manager who have been approved by licensing authorities after a qualification and criminal record check. MHRA guidance for Specials manufacturers state that production may be carried out in anticipation of an authorised order, based on the known future demand for a product. Finished drug product manufacturers must carry out routine Product Quality Reviews (PQRs) in which the full supply chain for ingredients is tracked and mapped, checking that all manufacturers, importers and distributors of API used in the finished product are correctly registered with the relevant licensing authority of their country.

MHRA guidance states that U-CBPM manufacturers must also demonstrate compliance with the European Commission's 'Notes for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicine products,' and future updates. The use of gamma irradiation is permitted in the decontamination of cannabis-based plant material, but the use of ethylene oxide is not.[75]

1.2.1.7. THE FINISHED MEDICINAL PRODUCT IS DISPENSED TO THE PATIENT BY A LICENSED PHARMACY

Once final quality checks have been made, the U-CBPM is delivered to the licensed pharmacy for collection by the patient. Specialist importers cannot directly supply medicines to patients, unless they have a licensed pharmacy division.

Upon receipt of the medicine, the pharmacy will conduct their own validation checks on the medicine, its packaging and the product labels. Dispensing label regulations require inclusion of the patient's name, the name and address of the supplier, and the date on which the product is sold or supplied.

Special warnings regarding driving should also appear on the label. MHRA guidance requires U-CBPM labels to 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.[76]

Unless the pharmacist is of the opinion that it would be inappropriate to include one or more of the following particulars on the dispensing label, it must also include the name of the product, directions for use and precautions relating to use. Once the final clinical checks have been conducted, the product may be dispensed to the patient.

1.2.1.8. A FIVE-YEAR RECORD KEEPING PROCESS COMMENCES

As applies to the supply of all specials medicines, prescribers, pharmacists, suppliers and manufacturers are all required to keep the following records for at least five years, and ensure that they are available for inspection by the licensing authorities:

- the source of the product and the date on which it was obtained by the patient.
- 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 supply was made; and
- details of any suspected adverse reaction to the product of which the person is aware or subsequently becomes aware.[79]

Adverse reactions are reported to the MHRA via a "Yellow Card" form, or an electronic Yellow Card, stating any suspected defects, the name of the manufacturer and that the product is unlicensed. Currently, all adverse effects related to any cannabis medicine should be reported to the MHRA, as is normal practice for all new medicines and all unlicensed specials. The MHRA requires reporting of all suspected adverse reactions, whether serious or non-serious, including reports of failure of efficacy.

1.2.2. CHALLENGES IN ACCESSING UNLICENSED CANNABIS-BASED 'SPECIALS' MEDICINES

Access to U-CBPM in the UK was severely limited in the first year following the 2018 amendment. The primary, underlying issue limiting access was, and continues to be, a lack of high-quality evidence on the safety and efficacy of individual unlicensed products. Although evidence does exist for the therapeutic potential of some cannabis- and cannabinoid-based products, as noted in Part 1 of the Home Office review, much of these data is provided by clinical trials in products that have gone on to achieve market authorisation. There is substantial reluctance to assume that these data can be extrapolated to other cannabis-based products, and there is little or no evidence on the specific safety or efficacy of most individual U-CBPM. These drugs, by definition, are not supported by sufficient clinical evidence to achieve product licences. Thus, there is very limited rationale on which to justify the use of U-CBPM over licenced medicines, or, indeed, the use of any one unlicensed product over any other.

Box 3. Advice for patients driving under the influence of cannabis medicines

Since, 2012, it has been an offence to drive with specific controlled drugs in the body above an accepted limit, and guidance is available for prescribers to provide information to patients whose medications may affect their ability to drive.[77] In the UK, it is an offence to drive under the influence of cannabis whether or not there is evidence of impairment. A 2013 expert committee recommended a threshold blood concentration of 5ng THC per ml of blood, but the lower level of 2ng/ml was adopted into law on March 2, 2015.[78]

Regular use of cannabis-based medicines is likely to cause blood concentrations that breach this limit. Patients who are investigated for driving under the influence of a cannabis medicine may raise the statutory 'medical defence' if the drug was lawfully prescribed and taken in accordance with medical direction, and if there is no evidence of impairment. However, there is no 'medical defence' for the offence of driving whilst impaired and it remains the responsibility of drivers, including patients, to consider whether their ability to drive might be impaired. Prescribers and suppliers of CBPM should advise patients who drive to carry evidence that they are taking the drug under prescription, and not to drive if any symptoms or signs develop suggesting impairment.

Since U-CBPM do not have market authorisation in the UK, they are not listed in either national or local drug formularies and are not routinely commissioned on the NHS. They may only be prescribed if funds are available, whether allocated from local NHS budgets in response to an Individual Funding Request or provided directly by the private patient. In practice, the costs are too steep for NHS commissioners to consider approving their use, and meeting this cost burden is unsustainable over the long-term for the vast majority of private patients. The high costs are partially explained by a dependence on international supply, as domestic production

of U-CBPM is not yet established. Importation from overseas in the first year following the 2018 amendment was intentionally limited by Licensing Authorities to reduce the risk of unintended harms associated with diversion and inappropriate prescribing, but these policies also raised costs and contributed to delays and interruptions in providing treatment. As of March 2, 2020, new regulations of import have been introduced that will serve to reduce the delays and costs of imports.

Further, U-CBPM are not recommended for use by NICE, nor in the guidelines of any specialist professional body. All specials medicines are considered options of last-resort and, even among specials medicines, U-CBPM are uniquely limited. They are Schedule 2 controlled drugs, derived from the most commonly-used recreational drug in the world, with no product licences for any indication either in the UK or in the country of manufacture. There is mixed evidence on therapeutic benefits of CBPM, but well-established evidence on the potential harms of CBP. Thus, prescribers, commissioners and regulators have been wary of permitting rapid, widespread access, despite substantial demand from patients and advocacy groups.

Notwithstanding these challenges, specialist physicians are permitted to prescribe U-CBPM if they believe that there is a special clinical need for an individual patient. However, knowledge and experience in prescribing cannabis medicines is still extremely limited. More than 60% of UK medical schools provide no teaching sessions on the endocannabinoid system in their preclinical curricula, and over 40% provide no teaching on any topic related to cannabis or cannabinoids. Education in endocannabinoid medicine is also limited during the clinical and specialist training provided at later stages of a medical career.

For these reasons, rates of prescribing have been extremely limited. These challenges are explored in depth in the following subsections.

1.2.2.1. EVIDENCE BASE & CLINICAL GUIDELINES

There is very limited high-quality evidence on safety, quality and efficacy

The most fundamental obstacle to access of unlicensed cannabis-based medicines through the UK healthcare system is a lack of high-quality clinical evidence on: (1) the quality and consistency of products; (2) the long-term safety of their use in clinical populations of interest (e.g. epileptic children); and (3) their efficacy and cost-effectiveness in the treatment of clinical disorders of interest.The paucity of evidence in this regard underlies many other obstacles to access. Medical education on the use of U-CBPM is limited partly because there is little high-quality evidence on which to base training. Commissioners are reluctant to pay for U-CBPM because there is little high-quality evidence on efficacy and cost-effectiveness to justify funding their use. Clinical guidelines take a precautionary approach and do not support the routine use of U-CBPM because there is insufficient data on which to base recommendations. And market authorisation has not been awarded to U-CBPM because the high standards of evidence required for application cannot yet be met.

In June 2018, the Chief Medical Officer published a review of the evidence base for cannabis-based products in which she argued that there was sufficient conclusive evidence of therapeutic benefit to justify moving CBPM out of Schedule 1 of the MDRegs 2001.[80] However, the evidence base for specific unlicensed cannabis-based products has been insufficient to demonstrate safety and efficacy of to the standard required for market authorisation in the UK.[81]

The majority of clinical witnesses to the Health and Social Care Committee (HSCC), as part of their Medicinal Cannabis Inquiry in March 2019, emphasised the low strength of the evidence base for unlicensed products and argued that prescribing should not become routine or widespread without robust evidence to support their use on the grounds of patient safety.

The most robust forms of evidence recognised in the evaluation of the safety and efficacy of medicinal products are RCTs and meta-analyses. There is little in the way of high-quality, double-blind RCT evidence on the use of most, if not all, U-CBPM. There are complex and nuanced reasons underpinning the lack of high-quality RCT evidence for U-CBPM, including regulatory and methodological challenges to clinical research, the extraordinary diversity of cannabis-based preparations and their constituents, and limited industry sponsorship of trials. These issues are

"[It] is very dangerous to have a kind of cannabis exceptionalism. These are drugs; they have side-effects and positive effects. That is clear. What we have to do is balance the two, but they are no different from any other drug in that sense. The history of medical development is littered with people rushing things through and ending up regretting it."

Professor Chris Whitty, Chief Scientific Advisor to the Department of Health and Social Care.

discussed later under Route 3 and in Part B of this report.

However, RCTs are not the only source of evidence, and are not always required for a drug to achieve licensing. The EMA and the FDA granted 76 medicinal product licenses without RCT data between 1999 – 2014 on the basis of findings from other types of study, including randomised uncontrolled trials, historically-controlled trials and observational studies.[82] 81% of these licenses were awarded to novel medicinal products that had not already achieved a license for other indications. Nor are RCTs the only form of evidence considered by NICE, whose report 'Widening the evidence base' emphasises the value of observational trials, electronic health record data, data collected from digital health technologies (e.g. apps and wearable technology) and real world data (e.g. from patient registries).[83] In 2008, the outgoing chairman of NICE, Sir Michael Rawlins, argued that RCTs have been given "too much attention" and that their findings do not necessarily apply "in the real world." He recommended wider use of observational data and other methods to inform licensing decisions and cost-effectiveness analyses.[84]

The president of the British Paediatric Neurology Association (BPNA) testified to the HSCC that non-randomised, non-blinded trials "almost invariable overestimate efficacy" and warned that results could be distorted by "severe biases." These concerns were echoed by other medical witnesses to the committee. The HSCC's report concluded that, whilst RCTs in CBPM should be supported, "other means of gathering evidence must also be investigated," particularly in rare paediatric epilepsies for which conventional trial designs may not be suitable.[85]

A report published by NHS England and NHS Improvement (NHS-E/I), titled 'Barriers to accessing cannabis-based products for medicinal use on NHS prescription,' made recommendations for a number of different forms of evidence collection, including standardised RCTs with several comparative treatment arms, a national UK patient registry, and the development of "an appropriate alternative study design that will enable evidence generation for those patients who cannot be enrolled into a standard RCT."[86] On 20 November 2019, the NIHR held a workshop for clinicians, researchers and NHS England to design a trial on medicinal cannabis in severe treatment-resistant epilepsy. Precisely one month later, the DHSC published a letter stating that the department was implementing the recommendations made in the NHS-E/I report, including the establishment of "a UK-wide paediatric specialist clinical network, clinical trials, and an alternative study for children and young people already in receipt of a CBPM."[87]

NICE guidelines on cannabis-based medicinal products have made recommendations for research in five key areas:

1. The clinical and cost-effectiveness of CBD as an add-on treatment for fibromyalgia or persistent treatment-resistant neuropathic pain;

2. The clinical and cost-effectiveness of CBPM as add-on treatments for symptoms of chronic pain in children and young people;

3. The clinical and cost-effectiveness of CBD to improve outcomes in severe treatment-resistant epileptic disorders in children, young people and adults;

4. The effects on seizure frequency, brain structure and neuropsychological performance of the addition of THC to CBD in the treatment of severe treatment-resistant epilepsies; and

5. The clinical and cost-effectiveness of CBPM other than Sativex for children, young people and adults with spasticity, particularly in regard to improvements in quality of life.

A variety of alternative clinical trial designs have been proposed to develop the evidence base in cannabis-based medicines. Suggestions have included the use of adaptive RCTs with interim analyses to guide design modification after trial commencement; basket trials to study the effects of a single intervention on multiple disorders that share the same underlying mechanism; umbrella trials to gather efficacy data in disorders known to have multiple underlying causes; N-of-1 trials in which individual participants pass through cyclical, double-blinded study and control phases, and thus act as their own controls; and patient registries to collect observational data from real-world prescribing.[88]

The medicinal cannabis industry claims that a substantial body of observational evidence already exists and should receive greater consideration from regulators, clinical professional bodies and prescribers in the UK. A statement published in the BMJ in October 2019 in response to a call for greater evidence of CBMPs and collaboration with industry made the following observation:

> *"In Canada, at the end of September 2018 there were 342,103 medical cannabis patients registered on Health Canada's database. The government of Australia has approved over 17,300 applications for unlicensed medicinal cannabis products. California alone in May 2018 had approximately 916,845 legal medical cannabis patients. In the European Union (EU), medical cannabis was legalised for use in Germany in March 2017, and costs to patients are fully reimbursed. There were over 185,000 prescriptions authorised, and an estimated 60-80,000 patients using medicinal cannabis products in 2018. In Italy, by the end of January 2019, 26,042 medical cannabis prescriptions, attributed to 12,998 patients were registered on the Italian Medicines Agency (AIFA) database to patients who had a mean age of 58 years, 63% of whom were women. More recently, in an effort to meet growing patient demand for medical cannabis, pilot programmes, which have been increasingly viewed as an effective mechanism for controlled access, have been introduced in France, Denmark, and Ireland."* [89]

However, it is worth noting that there are few high-quality national registries presently collecting standardised data on safety, efficacy and product quality, despite the large numbers of patients receiving cannabis-based treatments internationally. Two UK-based organisations have plans to develop good-quality national patient registries in the near future. The Twenty21 (T21) project, spearheaded by DrugScience, aims to establish a national patient dataset and provide access to U-CBPM to 20,000 UK patients by 2021. A similar model is being developed by the medicinal cannabis specialist unit Sapphire Clinics, which will collect standardised observational data from multiple sites across the UK in a national registry designed in consultation with NHS England.

Part B of this report explores a range of models that may increase safe patient access to cannabis-based products while contributing to the development of a robust evidence base, including national patient registries to collect observational data from real world prescribing, such as those being developed by T21 and Sapphire Clinics.

Clinical guidelines do not recommend use

Clinical guidelines on prescribing cannabis-based medicines have now been published by a range of medical organisations, including NICE, the Care Quality Commission (CQC), the General Medical Council (GMC), the British Paediatric Neurology Association (BPNA), the Association of British Neurologists (ABN), and the Royal College of Physicians (RCP) in collaboration with

the Royal College of Radiologists (RCR).[90 91 92 93 94 95] None of these guidelines make specific recommendations for the clinical use of U-CBPM, though some recognise that there may be circumstances in which prescribing is appropriate. In some cases, guidelines specifically recommend that U-CBPM should not be used.

The ABN observed that "[there] are likely to be large numbers of MS patients who may potentially benefit from these drugs and all patients will need to be assessed within specialist clinics and subsequently reassessed for benefit as well as continuing benefit." However, they also state that "[there] is very limited information on dosing of cannabinoids outside of Sativex" and recommend that "cannabis-based products are used only in people who have had an unsatisfactory response to conventional spasticity drugs." In the treatment of Lennox Gastaut syndrome and Dravet Syndrome, two rare, severe forms of epilepsy, the ABN recommend that "prescriptions should only be for cannabidiol (Epidyolex)."

Guidelines published by the RCP & RCR advise that there "is no robust evidence for the use of CBPM in chronic pain and their use is not recommended." Looking toward the future, the guidelines recognise the "potential benefit in the management of patients with chronic pain" and recommend that patient populations that may benefit "should not be denied access when the evidence is available." The guidelines also state that CBPM "should remain an option for [people with chemotherapy-induced nausea and vomiting] who have failed standard therapies but not used as a first-line treatment."

There is a clear implication throughout the RCP/RCR guidelines that U-CBPM are not recommended for routine use. They advise that "the medicinal use of cannabinoids needs to be carefully considered and researched in a comprehensive fashion, as would be the case for any new medicinal product reaching the therapeutic market. Anecdotal positive reporting is not a mechanism to protect public safety." The document states that whole-plant-based CBPM "containing a variety of cannabinoids and other pharmacoactive chemicals… cannot be supported due to the variability of preparations and lack of any trial evidence." This would exclude all unlicensed floral and extract-based CBPM ranges, such as the flowers produced by Bedrocan and the oils manufactured by Tilray.

BPNA guidelines observe that good quality evidence for CBPM in the treatment of epilepsy is confined to pure CBD (Epidyolex). The guidelines advise that Epidyolex, which was an unlicensed medicine at the time of publication, should be the "default choice" when considering prescriptions of CBPM to treat intractable paediatric epilepsy. The BPNA "do not recommend prescribing other non-licensed cannabis-based products for medicinal use whether or not they comply with good manufacturing practice or good distribution practice standards." The guidance notes that one open-label non-randomised study on an unlicensed Tilray CBPM, containing CBD and THC in a 100:2 ratio, "demonstrated some short-term safety and dosing data and some evidence of effectiveness," but concluded that the study design was not robust enough to constitute high quality evidence. "Clinicians," they advise, "should not feel under pressure to prescribe CBPM until they have undergone appropriate clinical trials."

Patients, their families, and the clinicians who support them have claimed that the clinical guidelines present a barrier to prescribing, according to the Health and Social Care Committee's (HSCC) report *Drugs policy: medicinal cannabis*. A review by NHS England and NHS Improvement (NHS-E/I) on barriers to accessing CBPM on NHS prescription, which focused heavily on treatment-resistant epilepsies in children, also cited concerns of patients, parents and carers that physicians were basing prescribing decisions too heavily on the clinical guidelines and not fully considering each case on an individual basis. Guidance from the MHRA, the GMC and the CQC all state that clinical decisions on prescribing specials should ultimately be made on a patient-by-patient basis. Senior representatives of the BPNA, ABN and the RCP/RCR defended the precautionary nature of their guidelines to the HSCC, arguing that they were based purely on the quality of the available evidence.

Physicians are not required to comply with clinical guidelines that do not recommend the use of a medicine, since such recommendations

are only advisory. The NICE guidelines manual states that clinical guidelines "[do] not override the responsibility of healthcare professionals and others to make decisions appropriate to the circumstances of each patient."[96] Most of the clinicians whose interviews contributed to the NHS-E/I review stated that they found the clinical guidelines on cannabis-based medicines to provide a useful outline of the available evidence and "framework to work within." Most medical witnesses reported that the lack of high-quality RCT data on safety and clinical-cost effectiveness was a major obstacle to prescribing CBPM, but many also stated that the potential risks of unlicensed medicines should be weighed against the clinical risks of not treating (e.g. the considerable clinical impact of continued seizures in children, with mortality in Dravet syndrome estimated at around 20%).

Surveys of physicians and health professionals reveal generally positive attitudes toward NICE guidelines, but also indicate limited adherence. A 2015 survey of 515 General Practitioners found that only 7% of respondents considered NICE guidance "extremely relevant" to their work, with the bulk of respondents (69%) choosing "somewhat relevant". 74% reported that they went against what was recommended in national guidance at least once a month, and 39% reported that they did so at least every week.[97] An online survey of 860 professionals from across the health and social care system (of whom 21% were medical and dental professionals), conducted by NICE, found that 65% scored the overall experience of using NICE clinical guidelines as good or excellent, and 76% reported that they used the guidance to "inform everyday practice."[98] However, 41% reported that the guidance "lacks people's real life experiences." Some respondents wanted to see less reliance on RCTs, including an anonymous consultant clinical scientist whose feedback read: "do not be too dependent upon RCTs which are more difficult to achieve in some clinical areas than others - take advice from clinicians who are absolutely aware of which patients are likely to benefit."

1.2.2.2. PRESCRIBER WILLINGNESS

The specialist doctor must decide that prescribing is the right decision

The first step in the long process of getting access to a cannabis-based medicine is the clinical decision to prescribe. Although prescribers should be aware of the clinical guidance on prescribing unlicensed medicines and on cannabis-based medicinal products, as well as the clinical governance procedures in the Trust or private clinic, the decision to prescribe is ultimately made by the specialist doctor on the basis of clinical judgement. This decision will take into account any evidence of potential benefit of cannabis-based treatment and evidence that other treatments have not been adequate to meet the patient's needs. When a specialist does decide that prescribing U-CBPM is the right decision, it must also be approved by a multidisciplinary team and, in an NHS setting, the Trust's Drug and Therapeutic Committee.

The NHS-E/I report on barriers to accessing CBPM observed a "spectrum of willingness to prescribe, with some clinicians more willing to prescribe on an individual case-by-case basis."[99] Verbal evidence, provided in interviews with clinicians, indicated that many specialists were cautious about a lack of high-quality evidence for the efficacy of CBPM and potential long-term adverse effects.

However, there are signs that some doctors may have had favourable views of the medicinal use of cannabis for some conditions well before the rescheduling. According to survey data gathered in 2012, 15.5% of small-scale cultivators of cannabis for medicinal reasons in the UK reported that their doctor had recommended it as a potentially useful treatment for their medical condition.[100] Additionally, the 2016 Inquiry Report on medicinal cannabis, published by the APPG on Drug Policy Reform, included a survey of health professionals linked to the Chronic Pain Policy Coalition.[101] It reported that 77% of respondents were aware of patients being prescribed L-CBM or making use of CBP with medicinal intent, and 66% made positive statements about the role of CBP for the conditions they worked with. Nonetheless, the available evidence indicates that only limited numbers of specialist physicians

presently feel comfortable prescribing U-CBPM, for a combination of the reasons listed in this section.

'Specials' medicines are not licensed and used only as a last resort

There are more than 75,000 different formulations of specials prescribed annually in the UK, accounting for approximately 1% of all prescriptions.[102] Though prescribing unlicensed medicines is relatively common, the vast majority of these prescriptions represent either 'off-label' use, or the special preparation of a licensed medicine in a form that is unlicensed. The BPNA have advised that prescribing completely unlicensed medicinal products, such as CBPM, is "largely untested in UK clinical practice" outside of clinical trials.

Unlike licensed medicines, which must demonstrate robust evidence of quality, safety and efficacy to achieve market authorisation, unlicensed cannabis-based specials medicines typically have little or no high-quality evidence to support their use. They are prescribed only when the prescriber is satisfied that a patient has a special clinical need "which cannot be met by a licensed medicine," or a licensed medicine used off-label, "and where established treatment options have been exhausted."[103]

U-CBPM are unique among specials medicines in that all of the following apply:

1. They are not licensed as medicines in the UK for any indication, in any patient group;

2. They are not licensed as medicines in the country of production;

3. They are controlled drugs listed as Class B under the MDA 1971 and as Schedule 2 in the MDRegs 2001;

4. They are subject to statutory and regulatory restrictions additional to ordinary specials regulations.

Further, CBPM rescheduling was driven by patient demand and has led to hugely raised patient expectations, but orders for specials cannot legally be solicited by the patient. The decision to prescribe must be initiated by the specialist. As a result of these unique considerations, the supply, manufacture, importation and distribution of CBPM are more strictly regulated by licensing authorities than with other specials medicines or controlled drugs.

The GMC provide ethical guidance to doctors on prescribing unlicensed medicines, recommending that decisions should ultimately be made on the basis of assessment of the individual patient.[104] These guidelines state that prescribing unlicensed medicines may be necessary either where there is no licensed medicine that will meet the patient's need, where a licensed medicine that would meet the patient's need is not available, or where prescribing forms part of an approved research project. The guidelines state that prescribers must:

a) be satisfied that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy

b) take responsibility for prescribing the medicine and for overseeing the patient's care, monitoring, and any follow up treatment, or ensure that arrangements are made for another suitable doctor to do so

c) make a clear, accurate and legible record of all medicines prescribed and, where [they] are not following common practice, [their] reasons for prescribing an unlicensed medicine.

Guidance from the Royal Pharmaceutical Society (RPS) outlines circumstances where prescribing a special (not specifically a cannabis-based special) might be appropriate. One such circumstance describes a lack of available licensed products to adequately meet the patient's clinical need and the existence of evidence that an unlicensed product may do so (e.g. in multi-treatment-resistant forms of disease).[105 106]

The use of a cannabis-based specials medicine, under RPS and GMC guidelines, would be reasonable if licensed cannabis-based medicines

or other licensed products used to meet the patient's needs were temporarily unavailable, if the patient had not adequately responded to licensed medicines, or if the prescriber had reason to believe that an unlicensed product may be more effective for a patient than licensed alternatives.

While also emphasising the need for each case to be "considered on its individual merit," MHRA guidelines on the use of unlicensed medicines provide a hierarchy of appropriate steps.[107] These guidelines reinforce the recommendations of the ACMD that "U-CBPM should be considered as a product of last resort and used only when no other drug with MHRA marketing authorisation meets the clinical need." The MHRA prescribing hierarchy is summarised as follows:[108]

1. An unlicensed product should not be used when a licensed product is available and could be used to meet the patient's special need.
   Licensed cannabis-based medicines that may be suitable to meet the clinical needs of patients being considered for unlicensed cannabis-based medicines include Nabilone, Sativex and Epidyolex (Categories 7, 9 & 10).

2. Off-label products should be considered for use before products that have no MHRA license for use in the UK
   (Categories 7, 9 & 10, as above).

3. If there are no UK-licensed products that can meet the patient's needs, an imported medicinal product which is licensed in the country of manufacture should be considered.
   This definition would include the synthetic THC product Dronabinol, which is licensed in US, Canada, Germany, Australia and New Zealand, but not the UK (Category 8).

4. If the above steps have failed to identify a product that meets the patient's special need, a completely unlicensed product may have to be used, manufactured in Good Manufacturing Process (GMP)-inspected facilities either in the UK or overseas.
   Unlicensed cannabis-based 'specials' medicines fall under this definition. (Category 4 items)

5. The least acceptable products are those that are not licensed as medicines in the country of origin and may not be made to expected standards of pharmaceutical GMP.
   This would include unlicensed products not manufactured to GMP standards, including artisanal cannabis oils (as might fall under Categories 1 & 12).

In summary, all available guidance on the use of completely unlicensed medicines, including CBPM, recommends that they should be considered only as a last resort when other interventions have failed. Specialist physicians may prescribe CBPM according to their own clinical judgement but must consider the available guidance and be able to justify that the unlicensed product was supplied to meet a special clinical need that could not be met by any licensed product. This special clinical need "does not include reasons of cost, convenience or operational needs."[109] Theoretically, this means that a physician should not prescribe U-CBPM to a patient before considering L-CBM (which, in turn, should only be considered if conventional treatments have not been intolerable or not adequately effective). Nor should physicians prescribe an unlicensed product merely because it would be less costly than a licensed product.

Some physicians have told us that, in practice, they would take into account the full biological, psychological and social circumstances of a patient and that there are situations in which they would feel comfortable offering U-CBPM before offering a L-CBM, assuming conventional treatments had not been adequate. Several reported to us that they would consider a history of successful self-medication with a CBP, by a patient in their clinic, as a form of evidence. Taking into account the limited evidence base for many U-CBPM, physicians in this situation should be cautious that they bear full personal responsibility for prescribing unlicensed products and in the instance of a severe adverse reaction, however improbable, they would need to justify their prescribing decision.[110] A 2019 article in the British Medical Journal proposed some questions for physicians to aid decision-making in regard to cannabis-based medicinal products.[111]

There is limited medical training in cannabinoid medicine

On July 3, 2019, the Health and Social Care Committee published *Drugs policy: medicinal cannabis*, a report on the use of cannabis-based medicinal products in the UK. To inform this report, the enquiry committee issued a public invitation for written responses to five questions, the fourth of which was: 'Do practitioners have the knowledge and products available to them to confidently prescribe medicinal cannabis?' Evidence was submitted from a wide range of medical practitioners, professional medical organisations, charities, campaign groups, parliamentary groups, companies producing cannabis-based medicines, and individuals.

Multiple sources claimed that practitioners did not have the knowledge to confidently prescribe U-CBPM, for reasons including:

- there is limited evidence on the safety and efficacy of U-CBPM on which to base medical training or support prescribing, and the rate at which patient demand and expectations has increased is incommensurate with the relatively slow growth of the evidence-base;
- there is professional uncertainty about long-term risks of cannabis-based medicines, particularly neurodevelopmental risks in children and adolescents;
- there are negative biases regarding cannabis and cannabis-based products among practitioners related to the stigmatisation of controlled drugs;
- there are many specialist practitioners who trained before the discovery of the endocannabinoid system and are not sufficiently educated in this area of medical science;
- there is still very limited training at medical school and in specialist medical training on cannabinoid pharmacology or the medicinal use of cannabis-based medicines;
- there is a lack of guidance on available U-CBPM of sufficient quality and safety for medical use; and
- there is no recent historical clinical experience of prescribing CBPM in the UK.

Other sources claimed that there was sufficient medical knowledge amongst specialist practitioners to confidently prescribe CBPM when medically appropriate, and to explain the potential risks, benefits and areas of uncertainty to patients. Some witnesses highlighted that specialist doctors have significant academic interest in their area of medicine and tend to educate themselves to a high standard in regard to relevant medical developments, including cannabis-based medicines. Others argued that the clinical guidelines issued by professional specialist bodies provided sufficient knowledge to make prescribing decisions.

To assess the quantity of cannabis-related content in early medical education, we sent a Freedom of Information request to all 40 UK universities with a medical degree programme to request the number of lectures and/or seminars in the pre-clinical curriculum for MBBS students, as of the academic year 2018/19, in which the following cannabis and cannabinoid-related topics were 'substantially covered' (*see Table 10*):

a. the role, function and/or disorders of the endocannabinoid system in humans;

b. the safety and efficacy, mechanisms of action and/or clinical use of the licensed cannabis-based medicines Sativex, Epidiolex/Epidyolex and/or Nabilone;

c. the safety and efficacy, mechanisms of action and/or clinical use of unlicensed cannabis-based medicines;

d. the acute psychopharmacological effects of cannabis and/or cannabinoids; and

e. the association between chronic, heavy use of cannabis and/or cannabinoids and increased risk of psychotic disorders.

Thirty-two medical schools provided curriculum data in full for the requested time period. Of those for which data was not provided, three schools had their first cohort of students in 2019/20 and did not yet have curriculum data;

Table 10. The number and percentage of UK medical schools providing cannabis-related training

TOPIC	Preclinical curriculum provides no teaching sessions	Preclinical curriculum provides one teaching session	Preclinical curriculum provides more than one teaching session	Average number of teaching sessions provided
Unlicensed cannabis-based medicines	29 (90.6%)	3 (9.4%)	0 (0%)	0.1
Licensed cannabis-based medicines	25 (78.1%)	6 (18.8%)	1 (3.1%)	0.3
The endocannabinoid system	20 (62.5%)	9 (28.1%)	3 (9.4%)	0.7
Cannabis use as a risk factor for psychosis	18 (56.3%)	8 (25.0%)	6 (18.8%)	0.9
Acute effects of cannabis	16 (50.0%)	11 (34.4%)	5 (15.6%)	0.9

two schools reported that they did not record curriculum data; two more reported that the request was not applicable because of the way their medical programmes were structured; and one school did not respond to the request within the time period.

Almost half of the universities who supplied data in full reported that they provide no pre-clinical teaching sessions at all on any of the five cannabis-related topics (44%). Training on unlicensed and licensed CBPM was provided at 9% and 22% of medical schools respectively. Less than two in five medical schools reported that there was at least one session on the endocannabinoid system (38%) and less than half provided any teaching on cannabis as a risk factor for psychotic disorders (44%). Precisely half provided teaching on the acute effects of cannabis (50%). The average number of teaching sessions provided across all schools was less than 1 for every topic.

The findings confirm a paucity of medical education in cannabinoid medicine at the earliest stage of training. However, many universities explained that these topics might be covered in the later clinical stages of the medical curriculum, that students received broad training on the importance of asking patients about recreational drugs, and that the use of cannabis-based medicines would generally be considered too specialist to be known in detail at the point of graduation. In regard to teaching on Sativex, Epidyolex, and Nabilone, St George's medical school told us:

> *"We don't specifically cover any of these medications. Our drug curriculum is based on the top 100 most commonly prescribed medications and those required in emergency conditions, in line with the requirements for a Foundation Doctor. All of these agents are prescribed by specialists only, and detailed knowledge on drugs used in very specialist practice not a requirement for Foundation Doctor level, which is the requirement by the end of the course. Our students are however trained to be able to look*

up and learn about other licensed medications e.g. using the British National formulary where the need arises."

The breadth of training on cannabis and cannabinoids varied substantially between medical schools. For instance, the University of Central Lancashire reported that the total teaching time provided specifically on cannabis totalled approximately five minutes of a wider lecture on drugs of abuse, while St George's reported that the listed topics were covered across nine lectures and two sets of three hour sessions covering a clinical case in which students derive their learning for a week. Two universities reported that there were optional modules or 'student selected components' available to students on cannabis and cannabinoids. Many others reported that students were able to design their own research projects at some point in their university training and could choose a cannabis-based project if they wished to.

U-CBPM have only been available for prescription since November 2018, and it is quite surprising that as many as 3 medical schools provided teaching on that topic in 2018-19, particularly considering that the academic year would have begun before CBPM were rescheduled.

A 2006 article titled "The Endocannabinoid System as an Emerging Target of Pharmacotherapy," which has since been cited almost 2,000 times (only 15,000 or so of almost 60 million scholarly papers available on Thomson Reuter's Web of Science have more than 1,000 citations), provided an overview of the endocannabinoid system as a therapeutic target in pathophysiological conditions.[112 113] It made the following bold claim concerning the importance of the system in clinical medicine:

"In the past decade, the endocannabinoid system has been implicated in a growing number of physiological functions, both in the central and peripheral nervous systems and in peripheral organs. More importantly, modulating the activity of the endocannabinoid system turned out to hold therapeutic promise in a wide range of disparate diseases and pathological conditions, ranging from mood and anxiety disorders, movement disorders such as Parkinson's and Huntington's disease, neuropathic pain, multiple sclerosis and spinal cord injury, to cancer, atherosclerosis, myocardial infarction, stroke, hypertension, glaucoma, obesity/metabolic syndrome, and osteoporosis, to name just a few."

However, endocannabinoid research has not found its way into early medical education in the 14 years since the article was published. Almost two thirds of UK medical schools (63%) provide no preclinical teaching on the role, function and/or disorders of the endocannabinoid system in humans. This may reflect a limited translational relevance of endocannabinoid science to current clinical practice, the small number of licensed drugs that act directly on cannabinoid receptors, and the specialist nature of the clinical use of those drugs.

The topics most commonly covered in preclinical education were the role of cannabis as a contributing cause of some psychotic disorders and the acute psychopharmacological effects of cannabis. Many universities reported that these topics were covered jointly in teaching on drugs of abuse, addiction, and/or psychosis.

Cannabis has been a controlled drug in the UK since 1971, almost forty years before the first medicine derived directly from the cannabis plant was licensed by the MHRA in 2010. The arrival of U-CBPM as specials medicines is more recent still. Accordingly, the evidence base on the risks and harms of recreational cannabis use is more developed and recognised by the medical community than the evidence base for cannabis-based medicines, as is reflected in the content of contemporary medical education. While this disparity is understandable, it likely contributes to an ongoing stigma among medical practitioners, and, conceivably, a negative bias about the harms of cannabis and cannabis-based products for medicinal use relative to potential benefits.

A range of learning modules on cannabis-based medicines are now available to healthcare professionals, though none are mandatory for specialist practitioners. The NHS commissioned the University of Birmingham to develop a cannabis education e-module, available on the e-Learning for Healthcare system.[114] It covers information on the pharmacology of cannabinoids, legislation governing medical use,

Box 4. Dr Dani Gordon MD CCFP ABOIM ABIHM, Advisory Board member of the CDPRG and double board certified medical doctor who ran a cannabis medicine complex chronic disease referral practice in Canada.

"If you would have told me in medical school or in my first years of practice that I would become an advocate for medical cannabis or even consider prescribing it to a patient I would have never believed you. I was taught in medical school that cannabis was a dangerous highly addictive drug that can cause psychosis.We had no curricula on the endocannabinoid system or that there was such a thing as 'medical' cannabis.

Only years later working as a GP who specializes in complex chronic disease management including orphan diseases and mental health conditions did I start to consider the potential medicinal effects of cannabis. This was largely due to my patient's own experimentation with cannabis use medicinally and its ability to help them improve their quality of life and reduce polypharmacy, especially pain medications including opioids but also including benzodiazepine overuse. I decided to educate myself and then made the decision to start offering medical cannabis to appropriate patients. Since then and years later, I have treated thousands of patients with medical cannabis successfully when other more mainstream drug options proved inadequate to meet their clinical needs.

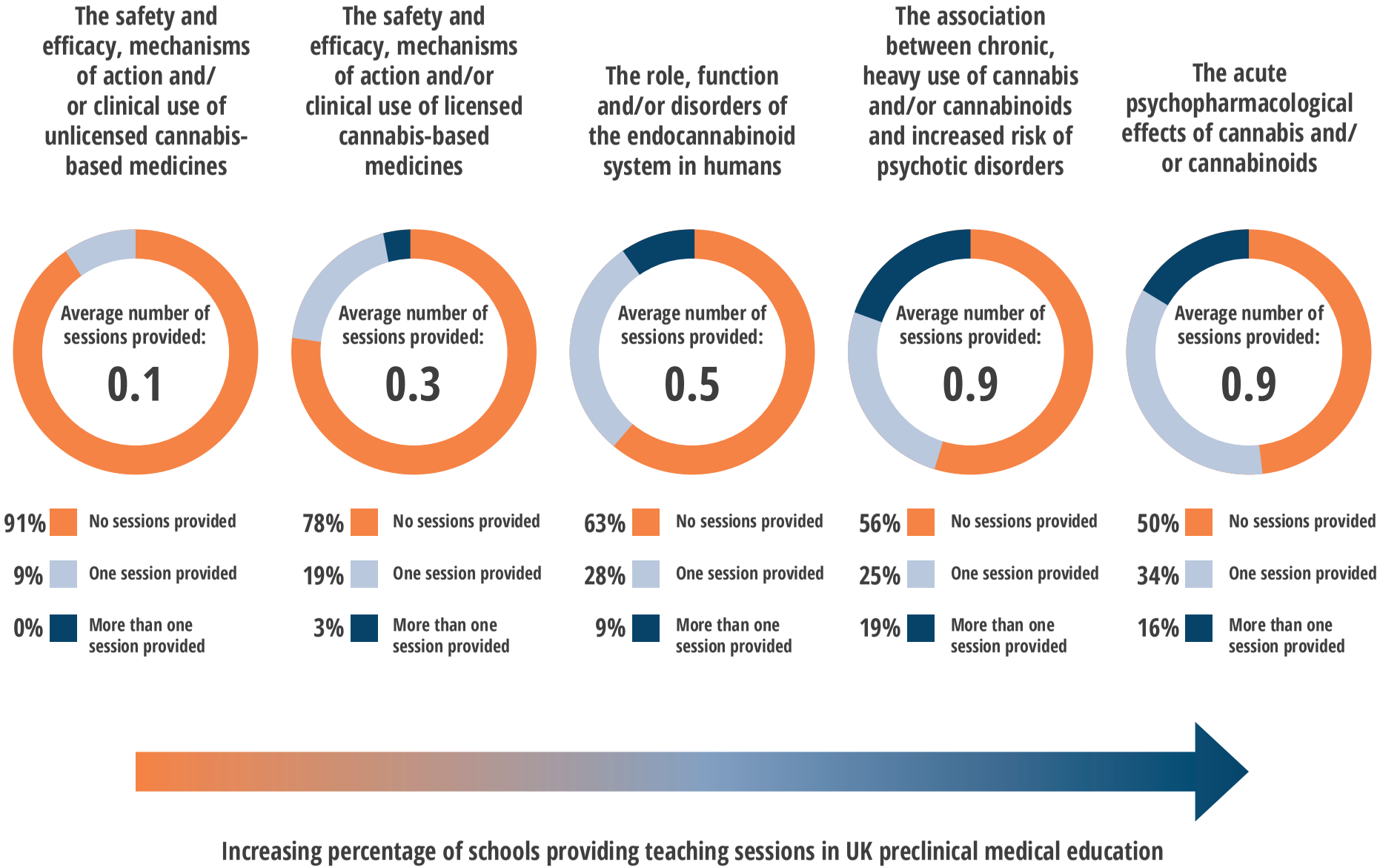
Most of my patients who have chronic pain also have other comorbid and overlapping conditions for which medical cannabis can often help with, including night pain and disrupted sleep, anxiety and even mood and energy in some cases. As a group of medicines, I now consider CBMPs to be the single most effective tool for helping manage complex chronic disease symptoms clusters, reduce polypharmacy and improve patients quality of life in carefully selected patients under medical guidance.My profession's acceptance of CBMP is already increasing, thanks to ever increasing research and education on this class of medicines and on our own endocannabinoid system, which was discovered 30 years ago but is only now making its way into medical curriculum."

therapeutic areas and evidence for the use of cannabis-based medicines.

Information and guidance on prescribing is also available in the guidelines issued by NICE and other specialist bodies. Training is also available from a variety of organisations outside of the NHS, although it should be noted that these providers have conflicts of interest and their training may contain positive bias. The Medical Cannabis Clinicians Society, a community-interest company providing free guidance on prescribing, has an online members' area with training resources, supplier information and peer support.[115] The Academy of Medical Cannabis provide a free Medical Cannabis Essentials course on their website and a catalogue of 12 specialist courses for between £40 - £80 per module.[116] In late December 2019, Sapphire Clinics, the first UK medical cannabis clinic registered by the Care Quality Commission (CQC), held their first two free online educational webinars, designed for physicians, on the endocannabinoid system, a review of the current evidence base for cannabis-based medicines, and the specialist clinical use of cannabis in the treatment of pain conditions.[117] Technion, the Israel Institute of Technology, is one of the world's leading centres for cannabis and cannabinoids research. In collaboration with the online learning platform Coursera, Technion provide specialist courses on cannabis-based medicines.[118]

It is arguable that prescribers do not need a detailed understanding of the human endocannabinoid system in order to safely and effectively prescribe CBPM, since there are many medicines routinely prescribed for which the mechanism of action is unknown. Knowledge on safety, side effects, drug-drug interactions, indications and contraindications, dosing, and available formulations may be enough to inform good clinical practice.

Figure 4. Percentage of UK medical schools providing preclinical teaching in a range of cannabis-related topics



There are gaps in knowledge and experience in prescribing and procuring

The Health and Social Care Committee's report *Drug policy: medicinal cannabis* found that "[there] is a lack of clarity amongst some as to the procedure for prescribing unlicensed products."[119] The Government's written response to the HSSC's report claimed that "[a] list of licensed UK wholesalers and products has been made to NHS Procurement Pharmacists and will be updated as new products become available."[120] However, Procurement Pharmacists advising the CDPRG have told us that no such list has been distributed.

The Unlicensed Medicines Imports & Defective Medicines Report Centre unit at the MHRA confirmed to us by email that no list of products has been provided to Procurement Pharmacists and that the MHRA evaluation consists of a vetoing process on the unlicensed products. The MHRA require evidence that the content/ratio of THC/CBD is declared and appears on the product label, that a Certificate of Analysis is available to support the batch specification, and that a valid GMP certificate is available for the site of manufacture. We were advised that "the prescriber responsible for the care of the patient holds responsibility for the product and treatment choice."

Prescriptions for U-CBPM must specifically state details of the product being prescribed, i.e. the name of the product or its common name; the manufacturer; the type of formulation – e.g. oil, tincture, whole flower or capsules; the content of THC and CBD in the product; directions for use; and quantity. However, in practice, neither prescribing physicians nor pharmacies have reliable information on what products are available or in stock, since specials companies were only permitted to import on specific prescriptions until March 2020.

Availability of stock from overseas manufacturers is also unpredictable, according to feedback from importers and pharmacists. The decision on what product should be prescribed therefore tends to be the result of a conversation between the specialist physician, the pharmacist, the importer and the manufacture in regard to what is available and appropriate. This process can be challenging and has been a setback to prescribing in the first year after rescheduling, though it is expected to improve as supply chains become more robust and stakeholders develop experience.

There are concerns about acute and long-term harms

Epidemiological research on the recreational use of cannabis has revealed a range of long-term adverse health effects, associated particularly with regular, heavy use of high-THC cannabis products at a young age.[121] [122] The severity and frequency of these risks has been disputed by some researchers, and the risks of recreational cannabis use may not necessarily translate into risks of medical cannabis use, but in the absence of robust evidence on the long-term safety of CBPM, the UK medical community has taken a cautious approach.[123] [124] This caution is reflected in the guidelines issued by specialist medical associations:

> ***"[Some] animal studies suggest that [THC] can also have pro-convulsant effects... There is concern about the effect of exposure to THC on the developing brain of both the younger child and adolescent.There is evidence that chronic high exposure to THC during recreational cannabis use can affect brain development, structure and mental health.These effects are seen more clearly in adolescents than in adults".***
>
> ***British Paediatric Neurology Association, Guidelines on the use of CBPM*** [126]

"There is currently little available information on teratogenic and neurodevelopmental effects for cannabidiol. In addition concerns remain for the effect of some cannabis-derived products on post-natal neurodevelopment."

Association of British Neurologists, Guidelines on the use of CBPM [125]

"CBPM have significant adverse effects including psychological, neurological and gastrointestinal. Psychosis is a particular concern."

Royal College of Physicians & Royal College of Radiologists, Guidelines on the use of CBPM [127]

Clinicians interviewed for the NHS England / NHS Improvement report on barriers to accessing cannabis-based products on the NHS stated that significant adverse effects are common in many licensed medicines (including those currently prescribed to children with treatment-resistant epilepsy) and that the potential risks of using U-CBPM should be assessed against the effect of not providing treatment where the condition has not adequately responded to conventional interventions.[128] In regard to severe treatment-resistant paediatric epilepsy, the report committee heard that the risks of continued seizures were significant, including the risk of sudden death. Accordingly, although physicians and medical associations will recognise that CBPM may have potential adverse health effects, and that no data is yet available for the long-term safety of either U-CBPM or medicines which have only recently achieved market authorisation, the clinical ratio of potential benefits to potential risks may, not infrequently, support prescribing.

1.2.2.3. COSTS

Procuring U-CBPM is expensive and not routinely funded by the NHS

NHS England (NHSE) receives the majority of the budget awarded to the Department of Health, amounting to £102 billion in 2015/16, and is responsible for distributing resources to Clinical Commissioning Groups (CCGs); clinically-led NHS bodies who plan and commission local services. Since 2012, CCGs have had statutory responsibility for commissioning the majority of NHS services and make local policy decisions on funding medicines.[129] CCGs may decide upon a policy that a particular treatment will not normally be funded, but they cannot declare a "blanket ban" and must "be able to consider whether to fund that treatment for an individual patient on an exceptional basis."[130] The process by which a prescriber may request funding, under exceptional circumstances, for an intervention that falls out of the range of services and treatments that the CCG has agreed to commission is known as an Individual Funding Request (IFR).

For some health care services, funding decisions are made at a national level. The National Institute for Health and Care Excellence (NICE) produce evidence-based guidance, quality standards, and information services for commissioners, health and social care practitioners and managers across the NHS. NICE clinical guidelines and health technology appraisals assess the efficacy and cost-effectiveness of treatments and provide recommendations concerning use. Where recommendations are made for the use of an intervention in NICE technology appraisal or highly specialised technologies assessments, commissioners have a statutory duty to provide funding for that intervention, where clinically

appropriate, within 3 months of the date of publication. Where NHS England makes a decision to directly commission a specialised health care service, their decision also applies nationally.

Most funding decisions, however, are made at the local level to meet local needs, which differ across the country. Since no U-CBPM are directly commissioned by NHS England, nor recommended for use by NICE guidance, funding decisions for prescriptions are made at the local level by Acute (Hospital) Trusts and CCGs.[131] According to local procedures, which vary somewhat across the country, it is expected that a hospital specialist who wanted to prescribe U-CBPM would send an approval request to the Trust Drug and Therapeutics Committee (DTC). The DTC would assess the evidence of efficacy, patient safety and cost-effectiveness and decide whether or not to pay for the cost of the treatment from the Trust budget, and whether to add the U-CBPM to the list of recommended medicines for the Trust (the Hospital formulary). Trusts are expected to meet costs in the first instance, since CCGs do not routinely commission unlicensed medicines, but if the CBPM is deemed to be of high-cost, the specialist may make an IFR on behalf of the patient to either the local CCG or to NHS England.[132] Requests must be supported by the DTC, Chief (or Deputy) Pharmacist and by the Medical Director of the Trust.[133]

Witnesses to the Health and Social Care Committee (HSSC) reported that, in the case of U-CBPM, the process of applying for funding was lengthy, burdensome, unsustainable for long-term provision, and that the chances of requests being approved were low. Professor O'Callaghan, President of the British Paediatric Neurology Association, testified that the cost of supplying U-CBPM may be as much as £25,000 to £30,000 per patient per year. Local commissioners, he advised, have limited budgets with competing demands and are not likely to fund U-CBPM on the basis of the available clinical evidence. Other medical witnesses observed that there would likely be inconsistency in funding decisions between trusts, giving rise to a postcode lottery of access.

Until the end of January 2020, limited evidence was available on the total and average costs to the NHS associated with U-CBPM prescriptions in the first year since the 2018 amendment. It is now known that the average cost to the NHS of all prescriptions for U-CBPM dispensed in the community from November 2018 – October 2019 was £2,789.21 per prescription, at a total cost to the NHS of £52,994.99. This average would reflect a total cost per patient per year of £33,470.52, in line with the predictions made by Professor O'Callaghan.[134]

Of the 18 prescriptions that were issued between November 2018 – September 2019 and submitted to the NHS BSA, cost data is provided in Table 11. Product information provided by the NHS BSA in response to FOI 08823 was cross-referenced with *Table 14 (Medicinal cannabis costs)* of the NICE *Cannabis-based medicine products: Evidence review for spasticity* document. The price per pack (Netherlands) is the cost of the drug as listed on www.cannabiszorg.nl, and the Net Ingredient Cost (NIC) is the total reimbursement cost of the drug to the NHS.

Access to U-CBPM through the private healthcare sector is also limited by reason of costs. It has been reported that patients achieving access through private means have faced costs of between £800 and £4,000 a month.[135] [136] Prescribers and pharmacists in the private sector have disclosed to the authors that costs fell by as much as 50% over the course of 2019, with some patients having paid as little as £125 per month for their medicines. Private patients must pay for the appointment (an initial consultation at Sapphire Clinics, for instance, will cost £250 and further follow-up appointments will cost £150) and for the costs of procuring the medicine.[137] Licensed importers have reported to us that the costs of the product are dramatically increased by UK regulatory restrictions on importation, limited levels of stock held by overseas manufacturers, and a lack of UK production. These issues inflated costs in both the private and public sectors.

Professor Goddard, President of the Royal College of Physicians, told the HSSC that "the prescription of unlicensed medicines is very difficult for good reasons, and the regulation is there for good reasons…" We agree that it is necessary for safeguards to be in place to prevent the widespread use of medicinal products which are not licensed and have limited evidence on adverse health effects and efficacy, since loopholes could readily be

Table 11. Costs of U-CBPM prescriptions to the NHS from November 2018 - September 2019

Product	Bedrolite® CBD 10% oil (a)	Bedica® THC 2.0% oil (a)
Ingredients	<1% THC and 9% CBD 0.05 ml = 5 mg CBD (b)	14% THC and <1% CBD 0.05 ml = 1 mg THC (b)
Total quantity prescribed (ml)	1,270 (a)	70 (a)
Product pack size (ml)	10 (b)	10 (b)
Price per pack, Netherlands (€)	77.12 (b)	46.78 (b)
NIC (£)	47,715 (a)	1,265 (a)
NIC per pack (£)	375.71	180.71

(a) https://apps.nhsbsa.nhs.uk/FOIrequests/requests/FOI_Request_(08823).csv
(b) https://www.nice.org.uk/guidance/ng144/documents/evidence-review-8

exploited at the possible detriment to patient safety. However, these risks must be weighed against the risks of restricting access. When considering patients who present with a history of use of black market or self-cultivated cannabis to treat a medical condition, whose symptoms have responded well to that intervention, prescribers and commissioners should take into account the significant risks posed to that individual if limited access to medicinal products encourages continued unlawful access (*see the case of Lesley Gibson in Chapter 2, Route 6a*). Though cannabis-based products obtained unlawfully may, in some circumstances, provide therapeutic benefit to individuals, there are risks in regard to product quality and consistency, and the potential for criminal sanctions. Policy models to address these and other issues are proposed in Part B of this report.

1.2.2.4. SUPPLY

Importation of controlled drugs is limited under UN drug conventions

As a Party to the 1961 UN Single Convention on Narcotic Drugs and the 1971 Convention on Psychotropic Substances, the UK also has international commitments to limit the total importation and exportation of controlled drugs to the estimated national requirements for scientific and medical purposes. The licensing authority of an importing country is required to satisfy itself of the following before authorizing any imports from a licensed importer:

- the UN International Narcotics Control Board (INCB) has confirmed an annual requirement estimate for the controlled drug; and
- the quantity to be imported does not exceed the total requirement estimate, taking into account the quantities already ordered in the course of the year.

Similarly, the licensing authority of the exporting country is required to satisfy itself that these conditions are met in regard to the importing country. If the estimate of the country is too low, the national authority should provide the INCB with a supplementary estimate and an explanation of the reasons necessitating the supplement. This must be confirmed by the INCB before importing and exporting countries

authorise further.[138]The estimated requirements of cannabis and cannabis-based products for the United Kingdom for 2019 and 2020, and therefore the total amounts that may be authorised for import per year, in grams, are provided in Table 12.[139 140]

The domestic legal controls introduced by contracting states on the production, distribution and the use of drugs are not directly bound by international conventions. However, we have heard from UK holders of Schedule 1 domestic and import licenses that, in practice, they have been unable to import THC into the country for use as an API in medicinal products, even in small quantities, because doing so would exceed the UK's annual import quota. Exporting countries have, accordingly, not authorised orders, even when the UK Home Office have granted approval.

In response to requests from UK pharmaceutical companies, the Home Office submitted supplementary estimates to the INCB in late 2019. The INCB assessments released in January 2020 still listed the UK requirement of Δ9-THC at 20 grams. However, updated estimates published in March have increased the UK quota to 1,120 grams per year. This will improve supply chains that rely on importation.

UK Licensing Authorities have not permitted bulk import to Schedule 2 license-holders

In 2018-19, UK licensing authorities (the MHRA and the Home Office) prevented specials importers from ordering the bulk import of either U-CBPM specials (i.e. importation in anticipation of prescription) or CBPM ingredients (i.e. importation for UK manufacture). These restrictions are not ordinarily applied to other controlled drug specials medicines that are not, or do not contain, CBPM. In March, 2020, restrictions on import were eased to allow manufacturers to import in bulk.[442]

The importation regulations that were in place from 2018-2019 intentionally limited the supply of U-CBPM into the UK to mitigate potential risks. However, they also contributed to supply and cost challenges that prevented the timely and reliable availability of CBPM specials to patients for whom prescriptions were written. In some cases, inflated importation costs have

Table 12. INCB controlled drug assessment for the UK

	2019	2020
Cannabis	6,772,571	196,347
Cannabis resin*	35	25
Δ9-THC	20	1,120

**Including cannabis tinctures (10g of tincture equivalent to 1g of cannabis) and cannabis extracts (1g of extract is equivalent to 7g of cannabis; 1g of Sativex is equivalent to 12.6g of cannabis) [141]*

forced private patients to travel overseas to collect and bring back prescribed CBPM on their person – an unlawful route of access which has led to prescribed medications being seized at the border (*see Chapter 2*).

There was no statutory requirement to limit the bulk importation of CBPM in this way, INCB limits notwithstanding. In 2019, the Licensing Authorities told us that these restrictions were justified in accordance with the ACMD's recommendation that appropriate 'checks and balances' should be applied to avoid risks of diversion.[142] There is no indication in the available correspondence between the ACMD and the Licensing Authorities that these recommendations for 'checks and balances' were meant to be applied specifically to importation, but it is understandable that a precautionary principle was taken in the regulation of all steps of the supply chain.

Long prior to the 2018 amendment, well established regulations had been in effect for the importation and supply of unlicensed specials medicines. The importer of any unlicensed medicinal product must hold a Wholesale Dealer's license or Manufacturer's 'Specials' license, and the details of each import must be provided to the MHRA 28 days in advance of the date of intended import.[143] Importers of controlled drugs must hold the appropriate domestic and importation licenses from the Home Office. The quantity of a specials medicine that may

be imported is limited to 25 administrations or up to three-month supply per notification.[144] The license holder may not import more than the quantity stated in the notification, but there is no restriction on multiple, sequential, notifications and there is no legal requirement for individual patients' named to be supplied.[145] In practice, licensed importers routinely submit multiple parallel import notifications to build stock of specials medicines in anticipation of prescription.

Importers must be able to provide evidence of the special need for an imported unlicensed product, such as a letter from a prescriber, but new evidence is not required for every supply.[146] The supply of unlicensed medicines to medical practitioners, pharmacies, hospitals or clinics must be in accordance with a prescription written by an authorised prescriber.

The memorandum to the 2018 amendment reads: "The [CBPM] that is therefore ordered/ prescribed... will need to be supplied under long-standing arrangements for the supply of what are known, in healthcare settings, as "specials"." This phrasing does not indicate an intention to treat CBPM import applications in an exceptional way to other specials medicines. However, the 2018 - 2019 policy was that importation of CBPM specials must be applied for on a prescription-specific, named-patient basis, rather than in anticipation of demand. MHRA regulations required CBPM import notifications to state "the quantity to be imported *which will be the quantity as written on the prescription*."[147] Updated MHRA guidance now states that the quantity that may be imported is limited to 25 administrations or up to three-month supply per notification, as is the case for all other specials medicines.

Other than the early MHRA guidance on CBPM quoted above, it was not clear that a requirement existed in legislation or other specials regulation to limit imports to a prescription-specific model. The 2018 amendment states that orders and supply, though not specifically importation, must be "in accordance with a prescription or direction of a specialist medical practitioner." The term 'direction' is not clearly defined in the Medicines Act 1968, the Misuse of Drugs Act 1971 or the Misuse of Drugs Regulations 2001, though it is used frequently. The term might, arguably, be interpreted to include letters from specialist physicians outlying a need for stock to guarantee continuity of supply to patients with chronic clinical needs in anticipation of repeat prescriptions. In 2019, importers made import applications in accordance with letters of this sort, but they were refused by Licensing Authorities. This was because 'direction' is interpreted by Licensing Authorities in a narrower way, namely, to denote the direction of another healthcare professional under the instruction of the specialist physician, such as a junior doctor prescribing a product on a hospital ward, or a general practitioner issuing repeat prescriptions for a patient in primary care.

Since we could find no legal definition of 'direction,' we corresponded with the Home Office, the MHRA and NHS England to inquire whether a prescriber's letter might be sufficient evidence of clinical need for bulk import. Under the 2020 import regulations, this form of direction is now an acceptable form of justification for a special clinical need, and may be used in import notifications.

To our knowledge, no importers were granted permission under Schedule 2 licenses to import bulk quantities that were not directly and fully accounted for by specific prescriptions for named patients. However, several companies were granted permission to import quantities associated with multiple prescriptions in a single shipment and subsequently claimed that they have accomplished bulk import. These claims were misconstrued by some stakeholders as meaning that CBPM had been imported in anticipation of prescription: in late 2019, the DHSC confirmed to us by email "it is not currently possible to import bulk quantities of CBPM" on such a basis.

Nonetheless, some importers managed to build limited stock of imported CBPM prior to the 2020 policy change. We assume that the stock held by some importers consisted of retained material from expired or unwanted prescriptions, or of excess material imported on a more frequent or otherwise greater basis than is needed to meet the individual's need, e.g. by requesting three-month quantities for individual patients every month.

In the circumstances that an importer is registered on the National Drugs control System (NDS) and in receipt of both a domestic license and an import licence covering Schedule 1 controlled

drugs, it is plausible that importation of bulk cannabis-based products was permissible under the old scheme. In 2019, the Home Office issued 362 domestic licenses covering possession of schedule 1 compounds, and 452 import licenses for shipments containing cannabis or with a controlled cannabinoid content. Controlled drug import licences are issued for individual consignments with reference to the drug substance(s) contained in the shipment. An import licence can cover up to four different types of drug substance or preparation.[148]

In 2019, Licensing Authorities did not formally clarify the circumstances under which licensed importers would be permitted to bulk import cannabis-based raw material for manufacture of finished CBPM products in the UK (e.g. cannabis-based API). However, it seems clear that bulk importation of API was not presently possible under Schedule 2 licenses for the same reasons that prevented the bulk importation of CBPM.

The definition of CBPM in the MDRegs 2001 includes "a substance or preparation for use as an ingredient of, or in the production of an ingredient of, a medicinal product." The definition of CBPM is not dependent on a prescription, though the order and supply of CBPM are. Accordingly, it might be expected that ingredients destined for use in a CBPM would have been controlled under Schedule 2. However, we heard from one importer that the Home Office advised them that all U-CBPM material, whether ingredients or finished products, would still be controlled under Schedule 1 until prescribed. Since ingredients are used in the production of a finished product, they are never directly prescribed. It was therefore unclear whether cannabis-based ingredients were considered Schedule 1 or Schedule 2.

On 24 January, 2020, Jo Churchill, a minister at the DHSC, responded to a Parliamentary Question on whether there were circumstances under which cannabis-based API could be imported: "CBPM may only be imported to meet the special clinical need of individual patients. It is not currently possible to import bulk quantities of these products... Importers registered with the MHRA can import active pharmaceutical ingredients where intended for the production of a medicinal product for use in humans."[149] Since bulk importation was not possible, we believe that the only circumstances under which importation of cannabis-based ingredients would have been permitted under Schedule 2 terms was if the full amount that was ordered was required for the preparation of the amount of CBPM as declared on a specific and valid prescription for an individual patient. It is very unlikely that this would have been a cost-efficient means of supply.

An alternative route existed, in theory, though we know of no cases in practice, to import THC for end use as an ingredient. Dronabinol does not have market authorisation as a medicine in the UK but it is authorised in Germany. Under the Parallel Import Licensing Scheme, which allows a medicinal product that is authorised in another EU member state to be imported and marketed in the UK, specials manufacturers could import Dronabinol as a finished product but then use it as an ingredient, assuming trades are not blocked on the grounds of INCB quotas.[150] It is unclear how Brexit will affect the Parallel Import Scheme in the future.

Prescribers, pharmacists and importers reported to us that the previous prescription-specific limits on importation hindered the legitimate medical use of U-CBPM in a variety of ways. We have been told that overseas manufacturers and regulators had not always been interested in supplying CBPM to the UK, or reserving stock for UK orders, because of low perceived demand. Reliance on importation for every order increased confusion among prescribers and pharmacists in regard to which products were available and could be reliably acquired. We have heard claims made that the old import regulations raised the cost of supply, leading to a greater burden of cost on private patients and in some cases leaving them with no options other than unlawful routes of access. The medical director of one CQC-registered private specialist clinic has claimed that delays in the supply chain, particularly associated to importation limits, were causing a range of harms to patients associated with interruptions in treatment. The challenges in importing API in 2018 – 2019 have limited UK manufacture, leaving suppliers reliant on importing medicinal products which are unlicensed in the country of origin, increasing risk to patients.

We also heard from multiple importers and pharmacists that UK Licensing Authorities had taken several weeks to approve some

importation notifications. These and other delays – associated with export approvals, shipping, quarantine, and quality checks – resulted in some patients waiting from 4 – 14 weeks from the date of initial prescription for the product to be available for collection. Since prescriptions for Schedule 2 CBPM are only valid for 28 days from the date of signing, some prescriptions expire before dispensing is possible and must be reissued. Stories attesting to the difficulties faced by patients have been described by the press, such as that of Jo and Martin Holden.

> *Martin Holden, 51, from North London, was diagnosed with a terminal brain tumour and prescribed U-CBPM to alleviate his suffering in his final weeks. In November 2019, his wife, Jo Holden, told iNews that the prescription had taken 3 months to arrive, by which time Martin had already passed away.*[151]

Our correspondence with the DHSC and Licensing Authorities in 2019 indicated that they do not believe the delays in supply associated with importation were attributable solely to UK regulations and licensing, noting that overseas manufacturers must also apply and wait for approval from their own Licensing Authorities before they can lawfully export. MHRA guidance indicates that this export approval may only occur after import authorisation is granted by the UK.

The DHSC told us that "where import applicants are providing the correct documentation, the Home Office and MHRA advise that they are treating these as emergency imports and applicants can expect decisions with 24-48hrs." In support of this claim, we have heard from some importers that they have experienced no delays in licensing approval from the Home Office or in the response from the MHRA to import notifications, and that they believe delays experienced by other importers relate to improper understanding of the guidance.

The challenges to importation addressed above were communicated to Government departments, regulators and the NHS administration, by various stakeholders along the supply chain, and we were told in late 2019 that changes to import policy were in development and would be communicated to stakeholders in early 2020. The Pharmacy Development and Regulation unit at the Department of Health & Social Care (DHSC) told us:

> *"The Department is aware that some wholesalers and pharmacies have reported experiencing challenges in importing a range of CBPM. It is clear that for some products, long lead times and delays in receiving export licenses from the authorities in the country of manufacture, have led to delays in the supply against first prescriptions and continuity of supply for repeat prescriptions.The Department, MHRA, Home Office and NHS England-NHS Improvement are in the process of agreeing what action can be taken to help alleviate delays to the import of CBPM, including exploring mechanisms to allow licensed wholesalers to hold a small reserve stock linked to an evidenced demand by specialist prescribers."*
>
> Stephen Knight, Pharmacy Development and Regulation, DHSC

This new policy will have a positive impact on access, reducing lead times of supply from months to days and reducing costs associated with import licenses. However, the policy will not affect products exported from the Netherlands, such as the Bedrocan range, since under Dutch law, CBPM can only be dispensed against a prescription. The majority of CBPM imports in 2018 – 2019 were for Bedrocan products, which means that continuation of those products for patients presently receiving benefit from them will remain subject to the same challenges under the old import scheme. The new policy will be of greatest benefit when affordable supply is available from other international producers.

There is no established UK production

The supply of U-CBPM has, so far, relied exclusively on importations – with the exception of Epidyolex, which was provided to patients as part of an early access programme before it received a product license. Government report that they are working with UK producers to establish a "stable UK supply" of U-CBPM that are safe and of adequate quality for medicinal use in humans.[152]

As of 25 October, 2019, there were 19 extant licenses to cultivate high-THC cannabis in England, Wales and Scotland – representing an increase of 400% since 2014.[153] There has been a modest 30% increase in the number of applications for low-THC cultivation licenses

Table 13. Cannabis-related API registrations in the EudraGMDP database[156]

API name	Registration holder	Operation	City	Country
Cannabidiol (CBD)	BSPG Laboratories	Manufacturing, Distribution	Sandwich	UK
	Sterling Pharma Solutions	Manufacturing	Dudley	
	Active Pharma Supplies	Distribution	Leyland	
	GW Pharma	Manufacturing	Sittingbourne	
	Aesica Pharmaceuticals	Manufacturing, Distribution	Cramlington	
	Chiracon	Manufacturing	Luckenwalde	Germany
	Alpha-Cannabis Pharma	Distribution	Bad Nenndorf	
	Arevipharma	Manufacturing	Radebeul	
	Fagron Hrvatska	Distribution	Donja Zelina	Croatia
	Farmabios	Manufacturing	Gropello Cairoli	Italy
	Farmalabor	Manufacturing	Canosa di Puglia	
	F.L. Group	Distribution	Vado Ligure	
	Galeno	Manufacturing	Carmignano	
Cannabis	Tilray Portugal	Manufacturing	Cantanhede	Portugal
	CannaXan	Distribution	Bayern	Germany
	Apurano Pharmaceuticals	Manufacturing	Bayern	Germany
Cannabis flower	Lenis Pharmaceutics	Distribution	Ljubljana	Slovenia
	Salus Wholesalers	Distribution	Ljubljana	
	Farmakem Services	Distribution	Maribor	
		Distribution	Ljubljana	Slovenia
Hemp	Kemofarmacija	Distribution	Ljubljana	Slovenia

Table 14. Cannabis cultivation licenses between 2010 - 2019

	Number of cultivation licenses granted by the Home Office	
Year	**Low-THC licenses**	**High-THC licenses**
2010	49 [(a)]	5 [(a)]
2011	31 [(b)]	5 [(b)]
2012	29 [(b)]	5 [(b)]
2013	6 [(b)]	5 [(b)]
2014	7 [(c)]	5 [(c)]
2015	14 [(d)]	12 [(d)]
2016	9 [(d)]	12 [(d)]
2017	9 [(d)]	12 [(d)]
2018	20 [(d)]	11 [(d)]
2019	33 [(e)]	20 [(e)]

(a) https://www.gov.uk/government/publications/cannabis-cultivation-licences-issued-in-2010
(b) https://www.gov.uk/government/publications/licences-granted-for-cultivation-of-thc-cannabis-plants-2010-to-2013/licences-granted-for-cultivation-of-thc-cannabis-plants-2010-to-2013
(c) https://ukcsc.co.uk/how-many-home-office-cannabis-licences-were-granted-in-2014/
(d) CDPRG FOI request 56882
(e) CDPRG FOI request 57170

submitted to the Home Office over the past decade, with 57 recorded in 2010 and 75 recorded in 2019.[154] [155] However, the success rate of applications fell over this period, with 86% of applications granted in 2010 compared to only 44% in 2019. A gradually decreasing trend in the number of licenses granted per year between 2010 – 2017 has since reversed, with the numbers of applications both submitted and granted increasing since 2018.

The authors are in communication with multiple UK-based manufacturers expecting to release CBPM and cannabis-based API product ranges in 2020. However, there are presently no companies registered to manufacture any cannabis-based API other than cannabidiol (CBD) in the UK. A list of companies registered in EEA countries to manufacture or distribute a range of cannabis-based API, for use in the manufacture of CBPM, is provided in Table 13.

1.2.2.5. STATUTORY RESTRICTIONS

Cannabis medicines are subject to controlled drugs guidelines and regulations

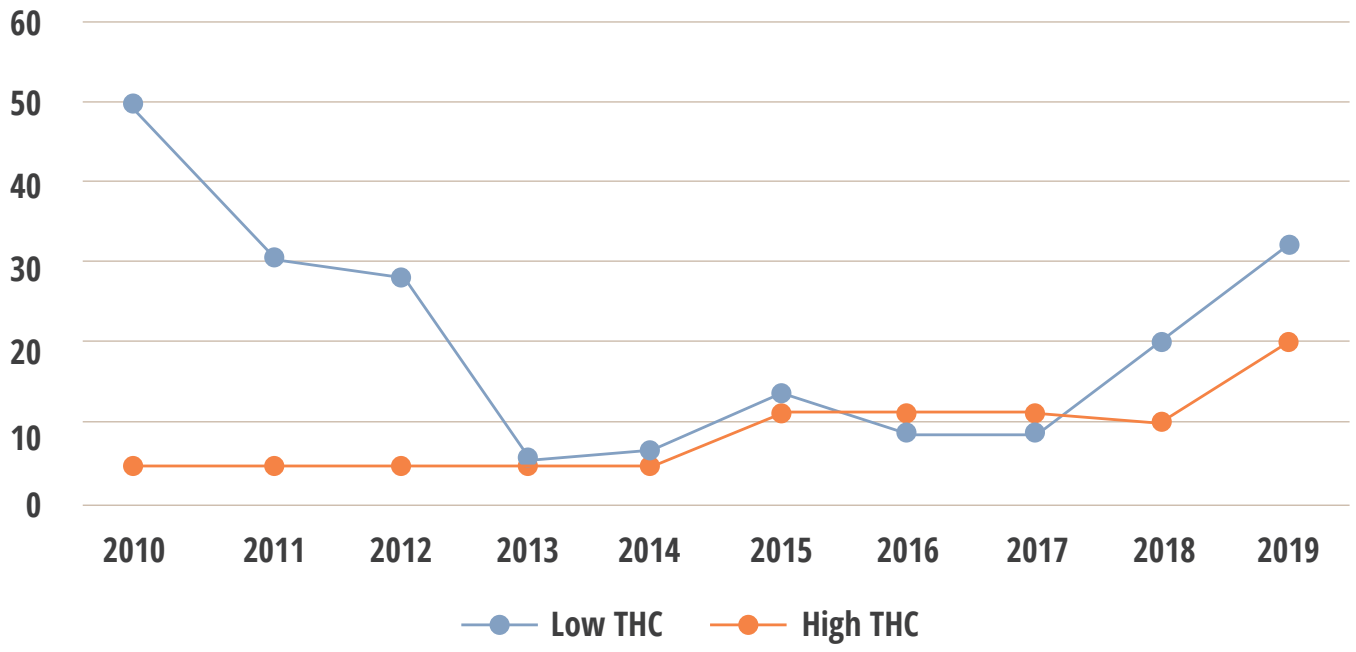
U-CBPM are listed as Class B controlled drugs under the MDA 1971 and as Schedule 2 drugs under the MDRegs 2001. The supply, prescription, storage, destruction and record keeping of Category 4 products are thus subject to the MDRegs 2001 and the MD(SC)Regs 1973, as well as professional guidance on controlled drugs for health practitioners.[157] [158] [159] See Route 1: §1.1.2.2 for an overview of controls on Schedule 2 drugs.

Regulation 16 (1.e) of the 2001 Regulations limits the validity of prescriptions of controlled drugs to 28-days. This poses a particular challenge to the supply of U-CBPM, since the lack of domestic production and the prescription-specific model for importation applications commonly result in delays that exceed this time period. In such instances, the initial prescription becomes invalid and a new prescription must be written. The Home Office have indicated to some suppliers that it would consider any controlled cannabis-based material that is not associated with a valid prescription to revert to control under Schedule 1 of the MDRegs 2001.

CBPM have unique statutory limitations on use

The 2018 amendment included additional regulatory access restrictions on the supply and use of CBPM, in order to ensure that access should be available where medically appropriate, whilst

Figure 5. Number of cultivation licenses granted by the Home Office between 2010 - 2019



maintaining safeguards against misuse, harm and diversion (*see Annex B*).[160] CBPM are legally defined not only by form but also by purpose to certify that existing controls continue to apply to products supplied and used without medical instruction. Prescriptions for U-CBPM (Cat. 4) can only be initiated by specialist physicians in secondary or tertiary care with competence in the condition and patient group for whom the prescription is intended. CBPM cannot be lawfully smoked as a route of administration.

1.3. ROUTE 3: CANNABIS-BASED INVESTIGATIONAL MEDICINAL PRODUCTS

An investigational medicinal product (IMP) is any medicinal product which is being investigated in a clinical trial, including products that do not yet have a marketing authorisation, and products that do have market authorisation but where the product is used in a different form or for a different indication to those specified in the authorisation.

Applications for a product to be authorised as an IMP must be supported by an IMP dossier (IMPD), containing information related to the quality, manufacture and control of the product and data from non-clinical and clinical studies. The production, assembly or importation of an IMP must be in accordance with a manufacturer's authorisation for investigational medicinal product (MIAIMP) and, if the product is a CBPM, under Home Office Schedule 2 production licenses and in accordance with Schedule 2 controls on storage, supply and use.[161] [162]

All clinical trials involving investigational medicinal products must be registered on the European Clinical Trials Database and obtain a Clinical Trial Authorisation (CTA) from the MHRA, who provide guidance on applications on their website.[163] Definitions of 'clinical trial' and 'investigation medicinal product' are provided in Annex A.

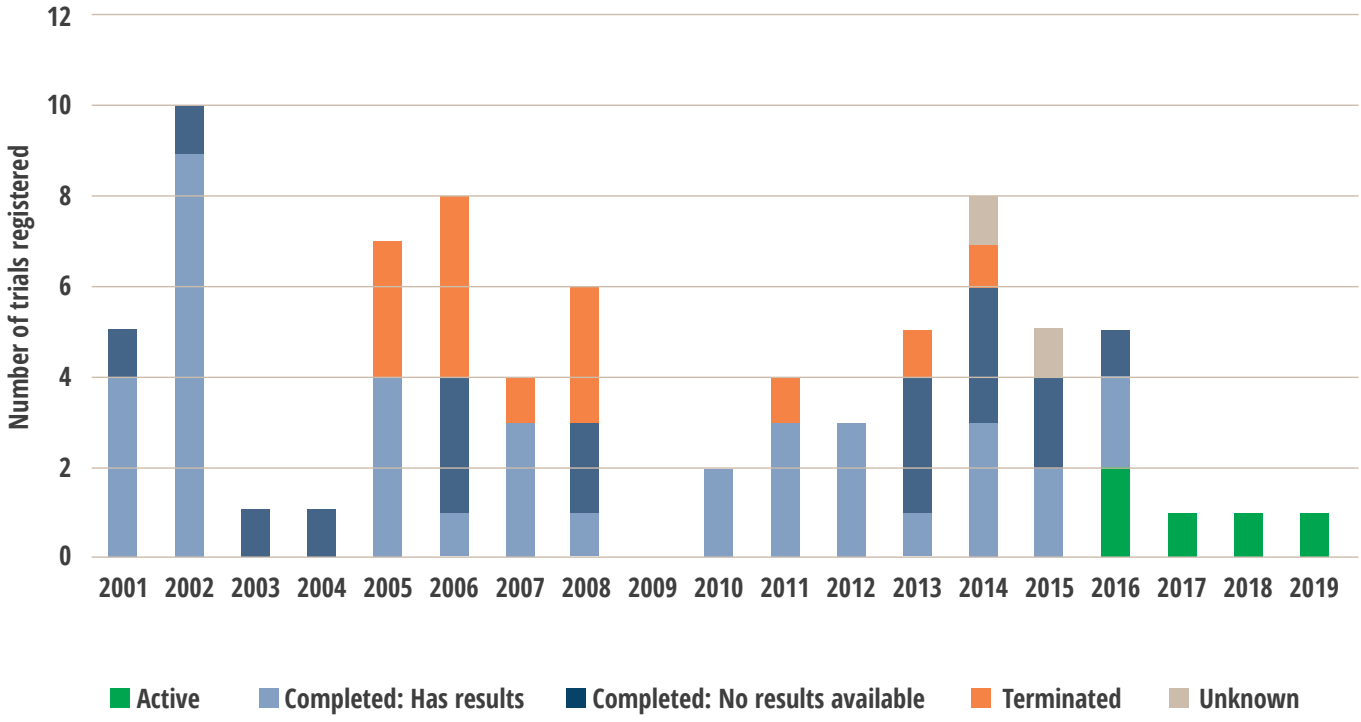
1.3.1. PRESCRIBING AND DISPENSING CANNABIS-BASED INVESTIGATIONAL MEDICAL PRODUCTS

A search of three clinical trials registries (ClinicalTrials.gov, ClinicalTrialsRegister.eu and isrctn.com) found a total of 77 unique interventional trials in cannabis- and cannabinoid-based medicines at sites in the UK since 2001.[164] The search revealed a total of 56 completed trials, 14 terminated trials, five active trials and two of unknown status. In 8/14 of the trials that were terminated early, the investigational product was Rimonabant, an inverse agonist for the cannabinoid receptor CB1 that showed promise as an effective treatment for obesity and achieved market authorisation from the EMA in 2006, but was withdrawn in 2008 after evidence from post-marketing experience and ongoing clinical trials demonstrated severe psychiatric side effects. According to the trial registries, 38/56 (68%) completed trials had results available. A total of 4,560 participants received a cannabis-based IMP across all completed studies with available data in this time period, excluding patients who withdrew before completion of the trial. The number of registered trials started each year is shown in Figure 6.

Of the five trials currently active, two are still recruiting: (1) a double-blind, randomized, placebo-controlled Phase 3 trial investigating the safety and efficacy of CBD in patients with Rett Syndrome; and (2) an open-label extension phase trial of CBD for seizures in Tuberous Sclerosis Complex, recruiting from patient participants in a completed randomised controlled trial on CBD for the same condition. These two trials are both sponsored by GW Research Ltd.

In October 2018 and March 2019, the National Institute for Health Research issued two themed calls (funding opportunities focusing on a particular research area) for cannabis-based products for medicinal use. Two NIHR programmes participated in these calls: Efficacy and Mechanism Evaluation (EME) and Health Technology Assessment (HTA). In response to a Freedom of Information request, the DHSC informed us that the HTA programme did not receive any applications over the two calls. The EME programme received one application from the first call and four from the second call. One application was considered to be within the remit of the programme and competitive for funding, but none were accepted. Nonetheless, the institute encourages research in this priority area. On 20 November 2019, the NIHR held a workshop for clinicians, researchers and NHS England to design a trial on medicinal cannabis and severe treatment-resistant epilepsy.

Figure 6. Interventional clinical trials in cannabis and cannabinoid-based medicinal products started between 2001 – 2019 at UK sites



A separate division of the NIHR, the 'Clinical Research Network', have historically supported 14 commercial clinical trials in medicinal cannabis products and are presently supporting a further two in setup. The CRN have reported to us that three additional trials are being assessed for feasibility. The number of clinical trials registered in cannabis- and cannabinoid-based medicines in the UK is expected to sharply increase in the coming years.

1.3.2. CHALLENGES IN ACCESSING CANNABIS-BASED INVESTIGATIONAL MEDICAL PRODUCTS

1.3.2.1. REGULATORY RESTRICTIONS

Cannabis-based IMPs were only recently rescheduled

Research in cannabis and its derived products has been tightly controlled, in the UK and internationally, by domestic drug laws shaped by commitments made under the 1961 UN Single Convention on Narcotic Drugs and subsequent treaties. In the UK, the Misuse of Drugs Regulations 2001 provides for the authorised use of controlled drugs, including scientific and medicinal use. These regulations listed cannabis under the most restricted category, Schedule 1, until the 2018 amendment rescheduled cannabis-based products for medicinal use under Schedule 2.

The restrictions on availability for scientific and medicinal use have, historically, made clinical trials in cannabis and controlled cannabinoids unusually challenging. Researchers commonly report that Schedule 1 designation dramatically increases the cost, duration and stigma of scientific drug research, and that these challenges are often enough to deter research altogether.[165] There have been only a handful of research centres and pharmaceutical companies that have conducted clinical research in CBPM in the UK, most notably GW Pharmaceuticals, who successfully brought Sativex and Epidyolex to market. Of the known clinical trials that have been completed since 2000, three-quarters were sponsored by GW.

The regulatory challenges to research in cannabis-based medicines have substantially lessened since the rescheduling of CBPM in

2018. However, as discussed below, it takes a long time to develop clinical trials and it will take years before the effects of the amendment on clinical research are clear.

Many cannabis-based IMPs are subject to controlled drugs guidelines and regulations

Since the amendment, IMPs containing cannabis or controlled cannabinoids are listed under Schedule 2 of the MDRegs 2001. As with all other controlled forms of cannabis-based product, they remain Class B controlled drugs under the MDA 1971. The supply, prescription, storage, destruction and record keeping of Category 4 products are thus subject to the MDRegs 2001 and the MD(SC)Regs 1973, as well as professional guidance on controlled drugs.[166] [167] [168] See Route 1: §1.1.2.2 for an overview of controls on Schedule 2 drugs.

1.3.2.2. CLINICAL TRIAL DEVELOPMENT

There have been limited numbers of clinical trials in CBPM

It is a slow and costly process to bring a new drug to market and pharmaceutical companies typically invest more than a billion pounds along the way, with clinical trials accounting for about 10% of total costs.[169] One systematic review reported a median overall cost of 17,020 USD per patient among 9 RCTs with published cost data.[170] Individual randomised controlled trials may take several years from initial approval to completion and, in the context of drug development, may be part of a three-phase trial process leading up to licensing approval that may take more than a decade.

Unless they are supplied as specials medicines, all medicinal products require a product license from the MHRA or the European Medicines Agency (EMA) before they can be used in the UK.[171] This license determines the medical conditions and patient groups for which the product can be prescribed, and for which medical claims may be made. New medicinal products must meet rigorous standards of evidence on safety, quality and efficacy to achieve a product licence. These standards ordinarily require high quality randomised controlled trials, though there have been a number of exceptions to this rule.[172]

The significant costs of these trials are ordinarily met by the pharmaceutical companies bringing the drug to market. However, witnesses to the Health and Social Care Select Committee (HSSC) reported that the CBPM manufacturing and supply industry have often not been willing to provide their products for analysis in RCTs, nor conduct large scale clinical trials on their products themselves. The HSSC reported that there can be difficulties in obtaining a patent for some CBPM and that manufacturers are unlikely to make significant financial investments in clinical trials without expectations of exclusivity following market authorisation.

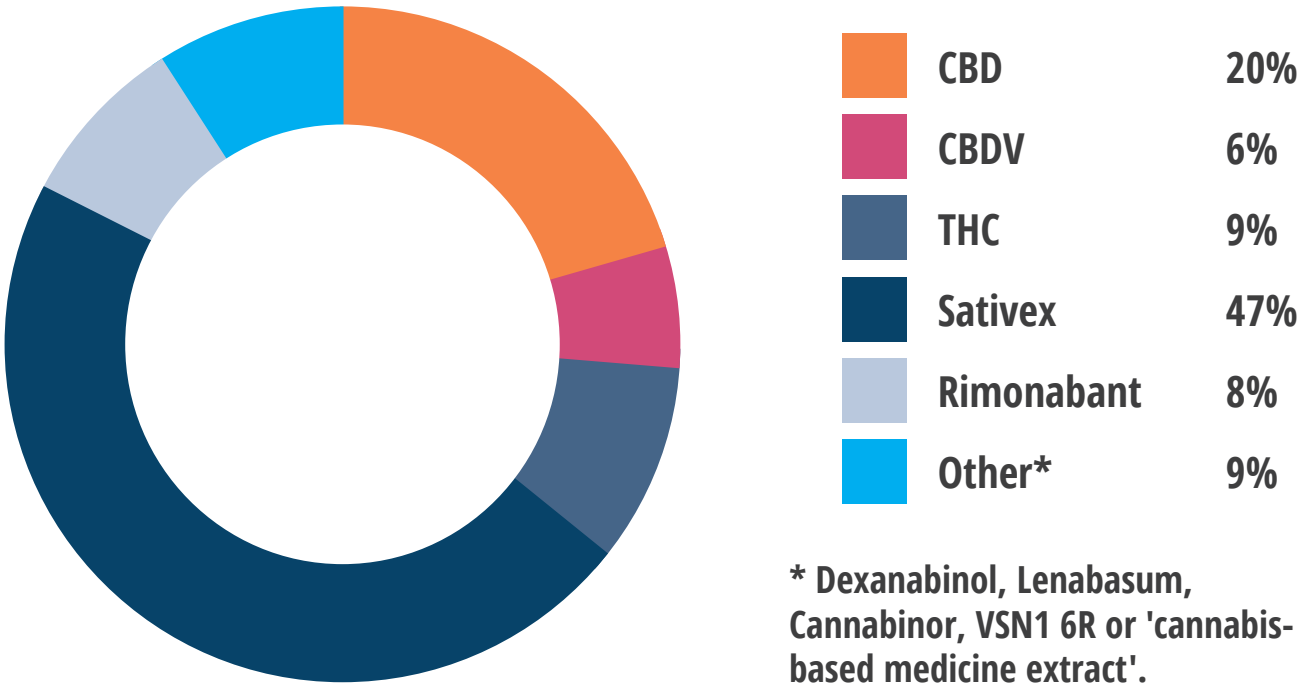
Professor Helen Cross, a paediatric neurologist at Great Ormond Street Hospital, suggested that the lack of industry engagement in research may be due to a belief within the industry that broad market access will naturally develop in the UK without the need for RCTs – as it has in other countries that have allowed CBPM to be widely available without product licenses. Industry have argued that RCTs are not a suitable methodology for developing cannabis-based medicines and that healthcare licensing authorities should consider observational data from countries that have already liberalised access.[173]

There have also been few clinical trials in CBPM in the UK that have been funded with public money, with no new known trials in the pipeline having been awarded funding from the recent NIHR themed calls.

The range of CBPM investigated in UK clinical trials has been limited

Completed and active clinical trials in cannabis-based IMPs have investigated only ten different products at UK sites over twenty years (*see Figure 7*). Sativex and CBD (usually Epidyolex) were the most commonly studied drugs by some margin. A fewer number of studies investigated the natural cannabinoids THC and CBDV, and the CB1 inverse agonist Rimonabant. Several other cannabinoid-based IMPs were also studied in a very limited number of studies, including the endocannabinoid analogue VSN16R, and the synthetic cannabinoids Dexanabinol and Lenabasum.

Figure 7. Percentage of completed or active UK clinical trials in which range of cannabis-based IMPs were investigated



There are limited patient populations who can receive investigational medicinal products

Where clinical trials in CBPM have been conducted, only small numbers of eligible people have received access. The numbers of participants recruited to clinical trials signify a small but representative sample of the population of interest (e.g. adults with spasticity associated with multiple sclerosis). Only people with characteristics that meet specific inclusion criteria will be considered for recruitment, and those with characteristics that fall under specific exclusion criteria are disqualified. Subjects may also be disqualified mid-trial if exclusion criteria are met, such as concurrent use of cannabis products outside the trial.

Once recruited, study participants are randomly assigned to either a study group or a control group. People in the former group receive the drug or intervention being tested and those in the latter group receive either a placebo treatment or an existing treatment known to be effective in the treatment of the indication in question. Thus, the number of people participating in a clinical trial in a CBPM is not equal to the number who receive the drug. On average, completed UK trials with available data had 127 people assigned to the study group.

1.4. ROUTE 4: NON-CONTROLLED CANNABIS-BASED WELLNESS PRODUCTS

Cannabis is known to contain over 540 phytochemicals (plant-based compounds, including 144 known cannabinoids, 200 terpenes and 20 flavonoids), many of which are believed to contribute to the medicinal value of the plant, and only a few of which are controlled under UK drug legislation.[174] [175] [176] [177] A 2016 report from the ACMD reviewed the legal controls on 97 phytocannabinoids and identified 12 compounds controlled under the MDA 1971 and the MDRegs 2001 (*see Annex B, Category 2 for the list*).[178]

Other cannabinoids in their pure form are not controlled by the MDA, including CBD-type compounds such as CBD, CBDA, CBDV and CBDVA (*see Annex B, Category 11 for an overview of other types of non-controlled cannabis-derived compounds*). However, it is possible that some of these compounds *would* be covered by the Psychoactive Substances Act 2016. Products containing CBD-type compounds are now widely

available in high street stores, pharmacies and online in a variety of forms.

This report will not explore the British CBD market in much detail, since reports already exist that cover this area in greater depth than we have scope for here, most notably the report CBD in the UK, published in June 2019 by the Centre for Medicinal Cannabis (CMC).[179] In late 2019, a new industry body, the Association for the Cannabinoid Industry (ACI), was formed by senior members of the CMC.

The CMC report estimated the size of the UK CBD market at £300 million per year, as of June 2019, with expected growth to just under £1 billion by 2025. The majority of UK consumers were found to be accessing products online, rather than High Street stores. There was some overlap between consumers on the CBD market and on other cannabis markets: people who had used a CBD product in the past year were six times more likely to report using cannabis for medicinal reasons in the past year.

Products on the CBD market are not prepared for medicinal use and cannot be advertised as having medicinal value, but are, nonetheless, used with medicinal intent by an increasingly large number of people in the UK. Polling commissioned by the CMC and the ACI in 2019 estimated that between 4 – 8 million adults in the UK had tried a CBD product, of whom approximately 1.3 – 1.7 million were regular users.[180] [181] The most common reasons for use were for overall health and well-being (54%), sleep (54%) and pain-management (42%).[182] A separate poll conducted by YouGov in August 2019 found that 9% of respondents had used CBD-containing products other than cannabis, of whom 61% had used CBD for medicinal reasons. If reflective of the general population, this would amount to approximately 5.5% of UK adults who have used CBD products with medicinal intent – a little under 3 million people. In this latter survey, 71% of users for medicinal reasons reported using CBD products to treat pain, 38% used products to treat anxiety or depression, and 24% to treat sleep disorders.[183]

The diverse range of CBD products on the Health and Wellness market includes products for human consumption (e.g. capsules, tinctures, oils and waxes for oral use, drinks, confectionary); human administration through other routes (e.g. 'vaping' products, subdermal patches, muscle rubs); cosmetics & toiletries (e.g. skin care products, shampoo, tampons); clothing (e.g. underwear and shirts infused with CBD); and products for animal consumption (oils for oral use).

The legal and regulatory controls over these products vary according to the type of product. If CBD suppliers make medicinal claims for their products, or supply them for medical use, the products are considered to be medicines by the MHRA and, accordingly, may not be lawfully supplied without market authorisation.[184] If products are for non-medicinal human consumption, the regulator is the Food Standards Agency (FSA), which requires companies to apply for 'novel foods' authorisation.[185] Where products contain any trace of controlled cannabinoids or controlled plant material, the Misuse of Drugs Act (MDA 1971) and subsequent regulations will be in force and under the remit of the Home Office.[186] Cosmetics are regulated by the Cosmetic Products Enforcement Regs 2013; the relevant Government body is the Department for Business, Innovation and Skills.[187] Products for use in animals are regulated by the Veterinary Medicines Directorate, which, since 2018, has required all veterinary CBD products to have market authorisation as veterinary medicines.[188] In addition to the above, Local Authority Trading Standards Services protect consumers from unfair trading practices and enforce product safety and trading regulations.

Although pure CBD may be lawfully supplied and possessed in the UK without a Home Office license, CBD-containing products commonly breach laws and regulations in a variety of ways. For instance, it is lawful to market CBD-containing cosmetics in the UK, but only if the CBD derives from synthetic production or from extraction from the seeds, stalk or leaves of cannabis. CBD derived from the flowers of the plant may not be lawfully used in cosmetic products.[189] Any product containing in excess of 1 mg of controlled cannabinoids per container is considered a controlled drug, regardless of the size of the container. Products on the CBD market commonly breach this limit. In some cases, UK vendors have been supplying raw 'CBD flowers' and informing consumers that these items may be lawfully sold and possessed. These products are controlled as Class B drugs under the MDA 1971 and as Schedule 1 drugs under

the MDRegs 2001.

1.4.1. CHALLENGES IN ACCESSING NON-MEDICINAL CANNABIS-BASED PRODUCTS

Access to cannabis-based products on the wellness markets is limited by regulatory confusion, prolific misinformation, and unreliable standards of quality and labelling accuracy. The UK market in lawfully available cannabis-based products has grown enormously in only a few years but has had little regulatory enforcement. The quality of products varies substantially between suppliers and the consumer can have little confidence in the purity or value for money of products commonly available. A limited number of products on the market are produced to GMP standards, because foods are not required to be, and a far tinier fraction of products are being made by API-registered companies. In the UK, only four manufacturers have API registration for CBD: BSPG Laboratories (Brains Biotech), Sterling Pharma Solutions, Aesica Pharmaceuticals and GW Pharma (*see Route 2: §1.2.2.4*). Of these four companies, only Brains Biotech is known to supply CBD to the wellness market.

1.4.1.1. REGULATORY ISSUES

Suppliers who make medicinal claims are in breach of medicines law

On 13 October, 2016, the MHRA declared that CBD-containing products that are used or advertised for medical purposes must have market authorisation as medicinal products before they can be lawfully supplied or advertised in the UK.[190] In parallel with the publication of this statement, the MHRA sent letters to 18 companies to advise them of their decision and provide a deadline of 31 December, 2016, for products to be removed from the market or satisfy the requirements of the HM Regs 2012. Similarly, the US Food & Drug Administration (FDA) have also sent notices to US suppliers of CBD products who had unlawfully made medical claims for their products.[191]

Since this time, CBD oils and other consumables on the wellness market that do not make claims of medical benefit have been considered foods and are thus subject to Food Standards Agency regulations. Although they cannot be lawfully advertised as medicinal products, many of these products are used for medicinal reasons by consumers.

Products have not been authorised by the Food Standards Agency

European Union (EU) law defines 'novel foods' as products for ingestion by humans for which no significant history of consumption within the EU can be shown prior to 1997. In 2015, EU law on novel foods was updated ((EU) 2015/2283 repealing and replacing (EU) 258/97), with the new regulations in force from 1 January, 2018. These regulations require novel foods to be evaluated and authorised before they can be placed on the market and are intended to support businesses bringing new foods to the market while maintaining a high level of safety for consumers.[192]

The EU manage a central Catalogue of Novel Foods listing foods and ingredients for which authorisation should be obtained. The catalogue has no direct legal effect on member states but provides recommendations for states to assist in novel foods enforcement.[193] In November 2018, the EU considered evidence on food products derived from the hemp plant, including CBD, to evaluate the breadth of their use prior to 1997. On January 15, 2019, the novel foods catalogue was updated in respect to cannabis-based products to clarify that "some products derived from the Cannabis sativa plant or plant parts such as seeds, seed oil, hemp seed flour, [and] defatted hemp seed, have a history of consumption in the EU and therefore, are not novel."[194] "[Extracts] of cannabis and derived products containing cannabis," however, "are considered novel foods as a history of consumption has not been demonstrated. This applies to both the extracts themselves and any products to which they are added as an ingredient (such as hemp seed oil)."[195] This definition classified all cannabinoids, whether synthetic or plant-derived, and whether extracted from cannabis or any other plants, as requiring evaluation and authorisation before being marketed as a consumable product.

Following this EU decision, the UK Food Standards Agency (FSA) reported that they

accepted the classification of CBD products as novel foods and were "committed to finding a proportionate way forward by working with local authorities, businesses and consumers to clarify how to achieve compliance in the marketplace in a proportionate manner." However, the regulatory status of CBD-containing products on the UK market remained ambiguous until further guidance was published by the FSA on February 13, 2020. This guidance stipulated a deadline of 31 March, 2021, for the industry to submit novel food applications for CBD products, and recommended that parallel applications should be sent to the European FSA (EFSA) and UK FSA. Providing that products are correctly labelled, not unsafe and not containing controlled substances, the FSA advised that business can continue to sell CBD products which were already on the market until the deadline, but that no new products should be sold without authorisation.[196] Food Standards Scotland have recommended that producers and suppliers "take immediate action to gain authorisation as a novel food."[197]

In addition, the FSA recommended that CBD products should not be consumed by people who are pregnant, breastfeeding or on existing medication. Healthy adults are advised to follow a maximum daily dose of 70 mg a day, unless under medical direction.[198]

Under the 2015 EU regulations on novel foods, all authorisations are generic rather than applicant-specific, meaning that any food business operator can place an authorised novel food on the market provided the authorised conditions of use, labelling and specifications are respected.[199] It remains to be seen how the FSA will evaluate and approve applications in the UK post-Brexit.

There are currently no authorised CBD extracts or isolates on the market, but at least 20 applications have been submitted to the EFSA, of which three have been validated, though not yet approved. The Swiss company Cibdol AG and the Czech company CBDepot have both submitted applications for synthetic CBD.[200] [201] Cannabis Pharma s.r.o, of the Czech Republic, have submitted an application for plant-derived CBD.[202] There is no fee charged for novel foods applications, though producing and preparing the dossier that must be included in support of an application may be associated with substantial costs. The dossier must provide evidence for a comprehensive risk assessment of the safety of a novel food for routine consumption. Producers must consider whether the novel food might also be consumed by persons other than the intended group of the population and must provide safety data for use by those populations. [203]

Novel foods regulations will not apply to CBD-containing products that are not marketed for human consumption, including cosmetics and products for vaping. We are already aware of some vendors selling CBD products ostensibly as oils for topical use but with verbal instructions for oral consumption. These attempts to circumvent regulations may be compared with the legal highs market, before the introduction of the New Psychoactive Substances Act 2016, in which psychoactive substances were commonly marketed as potpourri, plant feed, bath salts, or other non-consumable products, while being supplied and purchased with the expectation of oral consumption or inhalation.

Many products on the market are controlled drugs under the Misuse of Drugs Act 1971

CBD products are generally assumed by both vendors and consumers to be lawful to supply and possess. However, it is difficult, but not impossible, to isolate pure CBD without trace contamination of controlled cannabinoids, and many products available are technically controlled drugs under UK law. There are only three circumstances under which products containing controlled cannabinoids can be lawfully supplied without a Home Office license:

1. the product meets the definition of a Schedule 2 CBPM in the MDRegs 2001 and is prescribed according to the provisions laid out under Regulation 16A;

2. the product has a market authorisation as a medicine in the UK and is prescribed by or under the direction of an authorised prescriber;

3. the product meets the criteria of an 'Exempt Product' under the MDRegs 2001.

Only the third condition is relevant to non-medicinal products dispensed outside the health sector. An 'exempt product' is defined as "a preparation or other product consisting of one or more component parts, any of which is or contains a controlled drug, where all three of the following conditions are met—

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."[204]

All three limbs of this definition must be met for the product to be exempt. There is some ambiguity at present in regard to interpretation of the first limb and there has not yet been a court judgement that would provide clarity. It is not clear what the term 'administration' would specifically encompass, nor is it clear whether products with trace amounts of controlled substances could be said to be, or not be, designed for administration of those substances. However, Home Office policy is clear that products which contain more than 1 milligram of a controlled drug per container cannot be sold or possessed lawfully without a licence.[205] Cannabis-based products that exceed this threshold are controlled as Class B, Schedule 1 substances.

Numerous laboratory analyses of products allegedly containing pure CBD have identified concentrations of cannabinoids that differ from the amounts advertised – in many cases involving unlawfully high levels of THC.[206] [207] [208] [209] [210] [211] An analysis of 31 brands of CBD by Fera Science, a laboratory part-owned by the Department for Environment, Food and Rural Affairs, found that a third of products exceeded the lawful limit of THC, with one product containing more than 20 times the limit.[212] An earlier report by the CMC reported that 55% of 30 brands contained detectable levels of THC, though it was not specified how many exceeded the lawful limit of exemption from control.[213] High-CBD cannabis flowers are also being sold by vendors in the UK without a licence. However, all cannabis flowers are Class B, Schedule 1 controlled drugs, regardless of cannabinoid content, unless produced and supplied as a CBPM. The unlicensed supply of Class B drugs carries a maximum criminal penalty of 14 years imprisonment (*see Annex A*).

The regulatory framework for UK production is restrictive

Cannabis plants may only be cultivated and possessed lawfully under a Home Office licence, of which there are two separate types distinguished by the THC content of the plants.[214] Plants with a THC content not exceeding 0.2% may be cultivated for commercial use under a low-THC license, but the terms of this license do not grant the holder to use any parts of the plant controlled under the MDA 1971, namely the leaves and the flowers. Licenses will only be issued by the Home Office for the cultivation of approved seed types. The controlled parts of the plant remain subject to Schedule 1 restrictions, and their unauthorised use subject to Class A criminal penalties. Under a low-THC license, controlled parts of the plant must be retted at the licensed site or otherwise disposed of lawfully.[215]

Plants with a THC content exceeding 0.2% can only be lawfully cultivated or possessed under a high-THC Home Office licence. Controlled products from the plant can only be lawfully produced, possessed or supplied under specific Schedule 1 Home Office licences. Regardless of THC content, it is only lawful for growers to harvest and use the flowers and leaves of the cannabis plant under the terms of a high-THC licence.[216]

CBD can be extracted from the seeds and stalk of low-THC plants, but the yields are low. Some license-holders have had licenses revoked and have been ordered to destroy their crops after it emerged that they had unlawfully been harvesting the flowers of plants for CBD production.[217] UK producers may harvest the flowers of CBD-rich plants under high-THC licenses, but will

also need separate Home Office Schedule 1 licenses for every site at which the flowers or leaves are processed or possessed, unless the controlled material is to be used as an ingredient in a Schedule 2 CBPM or a licensed medicinal product. UK producers may also import controlled plant material if they are in possession of both domestic Schedule 1 licenses and shipment-specific import licenses, but these are not usually awarded except for scientific and medical use.

Schedule 1 licenses are required unless all products possessed, prepared or supplied at a particular site are not controlled under the MDA 1971 or are classified as exempt products under the MDRegs 2001, as described earlier in this section. Although the finished product may be exempt if it contains less than 1 mg of controlled cannabinoids per container, manufacturing sites in which the product is prepared or possessed in bulk may likely be in breach of this limit if trace amounts are present, in which case the manufacturer will require Schedule 1 licenses.

Schedule 1 licence-holders are required to comply with extremely strict regulations on storage, security and transportation, as per the Misuse of Drugs (Safe Custody) Regulations 1973. In 2019, the Home Office issued 33 low-THC cultivation licenses, 20 high-THC cultivation licenses, 362 domestic licenses covering possession of Schedule 1 compounds and 452 import licenses for shipments containing cannabis or with a controlled cannabinoid content. The Home Office provide a number of guidance documents on license applications and compliance.[218 219 220 221]

Understanding and complying with the regulatory landscape surrounding CBD production in the UK can be extremely challenging for producers. Although the Home Office do provide some guidance documents, there is limited transparency on license requirements, the approval process, or success rates. Producers have reported to us that information supplied by the Drugs and Firearms Licensing Unit (DFLU) at the Home Office varies depending on the staff member and that long waiting times are common before receiving a response. It seems likely that the DFLU receive a substantial number of license applications and inquiries concerning the production, importation and supply of cannabis-based products, and that the volume has increased since the 2018 rescheduling. Our impression is that the DFLU do not presently have the capacity to deal with cannabis-related inquiries in a timely manner, particularly when they come from small-scale businesses who may lack detailed understanding of the regulatory landscape.

It is worth noting that the role of the Home Office in regard to controlled drugs is to limit use and supply to authorised scientific and medical purposes, as laid out under the MDA 1971 and in subsequent regulations. This goal is prioritised over the development of a UK agricultural and manufacturing industry in cannabis-based products for non-medicinal use. Accordingly, the Home Office may not be best placed to meet the needs of commercial cannabis farmers and producers.

1.4.1.2. PRODUCT QUALITY AND CONSISTENCY

The quality and accuracy of labelling is low or inconsistent for many products

A 2019 analysis by the UK laboratory PhytoVista of 29 CBD oil products, commissioned by the CMC in collaboration with Nottingham University, revealed a wide range in terms of quality of products on the market.[222] Only 11/29 (38%) of samples were within 10% of the advertised CBD content. 10/29 (34%) contained half the amount of CBD or less. One product, which retailed at £90 for 30ml, was found to contain no cannabinoids at all.

The same analysis found that 4 samples (14%) provided neither a Batch Identifier or Use/Sell-By dates on their labels. Product information was inconsistent and confusing. 7 samples (24%) inaccurately advertised the extraction technique used in production. 11 samples (38%) contained concentrations of solvents that exceeded food regulations but were within limits for pharmaceuticals.

The report did not provide a detailed description of the sampling methodology used and it is not clear how representative the samples were of the market at large. While indicative of low quality, these findings may not give an accurate assessment of the average quality of the

market, nor of the quality of the products most commonly sold. However, the CMC findings are supported by analyses conducted on CBD products marketed in other countries.[223]

UK consumers also have concerns about the quality of CBD products on the market: a YouGov poll commissioned by the ACI in late 2019 found that 45% of those surveyed said they were not confident that all CBD products are correctly labelled and are properly tested.[224] It is expected that FSA requirements on product authorisation and approval will result in improved quality across the market for CBD consumables.

There are concerns about adverse health effects

According to WHO's Expert Committee on Drug Dependence, "CBD exhibits no effects indicative of any abuse or dependence potential." It was found to have a good safety profile, with relatively low toxicity, and to be generally well tolerated by humans. The Committee found no evidence of recreational use, nor of any public health-related problems associated with CBD. There was no evidence that CBD causes intoxication, psychotic symptoms or impairments ofmotor or psychomotor performance in humans.[225] In the January 2020 Board meeting of the FSA, the Chief Executive, Emily Miles, reported that the Agency had "not been made aware of any safety incidents relating to CBD products on the market."[226]

However, there have been some concerns raised by the FSA Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment regarding hepatotoxicity and drug-drug interactions between CBD and some prescribed medicines.[227] The US Food & Drug Administration (FDA) has expressed similar concerns, also noting potential risks of sedation and male fertility toxicity.[228] The FDA note that there is an absence of safety data for CBD in a variety of conditions, including health effects of long-term use; the effects of CBD on the developing brain; the effects in pregnancy and in breastfeeding; and in interactions with herbs, botanicals and prescription drugs.

Moreover, the low quality, contamination, and labelling accuracy of many products may be associated with adverse health effects that would not be seen with pure CBD. The CMC report notes that "in Utah, between 2017 – 2018, there were 52 cases of people who reported adverse reactions in products labelled as CBD that were inconsistent with CBD consumption, including seizures, vomiting, confusion and hallucinations."[229]

CHAPTER 2

Unlawful Routes of Access to Cannabis-Based Products

INTRODUCTION

While lawful medical routes of access to cannabis-based medicines remain limited in the UK, unlawful routes cater to the vast majority of patient demand. Latest estimates suggest that up to 2.8% of British adults are using illegally-obtained cannabis to treat a range of chronic conditions – based on a nationally representative survey of more than 10,000 participants conducted by YouGov for the Centre for Medicinal Cannabis (CMC) and Cannabis Patient Advocacy and Support Services (CPASS) in 2019.[230] Assuming this result is representative of the UK at large, this means that as many as 1.4 million British adults could be using illegally-obtained cannabis to help treat or manage chronic health conditions. Significant numbers of people self-medicating with cannabis from unlawful and unregulated sources have been the impetus for many countries to loosen the requirements for access to cannabis-based medicines or to reduce or remove the associated criminal sanctions associated with unlawful access.

An earlier survey of 1,750 medicinal users of cannabis, conducted in 2018 by the United Patients Alliance (UPA), found that 81% sourced their cannabis from the black market; and 9% from self-cultivation, friends who self-cultivate, or from growing collectives.[231] The latter figure is supported by the 2019 CMC survey which also found that close to 1 in 10 of medicinal users of cannabis (9%) spent nothing on cannabis, implying self-cultivation. Using the CMC's estimate of 1.4 million adults using illegally-obtained cannabis for medicinal use in the UK, this means that as many as 125,000 could be self-cultivating for medicinal reasons.

The 2018 UPA survey also found that 1% of respondents sourced cannabis-based medicines from abroad. Although cannabis-based medicines can be more easily obtained in countries like the Netherlands, it still involves travel costs, the cost of an international consultation with a doctor and the prescription cost. It is, therefore, unsurprising, that personal importation accounts for a relatively small proportion of unlawful access. However, families trying to access cannabis medicines to treat children who have severe forms of intractable epilepsy are, understandably, unwilling to use cannabis products without guarantees of quality or medical instruction. Instances of families using this route have been the cause of much attention in the media and Parliament over the past two years.

Chapter 2 will explore how and why individuals with chronic health conditions are using these unlawful routes (*Routes 5 to 7*) to access cannabis for medicinal use - and with what consequences. In *theory*, cannabis-based medicines are accessible through lawful medical routes, but in *reality*, access is very restricted, creating a 'two-tier system' where access is probable for those who can afford the exorbitant cost of a private prescription and highly improbable for those who cannot.[232]

The very public decision made by the Government in 2018 to reschedule 'cannabis-based products for medicinal use' was seen by many grassroots users of cannabis (CBP) to vindicate the claims that they had been making for decades. Namely, that there were legitimate medicinal applications of the plant, and that its prior status as a Schedule 1 drug had both prevented its clinical use and restricted scientific research into its potential value as a medicinal product.

The UK healthcare and regulatory sectors, understandably, want medicines derived from cannabis to meet the high standards of clinical evidence that are expected of all new drugs reaching the therapeutic market before approving wide access. Meanwhile, more than a million people with chronic health conditions are unlawfully obtaining CBP for medicinal reasons, many of whom believe strongly in the health benefits of doing so and do not feel as if they can or should wait for products to be licensed and widely available on the NHS. This chapter endeavours to bridge the gap between these perspectives.

Box 5. *Terminology*

Cannabis-Based Medicine or 'Cannabis Medicines'
A term used to cover both licensed cannabis-based medicines ((L-CBM) e.g. Sativex) on prescription and unlicensed cannabis-based products for medicinal use ((U-CBPM) e.g. Bedrocan) on prescription unless otherwise specified.

Cannabis or Cannabis-Based Products not authorised for medicinal use (CBP)
A term used here to cover a range of cannabis products that may be used by an individual for reasons that they identify as being 'medicinal,' i.e. to treat the symptoms or underlying pathology of an illness or disease. These include black market cannabis products, or self-cultivated cannabis that are not authorised for medicinal use but are used with medicinal intent. They may also be used by non-medicinal users such as those deemed recreational. However, some scholars have cautioned the use of such exclusive terms as 'medicinal' and 'non-medicinal use,' as making this distinction can be arbitrary.[235 236 237]

Medicinal users (or 'patients') and non-medicinal users
Throughout Chapter 2 we discuss individuals who identify as 'medicinal users' of cannabis. In some instances, we may also refer to these users as 'patients,' reflective of the chronic conditions these individuals usually have and for which they require medical intervention. However, it should be noted that a medicinal user may not necessarily be considered a patient by traditional definitions if they have not been formally diagnosed or do not interact with a medical practitioner regarding their condition. In some cases, we use the term 'patient' to refer to these individuals outside of the context of a medical interaction.

Many medicinal users self-medicate with cannabis, meaning they take it without the direction of a doctor. Furthermore, patients who choose to self-medicate with cannabis in the UK, do so with unlawfully sourced and unregulated CBP that is unauthorised for medicinal use. While self-medication can lead to increased access to treatment and give the patient autonomy over their own health, it can also potentially lead to incorrect self-diagnosis, separation or isolation from sound medical advice and oversight, inappropriate dosing or choices of treatment, adverse effects, dangerous drug interactions, and drug dependence or abuse.[443]

The illicit 'Black Market' and other unlawful routes
For the purpose of this report, the illicit 'black market' refers to organised, unlawful supply chains, with multiple nodes, through which cannabis-based products (CBP) can be accessed through transaction. Black market access does not include the importation of cannabis medicines from abroad, nor small-scale self-cultivation of cannabis for personal use or within a closed community of users with no profit motive.

Each unlawful route to access is considered to be distinct, although some level overlap is assumed to exist from the diversion of products from one to another. It is important to differentiate routes five, six, and seven because each differs in the types of product typically available and in the nature of the supply chain. For instance, there have been several high-profile cases of families importing cannabis medicines into the UK that have been prescribed by a doctor overseas (Route 5). These are products that could be lawfully possessed and used in the UK, if prescribed as specials medicines by a specialist physician. However, they are not widely available or affordable through the UK health sectors, for reasons discussed in Chapter 1. They are produced by licensed manufacturers for medicinal use in humans and are, accordingly, of high and consistent quality and labelled with the ratio and concentration of CBD and THC. The supply chain is known, registered and regulated.

Unlawful small-scale cultivation of cannabis for personal medicinal use does not tend to be linked with organised, criminal supply chains (Route 6a). These operations typically involve only the grower and the consumer, which may be the same person, or a carer (usually a family member, spouse or friend) who grows on the patients' behalf. Medically-motivated growers are often experienced and well-educated on the cultivation of cannabis for medicinal use. In some cases, personal growers have spent years determining which cannabis strains and products yield the most benefit in treating their condition.There may be some form of informal

or formal social supply occurring, but the small-scale size of these operations and the intended medicinal use mean these CBPs are generally not diverted onto the black-market and there is an absence of profit or profit incentive. Formal social supplies are usually referred to as Cannabis Social Clubs (CSCs) and generally do not source from the black-market, utilising a community of small-scale home-growers instead, based on key prerequisites of the CSC model (Route 6b).

Black market sources of cannabis tend to have much more complex supply chains and often require a certain level of organised crime to operate (Route 7). Since black market supply chains have many more nodes than personal grow operations, and none of the market regulation to which medicinal products on the therapeutic market are subject, cannabis products sourced from the black market do not come with reliable information on strain, content or quality, and carry higher risk of contamination and adulteration. It is known that some cannabis clubs exist in the UK which source cannabis products directly from the black-market, run themselves like a business and exist to make a profit. These so-called 'shadow clubs' contravene the prerequisites of the non-profit CSC model and would be considered to be black-market sources of cannabis.[238 239]

Unlike lawful routes of access, there are no prescription records, license applications, receipts, or certificates of analyses to guide our understanding of unlawful access. Individuals using cannabis to manage chronic health conditions who come to the attention of law enforcement are often conflated with recreational users, and inconsistent policing and applications of the law pertaining to cannabis-related offences in general means that recorded crime data is unable to give an accurate picture of the phenomena as a whole.[233 234] Accordingly, it is challenging to gather reliable data in this area. This chapter draws on the narratives of individuals who have broken the law to achieve access for medicinal reasons, campaign groups supporting such individuals, third sector organisations, and law-enforcement officials, as well as exploratory data to shed light on this large but hidden population. Where possible, we place these routes within an international context, comparing the UK situation with other countries to help fill in some of the blanks.

2.1. ROUTE 5: IMPORTED CANNABIS-BASED MEDICINES

Self-cultivation of cannabis and access through the UK black market do not provide access to suitable products for many patients, particularly those who need standardised doses, isolated compounds, or medical devices such as metered spray bottles. Cannabis medicines made by licensed and regulated producers at GMP sites, with accurate product labels and medical instruction, can only be reliably accessed through lawful prescription. Where the UK health system has been unable to meet this need, patients have sought prescriptions elsewhere. The parents of children who suffer from intractable epilepsy, who might benefit from cannabis medicines not accessible to them in the UK, are understandably unwilling to use cannabis products without guarantees of quality or medical instruction. This has put parents trying to access cannabis medicines for their children, whom they hope or know might benefit, in an extremely difficult situation and has therefore attracted the most media and political attention.

While it may be lawful to obtain cannabis medicines in a different country (such as the Netherlands, where the CBPM manufacturer Bedrocan is based), it is unlawful to import them back into the UK without specific Home Office approval, even if the patient has a valid prescription. Home Office rules only permit an individual to import controlled drugs on their person if they are habitually resident in the country in which they were prescribed. These rules apply to all drugs listed in Schedules 2, 3 or 4 (part I) of the MDRegs 2001, and so currently apply to all cannabis-derived medicines whether licensed or unlicensed.

A survey conducted by the United Patients Alliance (UPA) in August 2018 with 1,750 medically-motivated cannabis users found that 1% (n=17) sourced cannabis medicines from abroad.

Box 6. Hannah Deacon, mother of Alfie Dingley and 'End Our Pain' campaign supporter

"When the law changed on 1st November 2018, I felt joyful that my child's story and other familys' stories had been pivotal in making history. Our hope was that every child with refractory epilepsy would get to try medical cannabis containing not only CBD but THC and other minor cannabinoids and terpenes which make it so effective. The reality is not one of joy. My son Alfie Dingley and one other child in Northern Ireland are still the only recipients of an NHS prescription for an unlicensed CBPM nearly 18 months since the law changed and that has required demonstrating through the use of imported and private prescriptions that these medicines work in order to convince NHS doctors to prescribe.

The NICE guidance is very restrictive and only recommends Epidyolex for two rare epilepsy conditions, meaning that many families were left disappointed. It is worth noting that some of the families I support have also tried Epidyolex with no perceived benefit. Once they try Bedrolite, a full extract product, most of them have had a huge reduction in seizures and many days without any at all. This is due to the entourage effect which means full extract cannabis is more effective than CBD isolate. Families are now having to either pay thousands of pounds a month for private prescriptions or criminalise themselves on a monthly basis travelling to Holland to buy cannabis oil that they need to keep their children safe. It is notable that the many families I now know and support have children that are thriving and keeping out of hospital, reduced seizures, improved quality of life and parents who can live a more positive and happy life. Refractory epilepsy is a dangerous condition that kills children and adults regularly through Sudden Unexpected Death in Epilepsy (SUDEP). Having an improved quality of life and reduced seizures due to medical cannabis is imperative for these families and they are now stuck in a cycle of trying to pay for their children's prescriptions on a monthly basis. Some have even sold their houses and businesses. They would not do this if it didn't help their children.

The doctors of these families are impressed with how well the children are doing but the parents are told regularly they cannot prescribe due to guidance, cost and evidence. Yet these children are the evidence. Let's think about the long-term cost on the NHS of uncontrolled epilepsy, on the relationship of the parents; the fact that the mother, who is usually the full-time carer, cannot work or have any normality of life. The need for long term respite or a residential home, the need for beds night and day and drugs to stop the seizures, all or some of this is reduced hugely if a child or patient could access medical cannabis on the NHS. I believe the NHS could save millions if it accepted the exceptionality of medical cannabis and started to prescribe."

Without knowing how representative this data is of medically-motivated cannabis users in the UK, being a hidden group of individuals, it is not known how many people in the UK are obtaining medicinal cannabis products in this way. While there have been a few high-profile cases in which the Home Office Border Force have confiscated cannabis medicines prescribed overseas from the families of children with intractable epilepsy, we have spoken with several individuals who have successfully used this route without detection. Considering the cost of travelling overseas, along with the risk of criminal penalties or seizure of medication, it is not surprising that only a small proportion (1%) of medicinal cannabis users would choose this route of access. The fact that some patients do is demonstrative of the continued difficultly of obtaining these products lawfully in the UK, particularly when we consider the additional challenges that are involved if taking an unwell child abroad. Patients and families in this situation simply feel they have no other choice.

Some families and other adult patients in this situation have relocated to places such as Holland (either temporarily or permanently) in order to secure a reliable supply of a cannabis medicine. Most families left fighting for access to unlicensed CBPMs are having to pay thousands of pounds for private prescriptions and trying to negotiate reduced prices with producers and suppliers. It is hoped that the high costs and long lead times of private prescriptions may reduce under the new bulk import model once more affordable international supply chains are available (*see Chapter 1: Route 2*).

The rescheduling of CBPM in 2018 was provoked by the high-profile cases of Billy Caldwell and

Alfie Dingley, whose severe forms of childhood epilepsy were responding well to medicinal cannabis products sourced internationally. However, the rescheduling has failed to meet the needs of the parents and children who were so fundamental in provoking this change, with many families still having to rely on overseas supply or access through the private health sector at substantial cost.

In 2019, the UK press covered the stories of several more families facing these challenges. On April 6, 2019, Emma Appleby, mother of Teagan, was stopped by the UK Border Force as she returned with a CBPM that had been prescribed to her daughter in Rotterdam after she had failed to get a prescription on the NHS. Two days later, Sir Mike Penning MP issued an Urgent Question to the Health Secretary to ask about the return of the seized medication.[240] A number of other MPs shared stories of constituents who were in a similar situation to the Applebys. The Health Secretary, Matt Hancock, responded that CBPM had been rescheduled in the UK in order to improve access, but that prescribing was a clinical decision. "Without clinical authorisation," he said, "it is of course not possible to import controlled drugs, which is why the products were seized by Border Force on Saturday." Later in the debate, Mr Hancock reflected that the 2018 amendment may have actually impeded short-term access for some patients:

"One of the great frustrations for me, for the Home Secretary and, of course, for the families is that, before the law was changed on 1 November, that course of action was open [the issue of special Home Office licenses to allow the use of medicinal cannabis products]. For a few dozen cases, the Home Secretary made those special licences to allow for the use of medicinal cannabis. He and I changed the law together to try to make sure that medicinal cannabis is available on a mainstream basis. Now it is available on a mainstream basis, as a normal drug, it therefore needs clinical sign-off. The problem is there are so many cases where that clinical sign-off has not been forthcoming."

In some instances, the UK Border Force have seized cannabis medicines from patients and their families even when valid prescriptions have been issued in the UK. In June 2019, Emma Appleby was detained at the border for a second time. Despite her daughter being in receipt of a UK-issued private prescription for the seized medication, they were told that they could not lawfully bring it in to the country without a Home Office license. In July 2019, an unlicensed CBPM was seized from Tannine Montgomery as she returned from the Netherlands, despite holding a prescription for her daughter, Indie-Rose Clarry, issued by her UK doctor. In both cases, the families had travelled overseas to collect the product in person to reduce the costs associated with private prescriptions. Neither family had achieved access on the NHS.

"They went through everything and they seized everything we had." ... "I'm devastated. I've always tried to do the right thing. I've jumped through all the hoops but ended up being passed from pillar to post and being met with a flat 'no'... All I want is the best thing for my daughter. To have the medicine taken in this way is deeply upsetting."

Emma Appleby, mother of Teagan [241] [242]

"Seizing this medicine is condemning my lovely daughter to becoming comatose, wracked by seizures and to be at high risk of an unnecessary death. For the love of God, this medicine is legal in the UK and I have a full lawful UK prescription for it."

Tannine Montgomery, 2019 [243]

"We should not be treating patients or their families who are resorting to bringing medication here from abroad because they cannot obtain it on prescription here as if they are committing a criminal offence. Neither should patients have their medication confiscated, as happened recently to the mother of Teagan Appleby. We are pleased that following the outcry in Parliament and beyond, the medication was subsequently restored to Teagan's family. This cruel practice must not happen again."

Health & Social Care Select Committee, 2018 [244]

2.1.1. AVAILABLE, LICENSED MEDICINES ARE NOT ALWAYS ADEQUATE

Many parents have found that their children tolerate cannabis-based medicines better than licensed medicines. Hannah Deacon, mother of Alfie, was informed by Alfie's doctor that the heavy regimen of steroids that he had been prescribed before they switched to a cannabis medicines carried a high risk of psychosis and premature death.[245]

185 patients received Epydiolex as part of the early access programme in 2019 and it is now licensed and recommended for the treatment of two types of severe epilepsy in children, with funding in place from January 2020 (*see Chapter 1*). This will undoubtedly increase safe access to Epydiolex for some patients. However, the parents of Billy Caldwell, Alfie Dingley, and Indie-Rose Clarry, among others, have claimed that CBD alone (i.e. Epydiolex) does not manage the symptoms as well as medicinal cannabis products that contain additional cannabinoids.

Such products (sometimes referred to as "full-spectrum") contain multiple active compounds and are more difficult to study than isolated single-molecule drugs. Although many full spectrum products are currently unlicensed (U-CBPM), observational data supports the hypothesis that extracts combining multiple components or phytocannabinoids, such as CBD, THC, THCA, THCV, and CBDV, may have greater efficacy than single-compound products.

"CBD-rich extracts seem to present a better therapeutic profile than purified CBD, at least in this population of patients with refractory epilepsy. The root of this difference is likely due to synergistic effects of CBD with other phytocompounds (aka Entourage effect), but this remains to be confirmed in controlled clinical studies."

Ethan Russo, Director of Research and Development at the International Cannabis and Cannabinoid Institute [440]

Those seeking access to a wider range of medicinal cannabis products not presently licensed continue to face challenges.

2.1.2. UK PRESCRIPTIONS OF UNLICENSED CBPM HAVE BEEN EXTREMELY LIMITED

Although the 2018 amendment made it lawful to prescribe U-CBPMs, access through the UK health sector in the first year has been extremely limited (*see Chapter 1*). In view of the limited clinical evidence, many prescribers have been unwilling to offer U-CBPM and clinical guidelines have not supported their use. Where NHS specialists have been willing to prescribe, funding has not been widely available, since unlicensed medicines are not routinely commissioned. Access through private prescriptions is prohibitively expensive for many patients, and unsustainably expensive for others. For this reason, some patients and parents continue to import cannabis medicines from overseas where it is still cheaper in many cases (despite the costs associated with travel). Others continue to do so due to the delays many parents and patients have experienced with the supply of cannabis medicines prescribed in the UK, meaning that some patients do not always

receive their prescriptions on time.

2.1.3. THE CLINICAL BENEFITS OF UNLAWFULLY IMPORTED CANNABIS-BASED MEDICINES CAN BE SUBSTANTIAL

The unlawfully imported products prescribed to Billy and Alfie significantly reduced the frequency and intensity of seizures, transforming the quality of life of both the children and their families. Alfie's mother, Hannah Deacon, has reported that 'full leaf oil' has reduced the rate of his seizures from 500 a month to virtually none: "He's doing fantastically well... Medical cannabis has been a saviour for all of us."[246] Faced with the devastating effects and prognoses of many severe childhood epilepsies, it is understandable that their families are prepared to break the law to access potentially efficacious medicines.

"I am exhausted and shattered but I've seen how this medicine transforms my daughter's life... I have to find a way forward. The NHS just won't prescribe. This is unforgivably cruel and unfair."

Emma Appleby, 2019 [247]

"Eddie is thriving on cannabis oils. But there is only so long that we can hope to raise the funds needed to maintain Eddie's private prescription – it currently costs around £2000 a month. If the guidelines in their current form are likely to be final, keeping NHS access almost impossible, then the choice between allowing Eddie to go back to where he was or to begin criminalising myself by importing his medicine from abroad where it is much cheaper has been made."

Ilmarie Braun, 2019 [248]

2.2. ROUTE 6A: SMALL-SCALE CANNABIS-CULTIVATION FOR PERSONAL USE

Cannabis cultivation and cannabis growers have traditionally been equated with homogenous groups of profit-motivated criminal organisations working on a large, commercial scale with forced or coerced labour.[249] However, many are small-scale cultivators who grow a small number of plants at home for personal use. Both qualitative and quantitative accounts of small-scale cannabis cultivators suggest that there is an increasing population within this cohort who are growing cannabis for medicinal use to help themselves or others treat or manage chronic health conditions.[250 251 252 253]

2.2.1. AN INTERNATIONAL PERSPECTIVE ON CANNABIS CULTIVATION FOR PERSONAL USE

Small-scale cannabis-cultivation, meaning that only a small number of plants are grown, is decriminalised or legally regulated in a number of jurisdictions across the world. The practice is legally regulated in Canada, Uruguay and in at least 10 US states, where the commercial or government supply of cannabis for non-medical use is also permitted. In Spain, small-scale cannabis cultivation for personal use is permitted so long as it is within a private space and not in view of the public. In Belgium, the cultivation of one cannabis plant for personal use is 'tolerable.'[254] Italy's Supreme Court has also recently ruled, in December 2019, that the crime of growing narcotic drugs should exclude "small amounts grown domestically for the exclusive use of the grower," meaning cannabis grown for personal use is no longer illegal. Although the details of the ruling are not yet clear (such asthe quantity of cannabis which constitutes "small-scale cultivation") or the logic behind the court decision, confusion regarding the legal status of cannabis cultivation due to contradictory court decisions involving small-scale growers are thought to be an important driver of the decision.[255]

Some countries and several US states only permit the home-growing of cannabis to patients that have been authorised to do so for medicinal purposes. This was also the case in Canada until

Box 7. Canada: The right to self-medicate

In Canada, a successful 1998 Ontario court case, involving a HIV/AIDS patient who was charged with cultivating cannabis, opened up the legal provision of cannabis for medicinal use. The Ontario Superior Court recognised that individuals with a medical need had the right to possess cannabis for medical purposes and instructed Health Canada, the government department responsible for national public health, to create a process which would permit legal access to cannabis for medicinal use.

This was initially handled through a temporary exemption of the Controlled Drugs and Substances Act, which was subsequently replaced by the Marijuana Medical Access Regulations (MMAR) program in 2001. This made Canada the first country to allow the growth and consumption of the drug for personal use by people who had terminal illnesses and serious medical conditions. With the support of a medical practitioner, patients who successfully registered onto the program through Health Canada could obtain an authorisation for a legal supply of dried cannabis from Health Canada, or obtain a personal-use production license to grow it themselves, which could also be designated to someone else to cultivate on the patients' behalf, such as a designated carer. However, this early version of the scheme was not well-known among clinicians, had a very bureaucratic application process, and was limited to a narrow set of conditions, so many patients were not able to enrol on the scheme and continued to break the law to access cannabis for medicinal use.

In 2013, Canada's Conservative government replaced the MMAR scheme with the Marijuana for Medical Purposes Regulations (MMPR) program which created conditions for a commercial industry who would be responsible for the production and distribution of cannabis for medical purposes. This required patients to buy cannabis from a licensed commercial producer, approved by Health Canada, and removed the option for patients to grow their own, the justification being that the new MMPR program would provide access to 'quality-controlled cannabis for medicinal use,produced under secure and sanitary conditions'.

However, patients challenged the constitutionality of the new regime and the Federal Court of Canada ultimately concluded that requiring individuals to get their cannabis from licensed producers only violated liberty and security rights, protected by section 7 of the Canadian Charter of Rights and Freedoms. The Court found that individuals who require cannabis for medical purposes did not have "reasonable access" through the existing program, and this led to the Access to Cannabis for Medical Purposes Regulations (ACMPR), another evolution of the access program, which re-instated provisions for patients to cultivate a limited number of plants for medicinal purposes or to designate someone to grow on their behalf.

In order to grow cannabis, patients have to apply for a ACMPR license. Health Canada stipulate the safety and security procedures and will determine how many cannabis plants can be grown - based on the grams of cannabis prescribed by the clinician - and whether the plants will be grown indoors or outdoors (or a combination of both). The grow-your-own program allows patients with restricted incomes, and/or those who lived in rural areas, affordble access to cannabis for medicinal use under medical oversight and guidance. Canada went on to legally regulate cannabis for non-medical use in 2018 with the enactment of the Cannabis Act. This permits all adults to cultivate up to 4 cannabis plants per household, which cannot be sold to others. Patients have the option to grow more plants under the ACMPR program if the outcome of the license permits them to do so.[257 258]

the right to grow was extended to non-medicinal use following the legalisation of cannabis in 2018. Germany also permitted the self-cultivation of cannabis for patients before it took measures to significantly increase access to cannabis-based medicines through their healthcare system, revoking the sanction to grow for medicinal use. Similarly, Canada had some back and forth, initially having to sanction cannabis cultivation for medicinal use on the basis of case law, but later revoking this on the basis that legitimate medical routes of access would be increased. However, it was later reinstated following subsequent legal challenges from patients who were self-managing chronic health conditions with cannabis grown at home (*see Box 7*).

In several jurisdictions, the right for patients (or patients with particular diagnoses) to grow cannabis for medicinal use was introduced by case law, following court rulings that patients with unmet clinical needs who had no lawful means to access cannabis for medicinal use were entitled to produce their own. These successful cases have effectively forced some international governments to enact legal exemptions for such individuals and/or create a process which would permit legal access to cannabis for medicinal purposes.

The UK will not be forced to amend its laws pertaining to access to cannabis for medicinal use on the basis of case law, due to its different constitutional and procedural constraints. However, it is important to be mindful of the fact that the international emergence of medicinal cannabis programmes has been largely driven by the demands of patients already self-medicating with cannabis obtained unlawfully, often through self-cultivation. For more details on the conflict between human rights and drug control regimes internationally and domestically see Bone, M, 2020, *Human rights and drug control: A new perspective*.[256]

2.2.2. THE UK PERSPECTIVE ON CANNABIS CULTIVATION FOR PERSONAL USE

In the UK, it is unlawful for anyone to grow cannabis without a Home Office license under the MDA 1971 (section 6(2)), including patients, and those that do risk severe criminal penalties. The Home Office has the power to grant licenses for the cultivation of cannabis, but none have ever been granted to individuals who intend to grow for personal use. Cultivation licenses are designed for industrial operations, academic institutions and pharmaceutical development, not for individual patients.

Cultivating cannabis without a license may result in a maximum criminal sentence of 14 years imprisonment and an unlimited fine, compared to the simple possession of cannabis, which may result in penalties ranging from a police caution to a maximum of 5 years imprisonment (*see Annex A*). The severity of the penalty applied will depend on the individual circumstances and case, such as the size of the operation (the number of plants and expected yield), the individual(s) role in the operation, and any mitigating factors. As set out in the Sentencing Council's Definitive Guideline for Drug Offences, the court would determine the offender's level of culpability (A) and the harm caused (B) in regard to production and cultivation offences (*see Figure 8*).

Regarding the offender's level of culpability and role in cannabis cultivation, it is unlikely that patients growing cannabis would be found to have a 'leading role.' It is also likely that a patient with a small-scale grow would fall into the two lowest categories of harm (category 3 and 4). Nonetheless, if an offender is charged, the likelihood of being convicted is high, according to Release, a national centre of expertise on drugs and drugs law in the UK.[259] Convicted offenders are often sentenced to community orders, suspended sentences, and prison sentences - including patients growing small numbers of plants for personal medicinal use. In the case of patients, this also means that the plants and CBP they are using as their medicine are seized, meaning a sudden cessation in treatment for patients, which can be dangerous if the patient uses CBP as their primary treatment for the management of their condition.

Despite the risk of a possible 14-year prison sentence, the practice of cannabis cultivation is relatively widespread in the UK and it provides a source of CBP for tens of thousands of patients who wish to use it for its perceived therapeutic value. It is not possible to know precisely how many patients are growing cannabis for

Figure 8. Sentencing Council's Definitive Guideline for Drug Offences

Misuse of Drugs Act 1971 (section 6(2)): Cultivation of cannabis plant			
Offence range: Discharge – 10 years' custody. Maximum: 14 years' custody.			
A: Culpability demonstrated by offender's role. One or more of these characteristics may demonstrate the offender's role. These lists are not exhaustive.			
Leading role: • Directing or organising production on a commercial scale • Substantial links to, and influence on, others in a chain • Expectation of substantial financial gain • Uses business as cover • Abuses a position of trust or responsibility			
Significant role: • Operational or management function within a chain • Involves others in the operation whether by pressure, influence, intimidation or reward • Motivated by financial or other advantage, whether or not operating alone • Some awareness and understanding of scale of operation			
Lesser role: • Performs a limited function under direction • Engaged by pressure, coercion, intimidation • Involvement through naivety/exploitation • No influence on those above in a chain • Very little, if any, awareness or understanding of the scale of operation • If own operation, solely for own use (considering reasonableness of account in all the circumstances)			
B: Category of harm (cannabis). Indicative quantity of drug concerned (upon which the starting point is based):			
Category 1: operation capable of producing industrial quantities for commercial use	**Category 2:** operation capable of producing significant quantities for commercial use	**Category 3:** 28 plants*	**Category 4:** 9 plants (domestic operation)*

**With assumed yield of 40g per plant*

medicinal use, but based on the results of the CMC and UPA surveys, the number could be as many as 125,000.[260] Others estimate it could be closer to 200,000.[261]

Although there is no available data to indicate whether or not the practice of self-cultivation of cannabis for medicinal use has grown in the UK, it is entirely plausible that the 2018 rescheduling of 'cannabis-based products for medicinal use,' particularly within the context of greater cultural acceptance of cannabis both internationally and locally, may have been accompanied by increased demand across unlawful routes of access, particularly since the UK healthcare system has been unable to meet those expectations.

Criminal investigations of patients growing cannabis for medicinal use are problematic for law enforcement in the UK, who have no clear guidance on how to handle cases where there are claims of medicinal use. This has resulted in several high-profile court cases involving patients who have grown cannabis claiming medical necessity which have generally received both public and political sympathy, causing a headache for law enforcement, legal proceedings and court.

2.2.3. CHARACTERISTICS OF THOSE WHO GROW FOR MEDICINAL REASONS

Although the hidden phenomenon of patients growing cannabis for medicinal use is relatively understudied, there are some exploratory studies which provide an insight into the underground practice. In 2012-13, the Cannabis Cultivation Research Consortium (GCCRC) conducted a large international survey of predominantly small scale cannabis cultivators (who grow between 2 – 6 plants) which captured medically motivated

cultivators. The anonymous, online survey found that this sample of small-scale cultivators (n=418 UK participants) typically came from normal socio-economic backgrounds, had jobs and were law-abiding (i.e. engaged in minimal involvement in drug dealing or other criminal activities).[262]

The five most popular reasons for growing cannabis in the UK were as follows:

1. "It provides me with cannabis for personal use" (93%)
2. "It's cheaper than buying cannabis" (84%)
3. "To avoid contact with criminals" (83%)
4. "I get pleasure from growing cannabis" (82%)
5. "The cannabis I grow is healthier than the cannabis I can buy" (75%)

Small-scale cannabis cultivation for medicinal use was also found to be an important driver with more than half (53%) citing this as a reason to grow cannabis. This figure grows to 58% when we include those who said they were growing to provide medical cannabis for someone else. 9% selected "So I can sell it" as a motivation for growing, indicating that there may some risk of diversion for small-grows, though on a limited scale, and it is not known how many of those selecting sale as a reason for growing were also medically-motivated growers. [263]

A sub-analysis of medically motivated growers from the GCCRC survey explored whether the high prevalence of medical motivation, as cited by 53% of small-scale cannabis cultivators, might be a motive to justify and reduce the stigma of cannabis cultivation for non-medical use. The survey showed that 90% of individuals who said they grew for medical purposes claimed to have a formal diagnosis (i.e. medical record of their condition). A multinomial logistic regression analysis of the data was able to provide a more objective insight by looking for distinctive patterns between those who reported growing cannabis for recreational use; those growing for medicinal use but also reported the unlawful use of other controlled drugs; and those growing for medicinal use who did not use other substances.[264] The analysis revealed distinct differences between the groups. Though small-scale cannabis cultivation was male-dominated across all groups, a higher proportion of medicinal growers were female. Medicinal growers were also more likely to use cannabis more frequently, be less spontaneous in their use, and report health-related motivations for growing. The analysis also cited qualitative studies showing that medical users of cannabis are more likely to "deliberately monitor and titrate their use to optimise its therapeutic effect" compared to the leisure-oriented use of recreational users.[265] [266] Those who grew cannabis for medicinal reasons but did not engage in other unlawful drug use, tended to be older, use less alcohol and tobacco and were less likely to be involved in illicit activities other than cannabis-related offences.

> *"These findings suggest that claims of medical use are not simply an attempt to justify personal cannabis consumption, but do at least partly reflect a genuine belief in medical benefit. However, those growing cannabis for medical reasons form a heterogeneous group of people."* Hakkarainen et al., 2017

2.2.4. THERAPEUTIC ASPECTS OF CANNABIS USE

The medically-motivated cannabis growing cohort in the GCCRC survey reported a wide range of medical conditions, but physical pain and mental health (i.e. depression, anxiety, and PTSD) were the most common ailments. However, 40% mentioned 'other' conditions, demonstrating a breadth of indications (*see Table 15*).

These results do not prove or disprove the medical effectiveness of cannabis in these conditions, but indicate the prevalence and breadth of use within the community of self-medicating users. More recent surveys of medically motivated cannabis users, though not limited to those who self-cultivate, also show that pain, depression and anxiety were common ailments for self-medicating cannabis users - according to results from both the 2018 UPA survey and 2019 CMC survey.[267] These findings may reflect the high prevalence of these conditions in the general population, rather than high rates of self-medication with cannabis

Table 15. Therapeutic aspects of cannabis use

Illnesses, injuries or conditions for which cannabis was used as medicine the UK among small-scale cannabis cultivators (%)	
Conditions	**(n=219)**
Depression / other mood disorders	52.5
Anxiety or panic disorders	36.1
Chronic pain (e.g. Fibromyalgia)	31.1
Inflammation of the joints (arthritis)	29.7
Migraines and headaches	26.5
Bowel problems	16.4
Post-traumatic stress disorder (PTSD)	9.1
Asthma	8.2
Hypertension	7.8
ADHD	6.8
Dependence and withdrawal from other drugs	6.4
Autism and Asperger's syndrome	5.5
Cancer	4.1
Anorexia	2.7
Eye disease (glaucoma)	2.3
Nausea e.g. After chemotherapy	2.3
Multiple sclerosis	2.3
Hepatitis	1.8
HIV/AIDs	0.9
Schizophrenia	0.5
Tourette syndrome	0.5
Other	40.2
I don't know / don't want to answer	1.9

Source: Hakkarainen, P., et al (2015). Growing medicine: Small-scale cannabis cultivation for medical purposes in six different countries. International Journal of Drug Policy, 26(3), 250–256.

in those clinical populations.

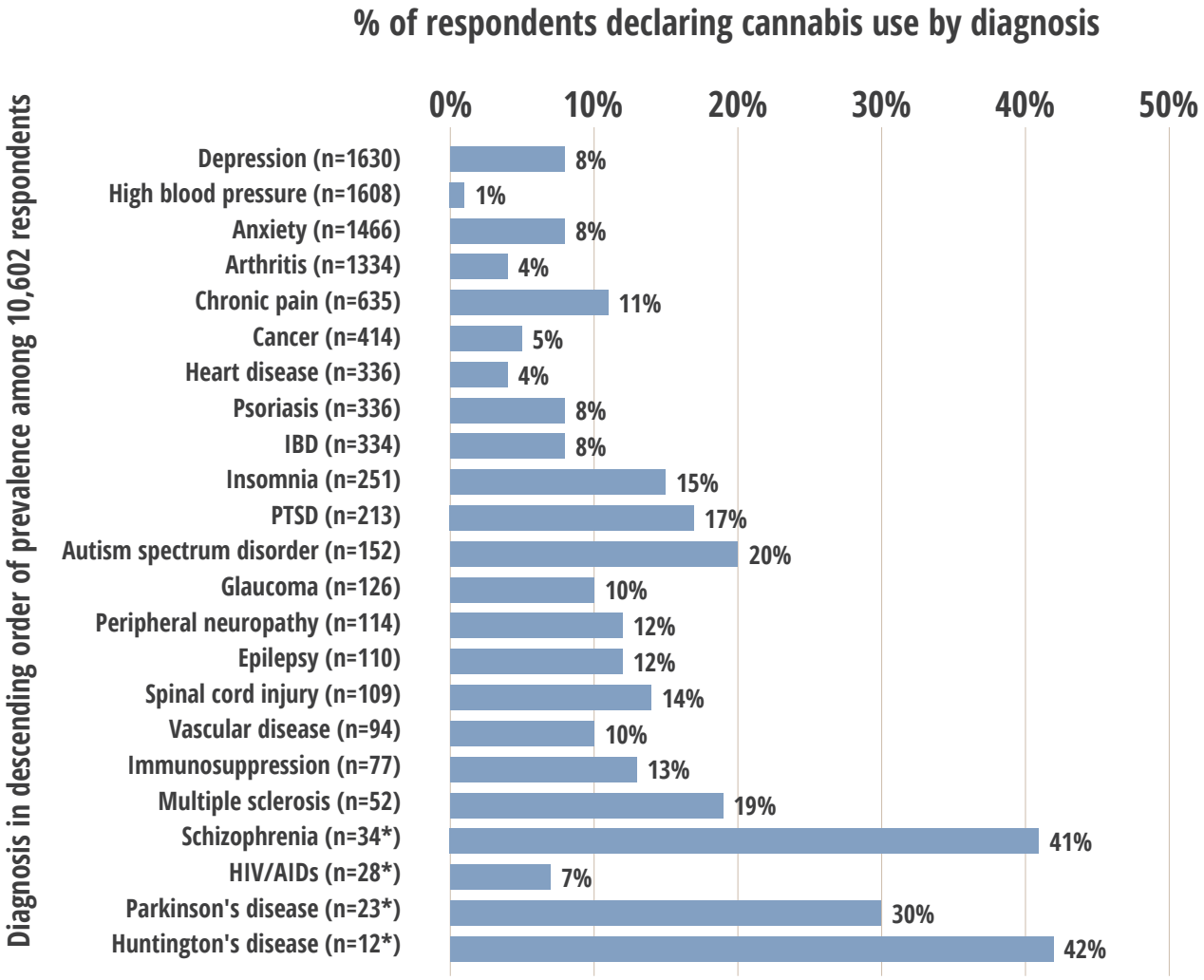
A closer look at the results from the CMC survey is able to demonstrate this point. From a nationally representative sample of 10,602 respondents in 2019, the CMC survey captured how many individuals had one or more of a set list of medical conditions, designed to capture any diagnosed medical condition that could potentially be symptomatically relieved by cannabis therapy based on a search of clinical, observational and preclinical literature. Just under half (43% or n=4916 respondents) indicated that they had at least one listed medical condition. Of those who had a listed medical condition, 6% (n=281 respondents) responded that they currently used cannabis to help manage or treat symptoms of their conditions or side effects brought on by treatment.

Depression, high blood pressure, anxiety, arthritis and chronic pain were the most commonly reported health conditions (*see Figure 9: Y axis)*. Accordingly, there were relatively large total numbers of respondents with these disorders who reported the use of cannabis for medicinal reasons, despite the percentage of people with those conditions who used cannabis being relatively low compared to other disorders (*see Figure 9: X axis*). The total number of respondents who reported using cannabis to treat depression (n= 134), for instance, was much larger than the number who used cannabis to treat autism spectrum disorder (n=31), MS (n=10), schizophrenia (n=14), Parkinson's disease (n=7), or Huntington's disease (n=5). However, the prevalence of cannabis use for medicinal reasons was much greater among people with those five conditions than it was in those with depression (19-42% vs 8%).

Due to the small sample size of some of these rarer conditions, the survey figures must be interpreted with caution, as they cannot be assumed to be representative of the total patient population. However, a UK survey with a much larger sample of MS patients (n= 3,994), conducted by the MS society in 2014, also found that one in five MS patients had said they used cannabis to help manage their symptoms, finding that it helped with muscle spasms or stiffness (spasticity) and pain.[441]

At the moment, lawful access to cannabis medicines through the NHS are generally limited to licensed CBMs (Sativex, Nabilone and Epidyolex) which have specific indications for: spasticity in MS, nausea caused by cancer chemotherapy, and two rare forms of childhood epilepsy, which represent a small clinical population. These licensed CBMs are also recommended as later line treatments, to be used only when other treatment options have

Figure 9. Cannabis use by health condition



Base: n=10,602 adults
*IBD (Inflammatory Bowel Disease), PTSD (Post-Traumatic Stress Disorder) *Caution: Low base size.*
Source: Centre for Medicinal Cannabis (2020)

been exhausted or deemed inappropriate by the attending specialist. Considering the limited range of indications and instances in which cannabis medicines can be prescribed via the NHS, there is a significant mismatch between the range of conditions where cannabis is medicinally used by self-medicating patients and those which are realistically available through the NHS under the current circumstances. It is easier for specialists in private clinic settings to prescribe a broader range of cannabis medicines (such as unlicensed medicines) in a broader range of conditions but the prohibitive end cost to the patient means both lawful medical routes cannot currently address the diverse range of indications in which cannabis is currently being used for by self-medicating users.

Internationally, in countries such as Canada, Germany, and some US states, where the provision of U-CBPMs are less restricted, this mismatch is less pronounced, bolstered by less bureaucratic prescribing conditions, lower costs associated with domestic supply, and special access programs. However, the majority of medicinal cannabis prescriptions, internationally, are written for chronic pain.[268 269]

Patients wanting to use medicines derived from cannabis are not only driven by the perceived

efficacy it may have in some health conditions – the side effect profile of cannabis is also a strong motive for use, with many users reporting a greater quality of life than they had experienced with conventional medications. This is particularly visible among chronic pain patients who find cannabis to be a more tolerable alternative to opioid-based analgesics. In a UK study of medical cannabis users collected from 1998-2002, 64% of respondents said the side effects of their prescribed pharmaceutical medicines were worse than the side effects of using cannabis to manage their condition instead (34% said '*much worse*' and 30% said '*somewhat worse*').[270]

"The medicine I take produces insane side effects such as fever, cramps, and muscle pains. Therefore I always smoke right after and usually also the day after, and it works completely like an anaesthetic (...) I usually smoke a joint before going to bed because it makes me sleep better or rather I do sleep (...) It may sound strange to you, but if I smoke a joint it also helps me control and coordinate my motor movements so I can handle the dish-washing."

Anonymous male, age 31 [273]

Other studies among pain patients also show that cannabis is effectively used as a substitute for prescription painkillers or to decrease or discontinue their use, affording better tolerability and improved quality of life.[271] The 2018 UPA survey found that 42% of its medically-motivated users of cannabis use CBP to replace analgesics.[272] While there is yet to be conclusive evidence of an "opioid sparing" effect of cannabis to minimise the risk of dependency or to reduce the use of opioids, its potential do so should be carefully considered. A review by Public Health England showed that 5.6 million people (13% of the population) received a prescription for opioid pain medicines between 2017 and 2018. Opioid medications play an important role in the clinical management of pain worldwide, but may cause unwanted side-effects such as constipation, sedation and nausea, and their use is associated with a risk of dependence disorders. Despite the risk of dependence and the fact that clinical guidelines state that long-term prescribing of opioids for chronic, non-cancer pain is not beneficial for most patients, the same Public Health England review also estimated that around 500,000 patients had been taking opioids continuously for at least 3 years (around 9% of all opioid prescriptions). [274]

"My "grow" works much better than those painkillers; it is cheaper and it has a milder impact compared to morphine, which leaves me ineffective and tired and with a stomach that doesn't work and also makes me feel like I'm another person, more distant as if I am not present here and now. I do not experience these things when using my own pot."

Anonymous female, age 47 [273]

2.2.5. WHY PATIENTS ARE RISKING CRIMINAL PENALTIES

It's important to consider why patients are willing to amplify the risk of criminal penalties by choosing to grow their own cannabis. For some, the decision to grow cannabis for medical purposes is a matter of personal preference, particularly among those who have been successfully managing their conditions in this way for some time. They may also feel that the type of cannabis they can grow and produce themselves, after what may often be years of careful cultivation, self-experimentation and study, is the most appropriate cannabis product for their condition. Others grow out of necessity, having not achieved adequate relief from licensed medicines and being unable to affordably access unlicensed CBPM through the health sector. They may have an established therapeutic response to cannabis products, but

do not want to use or rely on the black market, which offers no guarantee of quality or product content and requires patients to interface with individuals whom they may not know or trust. If they are able to grow cannabis successfully, self-cultivation permits these individuals to have a reliable, affordable and self-sufficient means of access with control over plant genetics and growing conditions. This route of access also lessens the risks of contamination from pesticides, heavy metals or other pollutants, as well as the risks of interfacing with organised crime networks. The avoidance of these risks is particularly important for individuals who are already unwell and vulnerable.

"I was fed up of having to deal with drug dealers and criminals to get cannabis from and with no assertion of quality of where it comes from... Growing it myself, gives me the ability to control to some degree the levels of CBD and THC in my plants." [275]

"My use of cannabis as medicine began when my Crohn's disease started aged 17 (...) I had paranoia attacks [due to high THC, <1 per cent CBD strains] which were extremely unpleasant until I realised that I needed an equal amount of CBD. I spent most of my time studying the endocannabinoid system, research papers and seed catalogues. But I found it impossible to get strains that were high enough in CBD (...) In 2015 I was donated CBD seeds (...) My aim was to make 1:1:1:1 CBDA:CBD:THCA:THC oil." [276]

People who grow their own cannabis for medicinal reasons tend to reject the image of being a criminal perpetrator because they are detached from the illicit market, neither buying from or supplying it. Many such individuals produce and consume cannabis for their own needs only, motivated by a belief in the plant's health benefits. People cultivating cannabis in this way disrupts the view of cultivation as an inherently criminal enterprise.[277]

2.2.6. CULTIVATION PROVIDES PATIENTS WITH MORE PRODUCT CHOICE AND CONTROL

Cannabis plants contain hundreds of distinct, pharmacologically-active compounds, and there is substantial variation in the concentration and ratio of these compounds between – and even within – plant strains. It is clear that different mixtures of cannabinoids (of which more than 140 have been identified in cannabis), terpenes (>200 identified) and flavonoids (20 identified), may have varying effects on different people and different health conditions.[278 279 280 281 282] Although isolated compounds may have therapeutic effects on their own or in simple combinations (e.g. CBD or CBD:THC isolates), it is thought that the combined action of multiple different compounds found in the plant, in different ratios, may have greater potential for therapeutic effects.[283 284]

This synergistic effect is often referred to as the "entourage effect," though conclusive evidence for this hypothesis is still lacking.[285] However, it is supported by some preclinical evidence, including the finding that different cannabis extracts selectively and differentially impair the survival and proliferation of cancer cells.[286] Isolated cannabinoids did not produce the same effects, and extracts with equivalent levels of THC but differing levels of other phytochemicals produced different antitumor effects in different cell lines.[287] Whether or not entourage effects have a significant clinical impact in humans remains to be seen, but the 'entourage hypothesis' has, internationally, been a driver of the demand for unlicensed CBPMs over the available licensed CBM, despite the weaker clinical evidence for their use.

Growing the cannabis plants themselves allows patients to try a much wider range of products than could otherwise be accessed, either through the black market or lawfully through prescription. Many of the patients we spoke to claimed that growing cannabis had allowed them to identify and select plants which best met their

individual needs, accentuating the therapeutic benefits over time. They had learned, through trial and error, that particular plant genetics and growing conditions result in products with different health effects.

For instance, one informant with MS explained that he grew some specific plants to help with fatigue and pain in the morning and other plants to use in the evening to unwind and improve the quality of sleep. Another informant, with Type 1 bipolar affective disorder, showed us a particular blend of cannabis flowers that he kept for times when he was feeling suicidal. He told us that using it at times of crisis had saved his life countless times over the years.

However, this selection and refinement process is neither easy nor convenient for many patients, and it may take a long time. Without access to laboratory analyses (unless they risk sending samples abroad to jurisdictions where they can have them tested, such as Spain), patients must rely on assumptions and first-hand experience on the type and constitution of their products. Cannabis grows are also difficult to maintain and crops can fail, interrupting treatment.

"Over eight years' experimentation I've found four plant strains that I grow myself that work better for my symptoms than any cannabis I can buy illegally—but I had to break the law by growing hundreds of different seeds to identify which ones to keep. Other growers hold genetic copies in case I am raided by police who would destroy any plants they find in my home."

Greg de Hoedt, patient & founder of UKCSC [288]

Although self-cultivation has its challenges, patients have more control over the product by having control over production – particularly in comparison to access through the black market, which has more of an incentive to supply a narrow range of high-strength products with a greater associated risk of dependence than to supply a broad range of products for medicinal use by patients. For this reason, some patients who feel they are successfully treating their ailments with cannabis grown at home wish to maintain this ownership over their health and the cannabis they consume.

The 2018 UPA survey found that a third (32%) of medically-motivated cannabis growers would continue to grow their own even if a wide variety of strains and types were available from a dispensary. Most of the respondents in this survey had been dealing with their primary health condition for more than ten years or since birth and had been using cannabis for several years. For some, the conditions under which the cannabis is grown and extracted is just as important as the cannabinoid profile so there is a disinclination towards cannabis-based medicines grown and produced on an industrial or commercial scale. Permitting patients to self-manage their conditions with cannabis grown at home carries obvious risk, as does the use of any medication without medical direction and supervision. However, research has shown that empowering individuals to make their own health choices can lead to better health outcomes (*see Waldstein, 2010; Csordas and Kleinman, 1996; Coomber, Oliver and Morris, 2003; Bone and Seddon, 2015; Department of Health and Social Care, 2019 as cited in M, Bone, 2020*).[289] The risks associated with self-medication should therefore be weighed up against an individual's health and well-being interests.

2.2.7. THE PATIENT JOURNEY TO CANNABIS CULTIVATION

"Simon's" journey towards growing and using cannabis as a medicine (*see Box 8*) follows a very similar trajectory to other patients. In 2017, an ethnographic analysis of 16 in-depth interviews with medically-motivated cannabis growers found that their journeys into cultivation often started with a life-changing illness. [290] Informants commonly reported incidents of misdiagnosis, inappropriate treatments, or surgical interventions which had either failed, made their condition worse, or created new health problems, including withdrawal symptoms from the prescription of opioid-based analgesics.

These experiences ultimately made patients feel increasingly sceptical of medical practitioners'

Box 8. *Patient case study: Simon, 55, Ex-firefighter*

"Dealers definitely aren't interested in strains like these"

"It was early 1991, I was a Firefighter. We'd been called to a flooding when my legs and body suddenly became very weak and I was struggling to walk. Three months later I was diagnosed with MS, three months after that I was no longer a firefighter and I'd began taking 999 calls. Three years later, that became too much and I was medically retired at age 31.

Until mid-1995, I was purely relying on prescription medicines for my symptom management. I'd heard whispers that cannabis was good for MS so I decided to find out for myself. Up until then, I'd never been to a drug-dealer, but because of my MS I'd now become a criminal and I found myself on the wrong side of the law.

I quickly discovered that it worked wonders for me. Thankfully, I was recommended an amiable dealer, but my wife was the person who had to go and get it for me, so now I was making her a criminal too.

Fast forward 8 years and my wife, the bread-winner and my carer, found it was becoming too much and went down to part-time employment. However, it also meant that we could no longer afford to buy my cannabis and this left us with only one option - to grow my own.

In 2003 I started growing my own and life carried on – with the dark cloud of being a criminal hanging over my head. In 2013, I discovered strains that were very high in CBD. Until then it was basically only high-THC strains that were available, with ratios of roughly 10-15% THC and negligible amounts of CBD. I'd found one that was 5% THC and 10% CBD. CBD was a game changer, for me. At last, I'd found a real medical strain - THC is a wonderful neuro-pain killer, wonderful at stopping spasms, and is a fairly good muscle relaxant. However, CBD takes muscle relaxation to a new level and works wonders for spasticity; there were parts of my body that were no longer painful – even though I hadn't realised they were painful before because it had become my normal.

All the while I was growing, I was always aware that I was on the wrong side of the law but not growing wasn't an option and dealers don't sell high-CBD strains…

I then started using two different strains and the CBD strain gave me the strength to talk to my GP about using it to try and get off of Citalopram; which I'd been stuck on since 1995. I'd tried before to get off of Citalopram but had failed due to the withdrawal-effects – electric shocks passing from one side of my brain to the other- so, with the consent of my GP, I started coming off the Citalopram. I'll never forget what happened – 36 hours after taking my last one, a fog lifted from my head (that I hadn't realised was there) and Simon was back! Medical-cannabis had got me off Citalopram, which led to my mind being clearer, which made me want to do something positive (I hadn't felt like this for a long time), and this led to me volunteering on the MS Society Helpline - which I still do.

Then, in 2018, I discovered another very high-CBD strain, 0.5% THC / 14% CBD, and this took muscle/body relaxation to another level – I was now using three different strains. Dealers definitely aren't interested in strains like this.

In August 2019, I get a knock on the door and it's the Police to say that someone has reported that cannabis is being grown at my address. The day that I'd always feared had arrived. They told me a week later that there would be no further actions because it wasn't in the public interest, but it's left me fearing another knock on the door from them... Because of my MS, I am now a criminal because of my medicine."

ability to understand their conditions or provide effective help. Where conventional healthcare systems and pharmaceutical drugs had ultimately let them down, it forced these patients outside of the conventional framework of mainstream medicine. The search for an alternative ultimately led these patients towards the medicinal applications of cannabis, which the medical community were not able to advise on or endorse. Interviewees reported having educated themselves on the medicinal use of cannabis, often seeking out experienced individuals (such as other patients with similar ailments) and groups (such as local cannabis clubs; *see route 6b*) who could advise them. In some instances, these contacts were able to donate small amounts of their own CBP in order to test whether using it led to an improvement in their symptoms.

The interviews revealed that the illicit 'black market' was considered to be the highest-risk route of access for people using CBP to treat chronic health conditions. Patients who are physically impaired are more vulnerable to being robbed. The quality and range of CBP available on the black market is also deemed to be of poor quality, 'produced without care and pride, simply for profit'. Patients can also be vulnerable to scams where drug-dealers claim to sell 'medical cannabis oils' or 'medical grade' CBP which they charge premium prices for, but have turned out to be oils with negligible amounts of CBD and THC or none at all, or raw CBP that are not flushed properly, posing health hazards. These concerns would ultimately culminate in the decision to start growing cannabis for themselves, in the pursuit of managing their condition and regaining control over their life and their disease. While the medicinal use of CBP may not provide a cure for many illnesses, these individuals believe it offers them the best quality of life possible.[290]

The lamentable conclusion arrived at by the authors of the 2017 ethnographic analysis was that these patients felt let-down in three fundamental ways. Firstly, by conventional medicines and the medical community who are had failed to help them. Secondly, by criminal operatives in the illegal markets who take advantage of them, with patients being more vulnerable to scams and robbery and finally, by the legal system that labelled them criminals for taking their treatment into their own hands by growing the cannabis themselves.

2.2.8. POLICING & PROSECUTION OF CANNABIS CULTIVATION IN THE UK

Law enforcement responses to cannabis cultivation in the UK vary within and between constabularies, leading to a confusing and unjust distribution of risk for penalties for offending. A number of police forces have publicly communicated that they have deprioritised or stopped pursing low-level cannabis users and growers, while other forces remain very actively intolerant of these offences.[291]

A gradual movement toward *de facto* decriminalisation – a term signifying that an offence has been decriminalised through the de-prioritisation of policing, rather than through formal legislative change (known as *de jure* decriminalisation) appears to be occurring across the country, mirroring wider international developments.[292] In response to a freedom of information (FOI) request submitted by VICE in April 2019, complete arrest data for cannabis cultivation offences was provided by 26 of the UK's 43 police forces.[293] It was revealed that the rates of arrests for growing had fallen by more than half (57%) over six years – from 6,859 in 2012 to 2,949 in 2018. Of those who were arrested, which VICE say included patients using cannabis for medicinal purposes as well as members of organised crime groups, fewer than half subsequently faced charges.

Cases from across the country illustrate the disparity in outcomes for small-scale medicinal cultivation arrests. In 2018, two agoraphobic patients were caught growing ten plants at their home in Cardiff to treat phobic anxiety. They were charged and sentenced to a 12-month community order, placed under an electronically monitored curfew, and ordered to pay £300 in court fees. A married couple in east Sussex, who were caught growing four plants to treat the husband's diverticulitis and the wife's extreme joint pain, only received a police caution. The couple now fear that one of them might lose their job, which requires a regular criminal record bureau check. Although they continue to use cannabis to manage their health conditions,

they now rely on cannabis oils sourced from other patients who grow and produce their own. This disparity in outcomes also exists for growers of cannabis who make no claim of medical motivation. VICE's investigation into police arrests for cannabis cultivation uncovered a case involving a non-medical grower, found to be cultivating 20 cannabis plants by police, who was never subsequently charged, while another was caught on 3 separate occasions before finally receiving a suspended sentence. The disparity in outcomes for medically-motivated cannabis growers cannot therefore be put down to leniency due to claims of medical necessity, but may be more of a reflection of divergent approaches between police officers and police forces towards all forms of cannabis use or cultivation, whether medically-motivated or not. As discussed at the beginning of this route to access, these divergent outcomes involving small-scale growers is thought to have been the impetus for Italy to exclude small amounts of domestic cultivation for the exclusive use of the grower from the law pertaining to the growth of narcotic drugs, as it was creating confusion over the legal status of cannabis.

The authors are aware of two medically-motivated cannabis growers who use cannabis to manage the symptoms of their MS and who were both caught by the police. They received very different legal consequences despite both growing no more than 10 plants for personal use with medicinal intent. On the grounds of a lack of public interest, former firefighter Simon (*Box 8*), received no further action when police found him growing cannabis, nor were his plants seized. However, in the same year, Lezley Gibson was arrested and held in custody for several hours when police discovered that she was growing cannabis. Although she, like Simon, was growing for personal medicinal use, her cannabis plants and flowers were seized and she was charged with possession and production, leading to a year-long court case.

2.2.9. THE PROSECUTION OF MS PATIENT LEZLEY GIBSON

In January 2019, Lezley Gibson's home was raided by Cumbria Police. Ms Gibson and her husband Mark were arrested and charged with possession and cultivation of a controlled class B drug following the confiscation of 10 baby cannabis plants and three home-made cannabis chocolate bars. The pair were faced with the prospect of receiving up to five years in prison, an unlimited fine, or both, if convicted.

Ms Gibson was diagnosed with MS at 19 years old. Her MS affects her speech, sight, and at times has left her partially paralysed. She struggled to find relief from the medications she was being prescribed, including steroids, which had challenging side effects that had to be managed on top of her MS symptoms. With pharmaceutical medicines failing to adequately help her, she changed her diet and lifestyle to improve her health. Eventually, she came across information on the potential therapeutic value of cannabis in the management of MS, which prompted her to try it for herself. Lezley found that cannabis use improved her condition and reduced her MS attacks. It was also more tolerable than some of the pharmaceutical medicines she had been using previously.

The confiscation of Lezley's plants and cannabis products during her arrest led to a sudden cessation of treatment, since her symptoms do not adequately respond to conventional treatments for MS. Lezley therefore endeavoured to find a lawful route of access to cannabis-based medicines. Lezley had been prescribed the cannabinoid spray Sativex on the NHS in the past and had responded well to the drug, but it had been withdrawn without explanation a few years before her arrest. During her year-long legal proceedings, Lezley repeatedly tried to be re-prescribed Sativex on the NHS, without success.

At the time of Lezley's arrest, Sativex was already a licensed drug for severe-to-moderate spasticity in MS where other treatments have failed but it was not yet considered cost-effective by NICE, which is likely to be why her prior prescription had been suddenly withdrawn without explanation. While Lezley's legal proceedings were underway, new NICE guidelines were published which recommended the use of Sativex as a cost-effective treatment for moderate-to-severe spasticity in MS patients who do not respond adequately to other medications.

Despite the updated guidelines, she was still denied a Sativex prescription and was told that her local NHS commissioners were not providing funding. Lezley's own GP explained to her lawyers that they were not able to prescribe Sativex to Ms Gibson on the NHS, as it was "now blacklisted," which meant it was "not available under Primary or Secondary Care as per the Area Prescribing Committee Guidelines issued by the North Cumbria Clinical Commissioning Group."

Given the barriers that Ms Gibson faced in accessing Sativex on the NHS, despite the drug being licensed as a treatment for her condition and considered cost-effective by NICE, she recognised the improbability of gaining access to an unlicensed CBPM. Despite the rescheduling of CBPM in November 2018, access remains extremely limited (*see Chapter 1: Route 2*). With no means to access cannabis-based products on the NHS, Ms Gibson obtained a prescription for Bedrocan at a private specialist clinic at a cost of £700/month. Lezley's legal team contended that the Gibson's had no option but to cultivate cannabis in their home due to the unavailability of cannabis-based medicines on the NHS and the financial unsustainability of access through the private health sector. Since her arrest, Lezley has paid for a private prescription using loans and credit cards.

At a Crown Court hearing in January 2020, the Crown Court Prosecution Service decided that there was no public interest in proceeding with the case, minutes before the trial was due to start at Carlisle Crown Court. The outcome rested on the fact that Lezley had managed to obtain a legal private prescription since her arrest. The prosecuting barrister maintained that the couple had broken the law and warned that they would be prosecuted if they did so again. However, simple means testing would show that the Gibsons are are not financially able to maintain such an expensive private prescription in the long term. The Gibsons are now left trying to negotiate reductions in price with the suppliers of their privately prescribed prescription on compassionate grounds.

This case raises important questions about the law enforcement response to individuals growing a small amount of cannabis for personal use where there is a claim of medical necessity

"I'm pleased to be acquitted but this case has been hanging over me for a year and the medicine that kept me well was taken by police. I don't want other patients to suffer the same. I hope the CPS will see sense and stop prosecuting patients."

Lezley Gibson [294]

"It can't be right to prosecute a person who has no choice other than to use medicinal cannabis to alleviate serious symptoms of a condition such as Multiple Sclerosis. I cannot see a situation where it would be in the public interest to prosecute a person in such circumstances. As it remains a criminal offence to cultivate cannabis for medical use, the law needs to be reviewed so that we no longer put seriously ill people through the humiliation and trauma of a police raid, arrest and prosecution only for the prosecution to be later halted because it is, so obviously, not in the public interest to continue it. The law clearly needs to change."

Tayab Ali, Solicitor representing Lezley Gibson

involved. Going through the criminal justice system is an ordeal for any individual, and Ms Gibson's symptoms and overall health visibly worsened over the course of the year long legal proceedings, corroborated by her own GP.

Although the case was ultimately abandoned by the CPS, with no legal precedent set, the question remains as to whether it was ever in the public interest to prosecute Ms Gibson in the first place. A nationally representative survey of British adults, commissioned by the CDPRG and

conducted by YouGov in June 2019, revealed that only 17% of the British public and 23% of Conservative voters support the prosecution of individuals for unlawfully using cannabis to self-treat medical conditions.[295] During Ms Gibson's legal proceedings, she received a groundswell of public support. Her case was covered by several news outlets including The BBC and The Times. A crowdfunder set up to support her legal fees raised over £10,000, with many donations coming from fellow patients.

In addition to the question of public interest, the process of arrest, custody and prosecution is paid for at the expense of the UK taxpayer. In 2018, the Taxpayers' Alliance estimated the total costs of enforcing cannabis-related criminal offences at approximately £200 million each year, accounting for costs to forensics and evidence collection, the prison system, the probation service, legal aid, the CPS, and the courts.[296]

Ms Gibson's case highlights the ongoing barriers to accessing cannabis-based medicines through lawful routes, and the outcome may encourage patients in a similar position to defy the law in order to manage their medical conditions. Regardless of whether or not they set a legal precedent, these cases still have weight and reflect the tide of public and political opinion.

2.2.10. FORCED TO BREAK THE LAW: HOW SHOULD POLICE RESPOND TO MEDICAL CANNABIS USERS?

On October 29, 2019, the All-Party Parliamentary Group (APPG) on Drug Policy Reform hosted a Parliamentary meeting titled '*Forced to Break the Law: How should police respond to medical cannabis users?*' The group heard testimonies from several patients, including Ms Gibson, on the positive impact that medicinal cannabis had had on their lives and the challenges of accessing these products through lawful medical routes. They spoke of living in fear of 'the knock on the door from police' and possible prosecution. In response to Ms Gibson's legal case and other patients who have found themselves either living in fear of the law, or directly impacted by it, the APPG for Drug Policy Reform wrote to the Director of Public Prosecutions (DPP) for clarification of prosecution guidance for patients cultivating cannabis for medical use. Ms Gibson's legal team also intends to ask the Director of Public Prosecutions (DPP) to review its prosecution policy in cases involving people using cannabis to treat illnesses.

It is likely that law enforcement would welcome additional guidance, as many medically-motivated growers who have come into contact with the police for cultivating cannabis have described the arresting officers as being understanding, sympathetic, and even reluctant to seize the patients plants: "One of the officers gave me a hug and said don't worry love, it will soon be legal for people like you."[297]

The APPG heard evidence from Carly Barton, a patient and medicinal cannabis user, turned campaigner, who had her plants sized by police several years ago. She described how her arresting police officer broke down in tears at having to confiscate what was her medication, enabling her to stay off medicines such as prescribed fentanyl patches.

Ms Barton proposes a scheme known as Carly's Amnesty, under which patients with certain health conditions for whom private prescriptions of CBPM are unaffordable are permitted to grow their own personal supply of cannabis for medicinal use under certain restrictions. Patients would have to declare and register with their local authorities where they are growing and agree to hand in anything above their needs in return for immunity from arrest and prosecution. The goal is to work in view of the law, rather than against it. Carly Barton, who initially reached out to her local cannabis social club for support, finds that the medicinal use of cannabis has greatly helped her manage her chronic pain without the need for opioid-based painkillers. Her experience has driven her to find ways to support other patients benefitting from the medicinal use of cannabis, leading to her proposal for the Carly's Amnesty scheme which already has the public support of several Police and Crime Commissioners (PCCs), MPs and foundations. Dr Rick Muir, Director of Police Foundation has said "patients with a recognised condition should be allowed to grow their own cannabis for medical purposes - otherwise we are forcing people who need to use cannabis for health reasons into the criminal

economy. Carly's Amnesty is a positive proposal and should be adopted nation-wide."[298]

The proposed scheme is designed to address the two-tier system that has developed in the UK, whereby those with the means to pay for cannabis medicines through private clinics can do so lawfully, while those who lack the financial means grow at their own risk, leaving patients in these circumstances to feel let down by their medical community and the criminal justice system. As affordable access to L-CBM and U-CBPM through the health sector increases over time, the numbers of patients who rely on homegrown products is likely to reduce. Access to standardised, high-quality medicinal products under the direction of a physician will be more favourable for many patients than self-cultivation, but this route is unlikely to be eliminated altogether. Those who have learned to successfully manage their conditions with homegrown products, particularly those who have spent years fine-tuning their production to their individual needs, often report low expectations of additional therapeutic benefits from mass-produced commercial cannabis medicines. Longstanding cultivators for medicinal use may feel some degree of propriety over the (re)discovery of the therapeutic aspects of cannabis and feel pride in their ability to self-manage their conditions where conventional medicine had failed to help.

Carly's Amnesty is intended to protect patients who feel that self-cultivation is their best option, and would also permit greater regulation and oversight of the practice. However, growing cannabis isn't feasible for many patients as setting up and managing the grow is time-consuming and requires a relatively well and physically able person to do so (although the scheme allows for patient carers to be named as designated cultivators). Responsible cultivation also requires a secure and appropriate space.

2.3. ROUTE 6B: SMALL-SCALE COOPERATIVE-BASED CULTIVATION GROUPS AND "CANNABIS SOCIAL CLUBS"

Some cannabis users and growers come together, as groups or clubs, in order to collectively cultivate and distribute cannabis among a closed circuit of members. This enables members to share the burden of responsibility and access cannabis without necessarily growing it directly or continually themselves. Nonetheless, cultivation remains relatively small-scale and cooperative-based, and allows them to circumvent the illegal black-market. These types of cooperatives are most formally recognised as Cannabis Social Clubs (CSCs) but they can operate in a variety of styles, often influenced by the legal context they exist in, from legally regulated models, quasi-legal models, and CSCs that exist with no legal basis to do so at all, such as those in the UK.[299]

2.3.1. CANNABIS SOCIAL CLUBS: AN INTERNATIONAL PERSPECTIVE AND PRINCIPLES OF SELF-REGULATION

CSCs are typically defined as non-profit associations where cannabis users collectively produce and distribute cannabis among themselves, and usually require the individual to become a paid member of the group to pool resources for growing.[306] [307] Usually, the clubs will also provide a private space to consume cannabis socially. Evidence of CSCs have been found across 13 European countries including the UK, and they cater to both medicinal and non-medicinal users of cannabis, with some known to exclusively work with patients, or provide special services for patients, such as an on-site doctor.[308] [309] [310] [311]

According to an exploratory analysis of 81 CSCs across Europe, conducted between 2018-2019, most clubs (75%) indicated that they were currently involved in cannabis cultivation and distribution. More than half of the clubs (53%) were based in Spain, which has a long history of CSCs dating back to 2001; 21% were from the UK; and the remaining 26% were from other European countries. Some clubs may pay growing members of the group a production cost, with the number of growers depending on the size of the club. In the UK, a much smaller proportion were involved in the production and distribution of cannabis compared to Spain, where the CSC model is well-established, the cultivation of cannabis for personal use is decriminalised/tolerated, and where all clubs tend to be involved in production and distribution.

In clubs that do not organise production or distribution, members benefit from the social aspects of the group, including the sharing of knowledge on best growing practices, information on the use of products, and legal advice.[312] They promote self-sufficiency and independence from the black market as well as best practice in terms of responsible growing and safer consumption methods and use. Although many UK clubs might not have an organisational role in the cultivation and distribution of cannabis, they do bring together individual growers who may arrange informal social supplies between themselves, though such supply is unlikely to be reliable as these individuals usually operate small-scale grows to meet their own needs and are motivated to keep a low profile. This means members may still access cannabis from the black market if the club itself or members within the club do not have their own organised supply to distribute.

In contrast, 42 out of 43 surveyed CSCs in Spain were involved in the production and distribution of cannabis. Spain, like some other European countries, has traditionally followed a more tolerant approach towards cannabis and other drugs.[313] The possession of small amounts of any drug is not considered a criminal offence, providing it is for personal use and consumed in a private space and not on display. Consumption or minor personal possession in public places, however, is punishable with fines (EMCDDA, 2019).[314] Cannabis cultivation for recreational or medicinal use is also decriminalised with these same public vs. private restrictions.[315] While the sale of cannabis is illegal, the clubs circumvent this by registering as non-profit organisations, only charging a membership fee to cover costs.

The CSC model is therefore able to exist as an extension of the decriminalisation policy in Spain. Clubs inhabit a legal grey area where they are generally tolerated, but some do become

Box 9. A *brief history of cannabis social clubs*

The concept of a cannabis club originates with the establishment of the San Francisco Cannabis Buyers Club in 1992, when a cannabis dealer converted to the cause of medical cannabis after discovering that it brought relief to the symptoms of AIDS – with which his partner was afflicted – and produced relief in palliative care.[300] This became the first known cannabis dispensary in the US and undoubtedly helped shaped the state of cannabis in California, which became the first state to legalise cannabis for medicinal use in 1996, and many other US states since.[301]

The term 'Buyers Club' is a throwback to the Buyers Clubs that arose around the AIDS epidemic in the mid-1980s. This was a result of a lack of treatment choices to treat AIDS due to long medical approval processes and a perceived lack of government action on the matter. Buyers' Clubs therefore smuggled large quantities of non-FDA approved drugs from other countries into the United States to be redistributed to the members of the club who paid a fee to join, enabling the buying power of the club.[302] Despite being entirely unregulated, many clubs adhered to an ethical code to not profit from the business and provide the drugs at the "lowest possible cost."[303] Clubs would also provide and/or recommend a number of different treatments options to help the many different aspects of AIDS, not just to combat the disease directly but also to treat infections, boost the immune system and provide general relief of symptoms. Similar clubs have been set up since in response to a prohibitively expensive drug for Hepatitis C, where the clubs import cheaper versions of the drug from China.[304]

The San Francisco Cannabis Buyers Club was therefore part of a dual response to the AIDS crisis, acting as a subsidiary club providing cannabis as an adjuvant treatment to AIDS medications. They became known as a social club due to the importance of the social interaction the club provided, which was a space where members could consume their cannabis, relax and connect with other patients and learn more holistic ways to manage their condition. According to an ethnographic study of former members in 1998, the club provided a 'crucial support mechanism which became an equally important part of the therapeutic process of cannabis use, improving their quality life and maybe even prolonging it.'[305]

subject to legal sanctions and have been shut-down.[316] However, it is not known whether these closures are driven by the noncompliance of clubs with the key prerequisites of the CSC model (*Box 10*). Despite their legally ambiguous status, CSCs are common in Spain and have influenced legislative reforms in other countries including Uruguay, which implemented the model within their legally regulated framework for cannabis. The clubs collectively grow plants proportional to the size of their membership and then distribute it to their registered members. This is permitted by pooling the legal cultivation quotas of all the members so that individuals do not have to grow it themselves. Individuals can usually specify the type of strain they are interested in and would like the club to grow on their behalf. No profit motive means there is no incentive to increase cannabis consumption, though CSCs can choose to employ reasonably remunerated staff, contributing to the creation of employment and the generation of tax revenue.

The clubs are a convenient source of cannabis for medically motivated users as no formal program for medical cannabis on prescription is currently supported in Spain.[317] With such a long history of CSCs in the country, the discussion of cannabis access for non-medicinal use predated pressure for medicinal access.[318] Arguably, policymakers in Spain may face less pressure to initiate a medical cannabis access program because access to cannabis through the CSC model is relatively straightforward and reasonably priced, or patients can choose to grow their own.[319 320]

Unlike Uruguay, which has a legal framework regulating the CSC model, CSCs in Europe are unregulated – a shortcoming of decriminalisation policies. Attempts have been made by autonomous regions in Spain to legalise the model, but these have been blocked by central government.[321] However, many tend to follow good practice codes and or the code of conduct set out by the European Coalition of Just and Effective Drug policies (ENCOD), a platform which unites and represents organisations working in the field of drugs (*see Box 10*).[322] CSC federations may produce their own, similar guides, which affiliated clubs need to adhere to should they want to have that affiliation with the federation.[323] It should be noted that there are other cannabis clubs in the UK which exist to make a profit and run themselves like businesses, buying cannabis from the illicit market and selling it on at a markup – with some charging extortionate prices. These are sometimes referred to as 'shadow clubs' and do not follow the ethos of the non-profit CSC model.[324 325] However, the term 'CSC' has become so popular that it is sometimes used to refer to any form of cannabis club.

Operating under these prerequisites of the CSC model, the clubs meet the needs of their members who want safe access to a higher quality and more diverse range of CBPs, as well as a social consumption space. By acting in a responsible manner towards both members and non-members in the wider public, the clubs receive some degree of leniency from law enforcement. Even in the UK where there is no legal framework for the clubs to exist, some clubs are known of and tolerated by police.[326 327]

Furthermore, the CSC model appears to be well suited to the delivery of harm reduction strategies, which some clubs already employ. Harm reduction refers to strategies and practices that aim to reduce the risks associated with drug use.[328] In the case of cannabis this may include the promotion of safer practices and consumption methods, and education of the risks associated with cannabis use. Some clubs host talks on the medicinal use of cannabis and CSCs in Barcelona, Spain, are known to employ physicians who offer services to individuals self-medicating with cannabis. These physicians also provide counselling services to its CSC members on any aspects of cannabis use that maybe a concern to them.[329] Some clubs have also expressed the desire to go a step further and develop relationships with testing facilities in order to check their products cannabinoid/compound profile and general quality.

The CSC model offers a middle-ground option between the false dichotomy of prohibition and creating a legal for-profit cannabis industry. Unlike some decriminalisation policies overseas, the CSC model detaches supply chains from the illicit markets. For example, in the Netherlands, personal possession and retail sales of cannabis in 'coffee-shops' are tolerated by law enforcement, but cultivation and production are still strictly forbidden. This means that the tolerated market in the Netherland is still supplied by organised criminal groups, which is known as the 'back-door problem.'

Box 10. Code of Conduct for European Cannabis Social Clubs: an extract

Due to the lack of a legal framework with regards to cannabis cultivation for personal use, we, cannabis consumers throughout Europe, have initiated our own model of regulation and control. This model, called the Cannabis Social Club, aims to prevent cannabis consumers from being involved in illegal activities and assures that certain requirements concerning public health and safety are being fulfilled.

Key prerequisites of Cannabis Social Clubs (CSCs) Regulations:

- *CSCs are registered, non-profit associations, formed by adult people who consume cannabis.*
- *CSCs organise the collective cultivation of an amount of cannabis that is exclusively meant for the private consumption of their members. The production capacity of a CSC is based on the expected level of yearly consumption of its members, increased with a reasonable buffer to counter the risk of failed harvest, provide emergency supplies for people who consume cannabis for medicinal reasons.*
- *CSCs have a protocol for adhesion of new members that includes an explanation on their rights and duties, an indication of the estimated amount of consumption and a private conversation on the history of use. This allows the clubs to recognise problematic consumption and to respond to this situation. CSCs apply an active policy of prevention of harms and risks and promotion of safer methods of consumption of cannabis by its members.*
- *The CSC model aims to prevent cannabis consumers from being involved in illegal activities and assures that certain requirements concerning public health and safety are being fulfilled and should promote safer methods of consumption of cannabis by its members.*
- *Methods of growth and cultivation should meet the standards of biological agriculture with sustainable use of natural resources.*
- *CSCs should be transparent and have an open dialogue with authorities to provide insight in their working methods.*
- *They can be set up legally in any country where cultivation of personal amounts of cannabis has been decriminalised. In countries where this is not yet the case, CSCs can operate as an experiment in order to prepare for the moment when the laws on cannabis cultivation for personal use will change.*

Although the CSC model advocates independence from the black market, clubs in the UK do not typically organise production and distribution and act rather as advocacy and support groups. Members who do not grow their own, or do not rely solely on doing so, may still rely on the black market for access. These clubs, therefore, do not meet the hallmark of a typical CSC, but do endeavour to fulfil other responsibilities of the CSC model.

In order to address the 'back-door problem,' a number of local governments in the Netherlands, including the city of Utrecht, are requesting an exemption from Dutch drug laws in order to experiment with the closed-member CSC production model. The intention is to undercut criminal involvement with the supply chain, which will also serve to improve the quality and safety of cannabis products sold in coffee shops. The CSC model can therefore operate as an experimental scale to trial how the model would work in isolated areas first.[330]

2.3.2. CANNABIS CULTIVATION GROUPS IN THE UK

Despite the lack of legal provisions for a CSC model in the UK, cannabis clubs exist all over the country, although typically of a smaller size and scale than those seen in Spain.[331] [332] [333] Some of the clubs exist primarily as advocacy groups for small-scale cultivation and support both patients and non-medicinal users to become

self-sufficient in their access to cannabis, rather than rely on the black-market.

United Kingdom Cannabis Social Clubs (UKCSC) is one such federation. As described on their website, they are a not-for-profit organisation founded in 2011 who "offer practical and legal advice and guidance to Cannabis Social Clubs, politicians and police forces in order to provide a self-regulatory framework to reduce risks." Operating as a private members club for both medical and non-medical users of cannabis, the UKCSC provides general cannabis information and harm reduction advice – such as promoting safer methods of consumption.

While the group advocates for the legalisation of all adult use of cannabis, the UKCSC has a strong impetus to provide and advocate for the medicinal use of cannabis. Its chairman and founder, Greg de Hoedt, is himself a medicinal user of cannabis who suffers from Crohn's disease. In 2010, he was told he had two to five years to live if he did not have major surgery and chemotherapy. After discovering that cannabis significantly reduced his symptoms, he travelled to the USA to explore different cannabis initiatives.[334]

Due to the illegality of cannabis cultivation and use in the UK, the UKCSC operate in a different way to models that operate within legal or quasi-legal frameworks, such as those in Spain, but they appear to adhere to some of the same principles outlined by the code of conduct by the ENCOD (*Box 10*). They have a registration process for members and ID is required to ensure members are not under 18. Smoking is not permitted unless the site has outside space (adhering to the anti-smoking legislation), encouraging vaporising instead and thus promoting a healthier consumption method than smoking. According to Stuart Harper, board member of the UKCSC, "all cannabis consumed by members is produced by collectives regulated by the UKCSC National Committee. These collectives grow their plants with serialised tags ensuring that all cannabis stays within a closed loop system."[337]

Harper goes on to explain that patients have found access to cannabis medicines and cannabis for medicinal use difficult, unreliable and of inconsistent quality, and that the UKCSC help patients better understand the medicinal use of cannabis and provide safer access for those who seek it. Acknowledging that some patients are not well enough to grow the plants themselves, clubs have often donated cannabis to patients for medicinal use. Since there are, typically, many medicinal users in these clubs, members are in a position to recommend certain cannabis strains and/or cannabinoid formulations they think will provide the best therapeutic response for other members. Patients within these cannabis communities draw their expertise from personal and convergent experiences. They learn from each other and their extended community to become experts and partners in the self-management of their condition with CBPs.[338]

Box 11. *Greg de Hoedt, patient and founder of UKCSC*

"I threw all of my energy behind the UKCSC. A few years later, after the number and the size of the clubs had grown, Stuart Harper [board member of UKCSC] and I took the collective evidence the UKCSC had and wrote a model inspired by the Mendocino, California, tagged plant model and linked it to the nine plant sentencing guideline limit (see Figure 8).

There are now over 150 CSCs registered with the UKCSC. I thought we just need to show in a self-regulatory way that home growing is safe and possible. If people use our model and their plants are tagged, then they become a member of the first cannabis growers union in the UK, and having many growing under the same model, as opposed to many growing under no model, shows some respect for regulation… It is a harm reduction initiative at the end of the day.

I want us to grow within this model to show that we are responsible citizens, and that we are not criminals, even though the law has labelled us this way. We created a detailed Operations Manual which covers everything including: the UKCSC's constitution, detailed models for growing and selling cannabis at fair trade prices, harm reduction measures and standardised posters designed to inform the police of the model."[335 336]

One witness interviewed by the CDPRG for this report spoke of the high levels of requests received by one 'compassion club' from desperate patients or their caregivers, who have exhausted other avenues and write to the club for help. Communications between the club and the patients revealed that significant efforts were made by members of the club in order to provide support. Detailed information was gathered about the condition and medical history of those making requests, including a history of past and current prescribed drug use, and advice was given when members believed that certain medications contraindicated individuals from using cannabis. In response to such requests, where possible, the club and/or its network try to arrange for the provision of cannabis oil, of which this particular club has two main types with varying THC:CBD profiles. However, any provision of cannabis is informal and reserved for the most urgent needs or requests. Members who only grow enough to meet their own medicinally-motivated needs may perhaps have some product that they are able to donate or share, but cannot offer any regular supply. People with chronic medical conditions, and their carers, who have found relief through the medicinal use of cannabis often feel duty-bound to share knowledge and help others suffering in the same way.

Groups like the UKCSC inhabit a space that the UK healthcare system has struggled to engage with – exploratory research has shown that at least three CSCs in the UK appear to serve medicinal users only and the UKCSC have been seeking to create a patient-specific model.[339] [340] While the very public rescheduling of cannabis-based products for medicinal use in 2018 raised patient expectations and demand, it has not lead to widespread supply. The ongoing challenges to access through the health sectors, coupled with growing public awareness and demand, may drive greater numbers of patients toward CSCs. While the absence of professional medical direction in these settings may be problematic, many patients will consider it a better option than no access at all.[341]

A recent interview conducted by JS Rafaeli (co-author of *Drug Wars*, which provides a detailed history of drug policy in the UK) covers the story of "Jim," a man who claims to distribute cannabis oils to people with medical conditions who might benefit – for free (*see Box 12*). This medically-motivated, non-profit operation is currently able to supply between 150 and 200 patients at any one time. Like CSCs, Jim encourages people

Box 12. Supplying unlawfully-produced cannabis oils to patients for free

"It's rare that one meets someone who has been described as a "Robin Hood figure," who actually lives up to the hype. Interviewing "Jim" was one of those moments. Jim supplies people who need it with high-potency cannabis oil. This is not for "recreational" use. The people who Jim supplies are very sick, often at the end of their lives. At any one time he may supply between 150-200 patients, his name getting passed through word of mouth – often between hospital beds. Jim takes no money for this service. He does it purely because these people need help. He runs a separate legitimate business, which pays for the underground operation.

Jim got into this because he was working in palliative care. He noticed that many of the people he was helping were using cannabis to treat their conditions, but they were "buying bad product from kids on BMX bikes." Jim thought he could do it better. Demand was huge, and he has worked with people from all walks of life, from judges and police officers to the unemployed – and of course, their children. When I remind Jim that what he is doing is still illegal, and ask if he worries about the police, he is philosophical. The police are a worry, but he cannot sit back while other people suffer needlessly, and he would be prepared to go before a jury – "they are people too, remember," he reminds me – and plead his case. The response Jim gets from his work is incredible. Patients relate that this product is a sea change in their quality of life as they and their families cope with very difficult medical conditions. It is impossible to speak to Jim, knowing that he is risking his freedom to provide this – for zero financial gain – and not be quite profoundly inspired."

JS Rafaeli

to become self-sufficient and avoid the illicit market.

Jim says that his supply decisions are based on the latest clinical studies from the international cannabinoid research field, so that he can offer everyone a "tailor-made treatment." He claims to have invested in the best available equipment so that people receive "the absolute highest quality products, in the correct doses and blends." In addition to producing and supplying products for free, he is also trying to collect meaningful data:

"We've had people from hospitals and major medical cannabis companies come down and talk to us, because essentially, we've been conducting a decade-long drug trial, and have generated all this unique data. My only regret is not having been able to gather all this in a strict enough way to be accepted by a wider scientific community... Some doctors have now given me data recording sheets, and I've been trying to adapt various charts to help people gain a more comprehensive understanding of pain management.. It would be ideal if there was a change in the law, but we're going to keep helping people no matter what."[342]

There are legitimate patient-safety concerns in regard to suppliers that make medical claims about unlicensed products and provide them to at-risk communities without accountable medical direction. In the absence of data, little can be said about the outcomes of Jim's operation, but it is important to note that restrictions on medical access lead to the emergence of unregulated supply chains to meet patient demand. The scale of this operation and the lack of a profit motive speaks to the sense of obligation that some feel to provide cannabis for medicinal purposes where no alternative means of access is adequate. In Jim's own words, 'everyone deserves the right to medicine.'

It is easy to underestimate the role that CSCs and similar networks can play for medicinally-motivated cannabis users, since such groups are typically associated with 'recreational' demand. Although they typically cater to both medicinal and non- medicinal users, they have significant patient representations within them. A greater range of CBP may be available to medicinally-motivated users through this route of access than on the illicit market. Goods are also produced locally, transparently, and often to the specific needs or demands of the end-user. Clubs are known to dedicate a lot of energy to patient advocacy and they enable patients who want to self-manage their condition with the use of cannabis to reclaim agency over their own health. They provide a more controlled and socially-embedded setting than isolated self-cultivation or reliance on the black market, and they explicitly try to divert people from organised criminal supply networks.

The CSC model aims to be a positive form of social enterprise in their local community and this appears to afford them a greater level of tolerance from police forces. Police and Crime Commissioners (PCCs) for North Wales and Durham have been vocal in their support of the "Spanish-style" CSC model. In reference to cannabis clubs in the UK, Arfon Jones, PCC for North Wales, has said: "If we did know where they were, we'd be very reluctant to interfere with them unless they were causing trouble or letting children in." Jones is among a number of other PCCs across the UK who publicly and privately support the clubs. To close the clubs would likely displace those who rely on them to black market sources of cannabis instead, which are deemed to be more problematic routes of access. This would disproportionately affect medicinal users of cannabis. This approach pushes the boundaries of our drug laws in a bid to demonstrate that models of responsible regulation can have positive impacts has been characterised by some scholars as 'better to ask forgiveness than permission.'[343] CSCs in the UK risk more in regard to this approach than clubs in other countries, due to less leniency in our controls on possession and cultivation. Although unevenly policed throughout the UK, and with inconsistent outcomes, cannabis offences continue to be considered serious crimes, potentially warranting imprisonment.[344] [345]

A risk to the CSC / UKCSC model is the emergence of shadow clubs', individuals or groups who intentionally market themselves as a CSC as a front for criminal entrepreneurs.[346] Greg de Hoedt explains that these clubs "are not growing in line with the model and there is no safety or accountability. I am now looking at how to develop a verification system, so that the CSCs

following the UKCSC model can be more easily identified, and consumers will know that they are trustworthy and are not operating to take advantage of the sick and vulnerable."[347]

Responsible, small-scale self-cultivation enables greater control over the types of cannabis product that a medicinally-motivated user can access, and negates the need to interface with organised criminal networks. Accordingly, we consider this route of access to be safer for the individual and for wider society than the illicit market, though substantially less safe than supervised access of prescribed products through the health sector. However, only around 1 in 10 patients who source cannabis unlawfully grow their own supply.

Self-cultivation requires some initial investment in seeds and equipment, some know-how and management, as well as physical capacity and a secure place to grow a small number of plants. This means that it is not a viable route for many patients who may not have the physical capacity to grow and tend to cannabis plants. Patients with chronic health conditions are also move likely to have a lower income and those who live in council houses risk eviction from their homes in addition to criminal penalties.

CSCs in the UK, although relatively widespread, are not established in a way to offer reliable supplies of CBP. Rather, they are focused on advocacy, the promotion of self-sufficiency through small-scale cultivation, and encouraging best practice. Under a more permissive legal and regulatory environment, or through police deprioritisation, UK clubs may adopt more formal 'Spanish-style' models.

The CDPRG are regularly approached by small groups of cannabis growers who wish to apply for a Home Office license so they can grow cannabis in a cooperative such as cannabis social clubs. Currently, this type of license does not exist in the UK.

2.4. ROUTE 7: THE ILLICIT 'BLACK MARKET' IN CANNABIS-BASED PRODUCTS

The illicit 'black market' is by far the most active access route for people who use cannabis for medicinal reasons. With an estimated 4 out of 5 medicinal users accessing CBP through the black market, this could equate to more than 1 million British patients.[348 349]

The illicit market is also considered the least safe of all the routes of access addressed in this report. The range of CBP available is typically limited to low-CBD, high-THC products. There is no reliable information available to consumers on what products contain or how they were produced. There are no guarantees of quality or good practice, nor will there be consistency between one batch and another.

Buyers are more at risk of coercion, deception and violence than in other routes of access, particularly if they are medically and/or physically vulnerable. At a broader level, the supply chains and revenue streams of organised criminal networks are linked to other forms of crime, including the exploitation of children, human trafficking, and terrorism.

"When you deny access to medical cannabis to appropriate patients who have tried everything else, what happens is that they end up accessing it on the black market, putting themselves and often their loved ones at risk from exposure to criminality, unsafe and untested products, and in isolation from the medical and public health system where they no longer feel welcome. This is one of the strongest arguments for medical cannabis regardless of personal feelings towards these compounds."

Dr Dani Gordon, MD

Nonetheless, the illicit market is also the most convenient. Access is quick and does not require a large investment of time, money or effort. Medicinally-motivated users face lesser risks of criminal penalties for possessing CBP obtained on the illicit market than they do for growing and

producing CBP themselves for personal use. Until other routes of access prove less challenging, it is likely to remain the default choice for most individuals who use CBP for medicinal use.

2.4.1. CRIMINAL PENALTIES FOR POSSESSION IN THE UK

Arrests for possession of a small amount of cannabis (i.e. amounts considered enough for personal use but not enough for supply, though no set amount is defined) typically result in a formal caution for first-time offenders with no previous cautions or convictions.[350] While a caution is not a conviction, it still becomes a criminal record and can affect future education, employment and travel.[351] If cannabis possession is not a first offence, or the offender is deemed to have more than a small amount of cannabis on them, the outcome is likely to be harsher, and could result in a prison sentence of up to five years.

As discussed earlier in regard to cannabis cultivation offences (*see Route 6a*), the court will determine the offender's level of 'culpability,' and the 'harm' associated with the offence. This involves determining whether the possession of cannabis was for the person's own use, or to provide to others. If intent to supply is suspected, it would need to be determined whether this was for profit, and how much profit was being made. The offender's role in the supply chain is also considered, whether they have control over others or if there is evidence of a community impact. In the case of cannabis possession, "offenders using cannabis to help with a diagnosed medical condition" is explicitly mentioned in the Sentencing Council's Definitive Guideline for Drug Offences (under "Section 5(2) of the Misuse of Drugs Act 1971"), as a mitigating factor warranting a lesser sentence. This is not stipulated in the sentencing guidelines as a mitigating factor for cultivation, but it likely to be considered. However, it is unclear how law enforcement determine what use constitutes medicinal use or which "diagnosed medical conditions" warrant a lesser sentence, which suggests that proper legal and medical representation would be important.

2.4.2. BLACK MARKET DYNAMICS

Black markets operate outside of the law, but they are subject to the same economic rules of supply and demand as lawfully regulated markets, and are shaped by economic and policy influences. Government overregulation and high taxes on products or services can create a secondary black market to provide those products or services at a reduced cost, or simply when the product is in limited supply or hard to access through lawful means. The goods or services themselves may be unlawful, such as the production, distribution, sale, or possession of controlled drugs. This is also relevant to controlled prescription drugs which have been stolen or diverted from legitimate medical markets to the black market, meaning they can be accessed without the need of a prescription nor consultation with a doctor. In both instances, both the buyer and seller and anyone else involved in the chain of supply are breaking the law.

The black market route to cannabis has become more convenient and accessible as technology has evolved. The term 'street cannabis' comes from a time when buyers would have to find a dealer on the street, with greater risks to the buyer than typical black market transactions today. Although buyers and sellers may still meet at 'street-level' or through 'person-to-person exchanges,' orders are often placed through encrypted messaging applications and delivered directly to the buyer by car, making detection of these transactions less visible than they have been historically.

Online crypto-markets (sometimes referred to as the 'dark web' or 'deep web'), where individuals can buy drugs anonymously and rate sellers on their products, are also becoming more sophisticated and easier to use. Drugs purchased on these online markets are typically delivered to the buyers' home by courier or national mail services in unmarked, unnamed packaging.[352] Crypto-markets are understudied, but exploratory research conducted between 2013 and 2016 found that the UK and Ireland were responsible for the largest proportion of 'cannabis resin' transactions (46.5%) and one third (33.3%) of the revenue generated.[353] It is unknown how many of these transactions could come from patients but is demonstrative

of the innovation seen in black market sales of drugs. As highlighted by the latest European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) report (2019), the black market for drugs quickly evolves and has become progressively more complex, making it increasingly difficult and resource-demanding for law enforcement to keep up. The report states that "cannabis is set to remain popular with consumers and as a consequence, will continue to generate significant profits for the organised crime groups (OCGs) involved in its production, trafficking and distribution."[354]

Those with a firm belief in the therapeutic use of cannabis and who feel they have no other option but to source their CBP from the black market might argue that the black market provides an essential quality-of-life service to patients who use cannabis to manage health conditions where conventional medications and lawful means of access have been inadequate. However, the wider activities of OCGs involved in the trafficking, production, and distribution of drugs for black markets, and the revenue they generate, are often linked to other crimes such as forced or coerced labour, the exploitation of children, terrorism, and human trafficking.

According to a 2019 report from Europoll, the drugs trade is the largest criminal market in the European Union (EU) and is conservatively estimated to generate around EUR 24 billion in revenue each year, with cannabis making up the largest proportion of the drugs trade.[355] The Institute of Economic Affairs estimate that the UK black market for cannabis is worth £2.6 billion per annum.[356] Around a third of OCGs active in the EU at an international level are involved in the production, trafficking or distribution of controlled drugs. The 2016 EMCDDA and Europoll report found that more than 75% of OCGs were involved in the trafficking of more than one drug, and two thirds of those involved in the drug trade were also involved in other criminal activities.

The purchase of cannabis from black market sources has a high chance of funding other crimes, such as the distribution of more dangerous drugs and the use of forced labour or trafficked individuals to grow cannabis on a large-scale.[357] By the time someone purchases a drug from a dealer at the bottom of the supply chain – who distributes the smallest amounts of cannabis at 'street level' (i.e. person-to-person exchanges) – both the buyer and the dealer may be unaware of the original source of the product, the conditions under which it was grown, how it was distributed, or where the profits end up.

The 2019 Centre for Medicinal Cannabis (CMC) survey into unlawful cannabis use among patients using with medicinal intent, for whom the black market was the most prevalent route of access, found that average expenditure was £162 a month. This figure varied by health condition, with Parkinson's disease patients spending the most at £357 a month and arthritis patients spending the least at £144 per month. Other research indicates that medicinal users of cannabis are more likely to use cannabis frequently (compared to non-medicinal or recreational use) in order to titrate their use and optimise its therapeutic effect in managing a chronic condition (*see Chapter 2: §2.2.4*). This is also reflected in some international polices pertaining to cannabis access, such as Canada, where patients are allowed to access a larger amount of cannabis than recreational users or grow a larger number of plants, should this be authorised by their doctor. Spanish CSCs also tend to allow patients to access a larger amount of cannabis, and have reserves for their patient members. In the UK, this means that patients buying cannabis from the black market could be, on average, contributing a larger sum of money per person to the criminal market that non-medicinal users. The finding from the CMC that patients are spending an average of £162 per month on black market cannabis – with at least 1 million patients thought to be sourcing cannabis in this way – suggests that as much as £2 billion per year could potentially be going into the black market from patients alone.[358] Such estimations can only ever provide rough guides, but this indicates that the input from patients alone may be substantial.

A notable disadvantage of the black market in cannabis is that it tends to be dominated by high-potency, high-THC varieties. While THC can be helpful in managing certain conditions, black market cannabis products often have little to no detectable traces of other compounds which may also have therapeutic value, particularly

CBD, which is known to mitigate some of the unwanted and more harmful effects of THC.[359] [360] The narrow range of product diversity, in conjunction with greater risks of contamination and adulteration of black market products, leads to increased risks of harms to individual consumers and public health. The black market is already aware of the demand for 'medical' cannabis, with patients increasingly being targeted by criminal supply networks selling 'medical grade' cannabis products or oils with spurious claims of medical benefit. While there maybe some intent to deceive and defraud patients willing to pay a premium price for 'medicinal' products, it may also foreshadow a greater range of 'medicinal' products coming onto the market. The most recent Europol report found that cannabis products are becoming increasingly diverse in Europe, including cannabis-based medicinal and health-orientated products and an increasing number of cannabidiol (CBD) or low-THC products are being sold in a range of formats.[361] [362]

2.4.3. POLICING & PROSECUTION OF POSSESSION IN THE UK

As with the policing of cannabis cultivation, there is also a pattern of patchwork policing of cannabis possession across the UK with a trend toward decreased enforcement. A 2019 Freedom of Information request obtained by VICE found that more than half of police forces had recorded 40% fewer cases of cannabis possession since 2012.[363] A investigation by The Times, using Home Office data, found similar patterns of decreasing arrest rates for cannabis possession among many police forces, with only 3 out of 43 Police Forces showing an increase, despite cannabis remaining the most popular black market drug.[364]

These results have led to claims that small-scale cannabis offences are being *de facto* decriminalised in the UK.[365] While this may seem like an encouraging trend for patients who rely on unlawful routes of access to cannabis for medicinal use, the de-prioritisation of cannabis policing is unevenly applied across the UK and lacks national and government oversight, meaning no policies are in place to evaluate its outcomes.[366] This has also led to a lot of confusion around the 'legal' status of cannabis as outcomes can be so divergent depending on the arresting police officer or constabulary. However, falling arrest rates, alongside public statements of support for drug policing reform from national police staff associations and an international shift toward the liberalisation of cannabis drug policies, indicate that attitudes are moving away from the penalisation of cannabis users toward initiatives that seek to advocate public health approaches and reduce harms. Whether or not this will materialise into a national approach and how this will affect patients is uncertain.

2.4.4. THE RELATIONSHIP BETWEEN LAWFUL AND UNLAWFUL ROUTES OF ACCESS TO MEDICINES

The unlawful supply of medications is not a novel phenomenon, nor is it unique to cannabis. Black markets for prescription drugs form whenever there is high demand and low access through legal routes, as we have seen in the case of 'buyers clubs' for HIV and Hepatitis C drugs (*see Chapter 2: §2.3*), and the trading of other prescription drugs on the black-market. Cannabis is somewhat unique in that it can be grown by individuals at home from seeds legally available online. Other prescription drugs on the illicit markets may more commonly be diverted from lawful sources or counterfeited, usually by OCGs. It is a criminal offence to be in possession of any prescription-only controlled drugs without a prescription, whether it be a cannabis-based medicine, codeine, morphine, or diazepam.[367] However, there appears to little evidence of enforcement of individual possession offences of prescription only-drugs, except in cases where individuals are in possession of large amounts with suspected intent to supply.

When black markets develop in order to meet demand for a drug, this can contribute to the opening up of regulated, legal forms of access as a way to address the problem of unregulated use. In the 1990s, the demand for the erectile dysfunction (ED) drug Viagra was so high – to the extent that it was already widely accessible on the black market before it achieved market authorisation in the UK – that the NHS refused to fund it when it became licensed, despite having proven safe, effective, and substantially cheaper

than other drugs. When Viagra first launched in the US, it quickly became the most commonly prescribed drug for ED and the size of the ED market quadrupled.[368] Viagra also attracted recreational users who were not prescribed the drug by their doctor for pathological ED, but who experienced situational ED due to other non-health issues, such as alcohol and drug use, and fatigue.[369] [439]

When Viagra launched in the UK, the Health Secretary admitted that "media coverage of this drug to date has created expectations that could prove a serious drain on the funds of the NHS. If this were to happen, other patients could be denied the treatment they need. I cannot allow this to happen." The Secretary's statement shows how high patient demand for a new treatment can cause implementation challenges for healthcare systems. However, if high demand is not being met through lawful routes, it is usually only a matter of time before operatives in the black market for drugs capitalise on the opportunity. This leads to the unregulated use of medicines which may also be adulterated or counterfeit, and poses greater risks to public health, while generating vast profits for organised crime. Japan's approach was to approve Viagra quickly as a way to address the thriving black market, limiting the profits to organised crime and the counterfeiting of products on the market.[370] Today, Viagra and other ED medication can be easily obtained from UK pharmacies without prescription.

We can observe from this example the importance of cost-effectiveness in regard to the provision of drugs on the NHS. Despite Viagra being a relatively inexpensive drug, the size of demand caused a concern that it would drain NHS funds and could affect the provision of other drugs to other patients. Comparably, the funding of U-CBPM on the NHS requires a balancing of cost-effectiveness, with budgets more likely to prioritise licensed drugs and treatments, particularly those that offer more than symptom management. Although we cannot simply pit one drug against the other in this way, the cash-strapped NHS need to carefully consider economic considerations, and a lack of robust clinical data for most U-CBPM makes cost-effectiveness calculations challenging and speculative. Unless ways are found to reduce costs, such as pay-for-responder agreements, it is unrealistic to expect the widespread funding of U-CBPM on the NHS. Most new drugs, even those found to be very promising or highly efficacious, will not necessarily be widely available at first, which is when they are at their most expensive and physicians lack familiarity with the new drug or class of drugs – often waiting to hear feedback from other physicians/colleagues who adopted the drug early on.

Unlike Viagra, which is a single-molecule drug that achieved market authorisation on the basis of robust safety and efficacy data from the traditional phases of clinical research, cannabis-based therapies represent a new class of polypharmacy drugs, rather than a single compound, and all but a few are still without market authorisation. Although unlicensed medicines are routinely prescribed in the UK, this usually refers to 'off-label' use in which a licensed product is used outside the terms of its market authorisation. In the case of U-CBPMs however, most have no product licenses at all.

The case of Viagra also illustrates that restricting lawful supply to a drug that is in high demand may inflate demand for the drug through unlawful means, which may compel the provision of the drug through the appropriate medical routes. However, it does not provide a solution to the problems of medicinal cannabis. Increasing access to cannabis-based products requires unpacking what that would mean: access to which products, for which patient groups, through what means, with what oversight and regulation, and at whose cost? Additionally, with such a diversity of cannabis-based products, we cannot easily predict the outcomes of increasing access to one type of product, through one route, on rates of access to other types of product through other routes.

CONCLUSIONS

Although recommendations had been made to HMG to reschedule cannabis-based products to allow their use as unlicensed medicines as early as 1998, the decision to reschedule in 2018 was made quickly and before detailed plans for implementation and public communications had been made. The rescheduling was reactive, pushed forward by high profile cases of children in desperate clinical need. As has happened in many other countries, models of access to cannabis-based products were driven by patient demand in advance of many products achieving market authorisation. Accordingly, the challenges to access that were experienced by patients and prescribers in the first year after rescheduling were, to some extent, inevitable.

With no robust evidence on safety, efficacy and cost-effectiveness, and in the absence of established production in the UK, the availability of U-CBPM for medicinal use in the first year after rescheduling was necessarily limited. Access was particularly limited on the NHS, as a public healthcare system with finite resources and with longstanding evidence-based processes in place for prioritising cost-effective treatments. Policy-makers, regulators and the NHS have had to strike a difficult balance between making access available where clinically appropriate, while limiting widespread access, since U-CBPM are products that have not been through the rigorous process of evaluation required for market authorisation. There has been an understandable reluctance to treat U-CBPM in an exceptional way to other medicinal products, for fear of unintended consequences and setting a precedent that could be exploited by producers wanting fast-track access to the market to the potential detriment of patient safety.

The challenge, however, is that the markets in cannabis-based products are already exceptional in a number of ways. Firstly, there is tremendous demand for cannabis among patient populations, but the prescription of specials medicines cannot lawfully be solicited by patients. Obstacles to lawful routes of access through the healthcare sectors have motivated large numbers of people to acquire cannabis products unlawfully, despite the substantial risks associated with interfacing with criminal organisations, using products of unknown quality and efficacy, and being caught and charged for committing criminal offences. It is not easy to confidently quantify human behaviours in hidden populations, but rough estimates indicate that there are presently hundreds of thousands of UK citizens unlawfully accessing cannabis products for medicinal reasons, and possibly more than a million. Many tens of thousands of people are growing cannabis themselves, or with the help of others, to meet clinical needs that have not been adequately met by existing treatments.

Secondly, as with many plant-derived products, cannabis is not a single compound. 'Medicinal cannabis' is an umbrella term denoting an overwhelming variety of polypharmacy formulations, and cannabinoid research is not yet advanced enough to identify which compounds and combinations may provide the most therapeutic benefit to different clinical populations, nor which may pose the greatest health risks. The complex pharmacology of cannabis poses challenges to drug development, since there are countless potential products to investigate and limited resources to invest. The few products that have achieved market authorisation as medicines in the UK represent only a small fraction of the potentially useful compounds and combinations that can be derived from cannabis. Although there is robust clinical evidence of quality, safety and efficacy for licensed medicines, they remain available for only small numbers of patients, and, for some, may not provide as much therapeutic relief as products that patients have grown and prepared themselves, or acquired through other unlawful means. Some cultivators of cannabis for personal use with medicinal intent have spent many years experimenting in search of a product that works best for their own individual needs.

Thirdly, the demand for cannabis products is not limited to those for whom there may be medicinal value. Cannabis is the most widely used controlled drug in the world and its appeal as an intoxicant is at least as strong a driver of demand on the illicit markets as its appeal as a treatment for medical conditions. Internationally, the campaigns to open up medicinal access have been difficult to disentangle from movements to liberalise laws on recreational use. HMG have been clear that there is political will to increase the availability of cannabis products for legitimate medicinal use, but not to amend existing legal controls over unauthorised use.

It can be extremely challenging to distinguish between medicinal and non-medicinal use even

at the level of the individual. Many licensed medicines may be used and abused beyond the threshold of medicinal benefit, as has been seen with opioids, gabapentinoids and other drugs of dependence. Equally, many non-medicinal products may be used by individuals to reduce symptoms or otherwise improve their quality of life. Patients and prescribers may disagree on what is and what is not of therapeutic benefit, and this is particularly challenging in conditions that are fundamentally subjective, such as chronic pain. What may be seen as the abuse of a drug for intoxication from one perspective may be seen from another as being a therapeutically useful relief of anxiety, rumination, pain, or any number of other benefits commonly reported by cannabis users. While medicinal and non-medicinal use may be easily distinguished at the extremes of the spectrum, there is a grey area between where opinions will differ.

It is worth noting that the phenomenon of cannabis-use in general was, for many decades, without any recognised evidence of medicinal benefit. Until 2018, all cannabis products were Schedule 1 controlled drugs, other than Nabilone, the few medicines that had achieved market authorisation in the UK, and those cannabis-derived compounds which were not controlled under the MDA 1971. The regulatory controls over Schedule 1 drugs do not prevent scientific and medical research, but it is widely recognised that they create administrative and financial challenges that substantially increase the difficulty and duration of research. The unauthorised use of cannabis, however, has been and continues to be widespread, despite the criminal penalties that such offences incur. For these reasons, it is not surprising that the use of cannabis for medicinal reasons in the lay sector is so much wider than the use of L-CBM and U-CBPM in the professional medical sector.

The challenges faced by legislators and policymakers are complex and the UK situation cannot be directly compared with other countries. Although lessons can be learned from developments internationally, the UK differs from other jurisdictions, particularly in terms of our healthcare, legal and political systems. The Government has not sat idly on its hands; the complexities of medicinal cannabis policy are well known and substantial attention is being paid to the problem. As the developments to import regulations in March 2020 demonstrate, Government are listening to the needs of stakeholders and working on the design and implementation of regulatory models that will continue to adapt and evolve, while remaining cognizant of potential unintended consequences.

In Part B of this report, we examine the goals and challenges of medicinal cannabis policy in the UK. The 2018 rescheduling had three primary objectives: (1) to increase safe access where clinically appropriate; (2) to support the development of the evidence-base on safety and efficacy; and (3) to minimise actual and potential risks and harms to individuals, society and public health. Legislators were concerned about the risks of inappropriate prescribing and diversion, and made clear that there was no political interest in liberalising legal controls on the unlawful use of cannabis, nor in sending a message that might affect public perceptions on the harms of cannabis as a drug of abuse.

Comparing and contrasting the UK situation with the various models of access to medicinal cannabis implemented in other countries, Part B will outline a range of potential options to meet the above policy goals in the coming years. Every regulatory model comes with trade-offs, and any changes that affect one route of access will also change and shape the flow of access through other routes. It is up to the Government to decide whether the best regulatory model for the UK should focus on specific routes of access or bring all the control of all extant routes under the governance of a single, integrated system. There are no simple answers to the challenge of medicinal cannabis policy, but there are options to be considered that can significantly improve the safety of access, reduce criminal activity, support UK industry, boost the economy, and develop valuable data sets to establish the UK as a global leader in cannabinoid medicine while informing the development of new licensed products. These goals can be accomplished without decriminalising or legalising the unauthorised use of cannabis products and may be implemented with minimal legislative change. Future policy must be approached with care and forethought, side-stepping the pitfalls experienced by other countries to find the right solution for Britain. The challenges are substantial, but the potential benefits are difficult to overstate.

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Authors

Dave King
Amber Moore

Reviewers

Rudi Fortson QC
Dr Dani Gordon
Carl Holvey
Dr Melissa Bone
Dr Chandni Hindocha
Paul Dunn
Dr Mikael Sodergren
Alex Davis
Dr Anna Waldstein
Dr James Rucker

Design

Laura Sallette
Mark Muldoon

Referencing

Nikki Wyrd

Proofing & Editing

Ros Stone
Freddie Blunt
Timmy Davis
Laura Sallette
Hannah Slater

ANNEXES

ANNEX A
LEGISLATIVE CONTROLS ON CANNABIS AND CANNABINOIDS

3.1. THE MISUSE OF DRUGS ACT 1971

The Misuse of Drugs Act 1971 ('the 1971 Act' or 'the MDA 1971') restricts the availability of drugs considered to be 'dangerous or otherwise harmful' to authorised scientific and medical use. The 1971 Act describes a number of criminal offences relating to the cultivation, production, supply, movement or possession of cannabis, and other 'controlled drugs,' and states the maximum penalties that may be imposed on a person convicted of any of the above offences, all of which are unlawful unless authorised by a valid Home Office license or by way of regulations made under the Act (*see Table 16*). Additional penalties may be incurred if the Proceeds of Crime Act 2002 applies. Schedule 2 of the 1971 Act provides three classes (A, B and C), which are intended to reflect the relative potential harms of the specified drugs when misused. Cannabis, cannabis resin, and the substances cannabinol and 'cannabinol derivatives' are listed as Class B controlled drugs.[371]

'Cannabis' is defined in the 1971 Act and its subsequent amendments as 'any part of the genus Cannabis or any part of any such plant' excluding the seeds, mature stalk, or fibre produced from the mature stalk after separation from the rest of the plant. 'Cannabis resin' is defined as 'the separated resin, whether crude or purified, obtained from any plant of the genus Cannabis.'[372] 'Cannabinol derivatives' are defined as 'tetrahydro derivatives of cannabinol and 3-alkyl homologues of cannabinol or of its tetrahydro derivatives,'[373] as well as 'any ester or ether of cannabinol or of a cannabinol derivative'[374] and 'any stereoisomers' of these substances.[375] These definitions have been interpreted by the Advisory Council on the Misuse of Drugs (ACMD) as being applicable to a total of 12 controlled compounds derived from the cannabis plant (phytocannabinoids), only two of which are explicitly listed in the 1971 Act.[376] These controlled cannabinoids, referred to later in this report as Category 2 items or as Cannabinol (CBN)-type compounds (including tetrahydrocannabinol (THC)-type compounds), are listed in Annex B.

Controlled cannabinoids, however, represent only a relatively small proportion of the cannabinoids that have so far been isolated from cannabis, of which the ACMD's report identified 97 and other reviews identified as many as 144.[377] [378] Cannabinoids to which the definitions of the 1971 Act are not applicable include Cannabigerol (CBG)-type, Cannabichromene (CBC)-type, Cannabidiol (CBD)-type, Cannabinodiol (CBDL)-type, Cannabifuran (CBF) type, Cannabicyclol (CBL)-type, Cannabacitran (CBT)-type, and Cannabielsoin (CBE)-type compounds.

Amendments to the 1971 Act in 2013 and 2016 added several 'generations' of synthetic cannabinoids to Class B, some of which have later been removed from control.[379] These generations define compounds which are not found naturally, but which bind to cannabinoid receptors in the human body. Many of these compounds are full agonists at the CB1 receptor, bind with high affinity, and have been associated with a greater potential for harm than naturally-occurring cannabinoids.[380]

Section 7 (3) of the 1971 Act requires the Secretary of State to make regulations which provide that it is not unlawful for "a doctor, dentist, veterinary practitioner or veterinary surgeon, acting in his capacity as such, to prescribe, administer, manufacture, compound or supply a controlled drug, or for a pharmacist or a person lawfully conducting a retail pharmacy business, acting in either case in his capacity as such, to manufacture, compound or supply a controlled drug." This section allows for the legitimate use of controlled drugs in medical practice. The associated regulations are the Misuse of Drugs Regulations 2001.

Section 7 (4) grants the Secretary of State power to designate certain drugs as exempt from Section 7 (3) if "it is in the public interest." Section 7 (4) provides that, under such circumstances, the "production, supply and possession of that drug to be either wholly unlawful or unlawful except for purposes of research or other special purposes." The Misuse of Drugs Designation Order (2015) lists drugs to which this Section applies, and which may not be used lawfully except under a license or other authority issued by the Home Office.

Table 16. An abridged list of offences and penalties for unauthorised actions pertaining to Class B drugs under the Misuse of Drugs Act 1971

			Maximum punishment	
	Offence	**Section**	**Magistrate's Court**	**Crown Court**
Production	Production, or being concerned in the production, of a controlled drug.	4(2)	£5,000 fine and/or 6 months' imprisonment	Unlimited fine and/or 14 years' imprisonment
	Cultivation of cannabis plant.	6(2)		
Supply	Supplying or offering to supply a controlled drug or being concerned in the doing of either activity by another.	4(3)		
Possession	Having possession of a controlled drug.	5(2)	£2,500 fine and/or 3 months' imprisonment	Unlimited fine and/or 5 years' imprisonment
	Having possession of a controlled drug with intent to supply it to another.	5(3)	£5,000 fine and/or 6 months' imprisonment	Unlimited fine and/or 14 years' imprisonment
Occupier	Being the occupier, or concerned in the management, of premises and permitting or suffering certain activities to take place there.	8		
Contravention	Contravention of directions relating to safe custody of controlled drugs.	11(2)	6 months imprisonment and/or a fine	2 years imprisonment and/or a fine
	Failure to comply with notice requiring information relating to prescribing, supply etc. of drugs.	17(3)	Level 3 on the standard scale	
	Contravention of terms of license or other authority.	18(2)	6 months imprisonment and/or a fine	2 years imprisonment and/or a fine
	Giving false information in purported compliance with notice requiring information relating to prescribing, supply etc. of drugs.	17(4)		

3.2. THE MISUSE OF DRUGS REGULATIONS 2001

The Misuse of Drugs Regulations 2001 (the '2001 Regulations' or the MDRegs 2001') stipulate the conditions under which the use of controlled drugs can lawfully occur (e.g. importation, exportation, production, supply and possession) and imposes regulations concerning their prescribing, labelling, storage, security, administration and destruction. The 2001 Regulations particularise controlled drugs into five Schedules (1–5), intended to reflect the therapeutic value of drugs relative to their potential to cause harm when misused. It is commonly claimed by Government departments, politicians, regulators, and other parties that the Schedules reflect specific categories of potential harm and value; for instance that Schedule 1 drugs "have little or no therapeutic value" or "have low value relative to a high potential for harm when misused."[381 382 383] The 2001 Regulations themselves make no such statement; the terms "harm" and "value" do not appear at all.

Schedule 1 includes substances that are not available for scientific, medical, or other purposes without specific Home Office approval. A Controlled Drug register must be used to record details of any Schedule 1 drugs received or supplied by a pharmacy.

Schedule 2 includes drugs that are available for prescription with special requirements in regard to safe custody, prescription and record keeping. A Controlled Drug register must be used to record details of their acquisition and use. Schedule 2 drugs may be legally possessed and supplied by medical professionals, and lawfully possessed by individuals with a prescription.

Schedule 3 includes substances subject to special prescription regulations and safe custody regulations (with some exceptions). Schedule 2 requirements for record keeping and storage do not apply to Schedule 3 drugs.

Schedule 4 (Parts 1 & 2) includes substances that are not subject to special prescribing arrangements nor safe custody requirements (with the exception of Sativex). Predominantly, Pt 1 lists benzodiazepines and Pt 2 lists steroids. Pt 2 drugs are exempt from the prohibitions on importation, exportation and possession when in the form of a medicinal product.

Schedule 5 is reserved for preparations with low concentrations of active ingredient, and therefore low strength. These substances are exempt from most of the requirements pertaining to controlled drugs.

Cannabis, cannabis resin, cannabinol and cannabinol derivatives, as defined in the 1971 Act, are all listed under Schedule 1 of the Regulations and, consequently, are prohibited for medicinal use, except when authorised by a Home Office license or other authority issued by the Secretary of State under section 7(4).

Some specific cannabis-based products are exempt from Schedule 1 control, having been individually rescheduled. Nabilone, an encapsulated synthetic THC-type compound licensed for chemotherapy-induced nausea and vomiting, was approved for marketing by the Medicines and Healthcare products Regulatory Agency (MHRA) in August 2007 and rescheduled to Schedule 2 in 2009.[384] Sativex, a liquid formulation containing a cannabis extract with an approximately 1:1 ratio of THC:CBD, was approved for marketing in June 2016 and rescheduled to Schedule 4 of the 2001 Regulations in 2013.[385] Dronabinol, a synthetic stereoisomer of THC ((-)-trans-Δ9-tetrahydrocannabinol), was listed as Schedule 2 when the Regulations came into effect in 2001, having been moved from Schedule I of the 1971 UN Convention to Schedule II in 1991).[386]

On November 1, 2018, an amendment to the Regulations came into effect (Statutory Instrument 2018/1055, 'SI2018/1055' or 'the 2018 amendment') which rescheduled a defined category of cannabis-based products for medicinal use in humans (CBPM) to Schedule 2, with specific provisions. The amendment allows cannabis-based products that meet the definition to be prescribed without a Home Office licence, prohibits the self-administration of CBPM by smoking, and limits their order and supply to be made only in accordance with the direction of a physician on the GMC's specialist register.

The definition of a CBPM is as follows: "a preparation or other product," (not being Sativex) "which-

1. is or contains cannabis, cannabis resin, cannabinol or a cannabinol derivative" (not being synthetic dronabinol) "which;
2. "is produced for medicinal use in humans; and-
3. is –
    - a medicinal product, or
    - a substance or preparation for use as an ingredient of, or in the production of an ingredient of, a medicinal product"

Regulation 16A provides the circumstances under which a CBPM may be ordered and supplied, namely, if the product is any of the following –

1. "a special medicinal product that –
    - is not also an investigational medicinal product, but
    - is for use in accordance with a prescription or direction of a specialist medical practitioner;
2. an investigational medicinal product without a market authorisation that is for use in a clinical trial; or
3. a medicinal product with a marketing authorisation."

The definition of 'direction' is not provided by the 2001 Regulations, nor by other Acts and Regulations described in this chapter. The definitions of a 'special medicinal product' and an 'investigational medicinal product' are provided by the Human Medicines Regulations 2012 and the Medicines for Human Use (Clinical Trials) Regulations 2004, respectively. These regulations are described later in this chapter.

The phytocannabinoid classes not included as controlled drugs in the 1971 Act are not controlled in the 2001 Regulations either, nor would they be included in the provisions of the 2018 amendment. However, if there was evidence that a cannabinoid was psychoactive under the definition laid out in the Psychoactive Substances Act 2016, it would be covered accordingly. The medicinal use of pure cannabinoids which are not psychoactive nor controlled by the 1971 Act or 2001 Regulations would not require a Home Office licence, and their prescription as 'specials' medicines would, presumably, not be bound by the specific limitations described in Regulation 16A, merely by the ordinary restrictions placed on all other 'specials,' as laid down by the Human Medicines Regulations 2012.

Lastly, cannabis-based products consisting of one or more component parts, any of which contains a controlled drug, are also exempt from the provisions of the Regulations where all of the following requirements are met:

1. the preparation or other product is not designed for administration of the controlled drug to a human being or animal;
2. 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
3. no one component part of the product or preparation contains more than one milligram of the controlled drug."

The Home Office have released guidance stating that condition (c) is interpreted to mean more than one milligram of the controlled drug per container of the 'exempt product'.[387] Epidyolex, which contains trace amounts of THC, was previously considered an exempt product on this basis.[388]

3.3. THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004

The Medicines for Human Use (Clinical Trials) Regulations 2004 (the 'Clinical Trials Regulations') define an 'investigational medicinal product' as:

"a pharmaceutical form of an active substance or placebo being tested, or to be tested, or used, or to be used, as a reference in a clinical trial," including products with a marketing authorisation but which is provided in a different formulation, used for a different indication or used to gain further information about the use for which it is licensed for the purposes of the trial.

A 'clinical trial' is "any investigation in human subjects, other than a non-interventional trial, intended -

1. to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products,
2. to identify any adverse reactions to one or more such products, or
3. to study absorption, distribution, metabolism and excretion of one or more such products, with the object of ascertaining the safety or efficacy of those products;"

The Clinical Trials Regulations (Pt 2, 11) require authorisation to be requested and granted for clinical trials, and state that the request must include a dossier on each investigational medicinal product to be used in the trial, containing:

1. "summaries of the chemical, pharmaceutical and biological data on the active substance and the finished product;
2. summaries of the non-clinical pharmacology and toxicology data on that product, if available; and
3. summaries of the available data from previous clinical trials of, and human experience with, that product."

3.4. THE HUMAN MEDICINES REGULATIONS 2012

Part 1 of the Human Medicines Regulations 2012 ('the 2012 Regulations' or 'HMRegs 2012') define a 'medicinal product' as:

1. "any substance or combination of substances presented as having properties of preventing or treating disease in human beings; or
2. any substance or combination of substances that may be used by or administered to human beings with a view to -
    - restoring, correcting or modifying a physiological function by exerting a pharmacological, immunological or metabolic action, or
    - making a medical diagnosis."

Part 4 of the 2012 Regulations prohibits the sale or supply of unauthorised medicinal products - specifically, any product supplied without or outside of the terms of a market authorisation, certificate of registration, traditional herbal registration or other authorisation. Part 10 of the 2012 Regulations stipulates certain exceptions to this rule. Regulation 167 provides that the prohibitions in Part 4 do not apply in relation to a 'special medicinal product,' defined as a medicinal product which is –

1. "... supplied in response to an unsolicited order;"
2. "... 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;"
3. "... for use by a patient for whose treatment that person is directly responsible in order to fulfil the special needs of that patient;" and for which the following conditions are met:

The product -

- is supplied to an authorised prescriber or for use under the supervision of a pharmacist in an authorised place;
- is not advertised;
- is manufactured and assembled to standards of adequate quality to ensure that it meets the prescriber's specification, and documents are kept that can verify this;
- is manufactured, assembled or imported by holders of all required licenses awarded by the licensing authority (namely 'manufacturer's' and 'wholesale dealer's' licenses granted by the MHRA).

3.5. THE MISUSE OF DRUGS DESIGNATION ORDER 2015

Part 1 of the Misuse of Drugs Designation Order (the '2015 Order' or 'MDDO 2015') lists controlled drugs which are thought to have no legitimate medicinal use beyond use in research (i.e. drugs to which Section 7 (4) of the MDA 1971 applies). Drugs designated by Part 1 of the 2015 Order are available only under a Home Office license for "research or other special purpose". Part 2 lists drugs which are exempt from designation. The 2018 amendment (SI2018/1055) moved cannabis-based products for medicinal use from Part 1 to Part 2 of the 2015 Order, thus removing the restriction on their use to holders of a Home Office license. Non-medicinal forms of cannabis-based product remain in Part 1.

ANNEX B
TERMINOLOGY AND GROUPING OF CANNABIS-BASED PRODUCTS IN THIS REPORT

On the basis of the regulations described in Annex A, we have identified 17 categories of cannabis-based products, distinct from one another in terms of form, quality, potential harms and therapeutic value, intended use, and/or regulatory control. Categories 1 – 10 are considered controlled drugs under the MDA 1971 and MDRegs 2001 and are summarised in Table 21. Categories 11 – 17 are exempt from control under the MDA 1971 and MDRegs 2001 and are summarised in Table 22.

It is worth remembering that when we talk about 'illegal drugs,' we are really talking about illegal actions. A drug can be neither legal nor illegal, criminalised nor decriminalised, because drugs don't commit crimes. Human actions are legal or illegal, and it is only humans and their actions that can be criminalised or decriminalised.[389] This may seem obvious – courts do not sentence drugs to prison terms (though drugs find their way into prisons nonetheless) – but it is a point that will be important when we discuss the different categories of cannabis product, since they are defined according to both form and use. For instance, there is no law criminalising the mere consumption of any form of cannabis, no matter how it was produced or acquired.[390]In that very particular sense, all forms of cannabis and cannabis-based product are equal in the eyes of the law. However, there is a law criminalising an occupier or a manager of premises for knowingly permitting or suffering the consumption of cannabis on those premises,[391] just as there is a law criminalising the drug's possession.[392] Hence, when we talk about the legal classification of any cannabis-based item, we may describe it both in terms of its form (e.g. quality standards, composition) and in its relation to human behaviour (e.g. who is using it, for what purposes, under what conditions).

This is a report on 'medicinal cannabis' in the UK. It is not possible to accurately describe the current situation on medicinal cannabis without also discussing a variety of cannabis-based products that are not 'medicinal products' as defined by the HMRegs 2012 but are used 'with medicinal intent' by large numbers of people in the UK, sometimes lawfully (e.g. CBD oils), sometimes unlawfully (e.g. black market products). Defining this variety of distinct products is important for a number of reasons.

Firstly, it is the popularity of 'non-medicinal' cannabis products, used unlawfully but 'with medicinal intent,' that has driven the 'legalisation' of 'medicinal cannabis' in the UK and globally (the terms 'legalisation,' 'decriminalisation' and 'medicinal cannabis' mean different things to different people and don't mean much without reference to specific policies, e.g. precisely what behaviours, under what conditions, are criminal offences, and which are not?).

Secondly, and conversely, restrictions on the lawful access of cannabis-based medicinal products may have driven the expansion of unlawful access to non-medicinal products. Policy changes that affect one route of access will indirectly affect other routes, and many people flow between routes of access. While there is demand for products, licit and illicit markets will compete.

Thirdly, 'legalisation' policies, in their various forms, have been opposed or critiqued for fear of the potential harms to the individual and to society that are known or perceived to be associated with the misuse of 'non-medicinal' cannabis products. Policies that are perceived to be liberalisations of drug law cause concern for some that they will be exploited or shortly followed by more sweeping liberalisations of control.

Finally, generic terms such as 'medicinal cannabis' or 'cannabis-based medicines' are regularly used by policy commentators with little clarity, obscuring important differences between subcategories. The authors have attempted to be as accurate as possible in the writing of this paper, using generic terms only where we refer to multiple categories of product, and using specific terms in all other instances.

Table 17. Phytocannabinoids controlled under the 1971 Act

	Name	Common abbreviations	Listing in MDA/MDR
1	Δ^9-tetrahydrocannabivarin	THCV	Generic definition
2	Δ^9-tetrahydrocannabiorcol	THC-C1	Generic definition
3	Δ^9-tetrahydrocannabinol-C4	THC-C4	Generic definition
4	trans-Δ^9-tetrahydrocannabinol	THC-C5 (THC)	Generic definition
5	cis-Δ^9-tetrahydrocannabinol	cis-THC-C5 (cis-THC)	Generic definition
6	Δ^8-tetrahydrocannabinol	Δ^8-THC	Generic definition
7	Cannabiorcol	CBN-C1	Generic definition
8	Cannabinol-C2	CBN-C2	Generic definition
9	Cannabivarin	CBN-C3 (CBV)	Generic definition
10	Cannabinol-C4	CBN-C4	Generic definition
11	Cannabinol	CBN-C5 (CBN)	Explicitly listed
12	Cannabinol methyl ether	CBNM-C5 (CBNM)	Explicitly listed

4.1. CATEGORY 1 ITEMS: CANNABIS & CANNABIS RESIN (SCHEDULE 1)

Any items containing or being raw cannabis or cannabis resin are Class B drugs under the MDA 1971 and Schedule 1 drugs under the MDRegs 2001, regardless of THC content, unless the definition of another Category applies (e.g. Categories 4, 5, 6 or 16). The cultivation and production, supply, import, export and possession of any plant of the genus Cannabis, or of the resin of such plants, or the separated flowers and leaves, is unlawful except under a Home Office license or other authority issued by the Secretary of State or subject to a statutory defence. This includes 'hemp' or 'CBD' flowers – which are presently being sold by a variety of online and commercial outlets in the UK under the incorrect assumption that all products from low-THC cannabis strains can be imported, possessed or supplied without a Schedule 1 licence. Only uncontrolled products from low-THC strains can be supplied without a licence (e.g. Categories 11, 12, 16, 17).

Cannabis plants may only be cultivated and possessed lawfully under the terms of Home Office licence, of which there are two separate types distinguished by the THC content of the plants.[393] Plants with a THC content not exceeding 0.2% may be cultivated for commercial use under a low-THC license, but the terms of this license do not grant the holder to use any parts of the plant controlled under the MDA 1971, namely the leaves and the flowers. Licenses will state a defined commercial end use for the product (e.g. the production of fibre for industrial use, or the production of seeds for oil) and will only be issued by the Home Office for the cultivation of approved seed types. The cost of a low-THC licence is £580 for a new application, or £326 for a renewal. The cost of a compliance visit, if required, is £1371. The controlled parts of the plant remain subject to Schedule 1 restrictions, and their unauthorised use subject to Class B criminal penalties, unless the definition of another category applies (e.g. Category 4, 5 or 6 items). Accordingly, they must be retted at the licensed site or otherwise disposed of lawfully.[394]

Plants with a THC content exceeding 0.2% can only be lawfully cultivated or possessed under a high-THC Home Office licence, and products from the plant can only be lawfully stored or administered for scientific and medical purposes under a Schedule 1 Home Office licence. Regardless of THC content, it is only lawful for growers to harvest and use the controlled parts of the cannabis plant under the terms of a high-THC licence. The cost of a high-THC licence is £4700.[395]

4.2. CATEGORY 2 ITEMS: CONTROLLED PHYTOCANNABINOIDS (SCHEDULE 1)

A 2016 report from the ACMD reviewed the legal controls on 97 phytocannabinoids and identified 12 compounds covered by the generic definition as provided in the MDA 1971 and the MDRegs 2001 (*see Annex A: §3.1 - 3.2*).[396] These controlled compounds, which are listed in Table 17, are

referred to elsewhere in this report as CBN-type compounds (including THC-type compounds). Products with trace amounts of Category 2 items may be considered exempt from scheduling regulations if certain conditions are met (*see Annex A: §3.2*).

Versions 1 and 2 of the Home Office's *Drug Licensing Factsheet on Cannabis, CBD and other cannabinoids*, stated that CBD-V (cannabidivarin) is a controlled drug. CBD-V is not a CBN-type compound and was specifically named in the ACMD review as a non-controlled cannabinoid. Version 3 and subsequent versions of this Factsheet have been corrected to state that THC-V, rather than CBD-V, is controlled.[397] [398]

4.3. CATEGORY 3 ITEMS: SYNTHETIC CANNABINOIDS (SCHEDULE 1)

Synthetic cannabinoids (also known as Synthetic Cannabinoid Receptor Agonists (SCRA)) are a diverse group of compounds that bind to cannabinoid receptors in humans and produce psychoactive effects similar to those produced by plant-derived cannabis products.[399] However, SCRA are commonly full agonists at cannabinoid receptors, bind with greater affinity than THC, and may be up to 100-800 times more potent than cannabis.[400] Resultingly, the effects of SCRA typically have a quicker onset, greater intensity and more severe health risks than cannabis.[401] [402]

More than 200 SCRA compounds are now known, with an estimated 150-160 available to UK consumers in 2016, and they represent the largest group of novel psychoactive substances (NPS).[403] [404] Amendments to the MDA 1971 and MDRegs 2001 were introduced in 2009, 2013 and 2016 to control SCRA as Class B, Schedule 1 drugs. Each amendment widened the definition of controlled SCRA, as new compounds entered the market that were designed to evade existing legal controls. Compounds controlled by the 2009, 2013 and 2016 amendments are known as first, second and third generation synthetic cannabinoids respectively.[405] These compounds were not affected by the rescheduling of cannabis-based products for medicinal use in 2018.

4.4. CATEGORY 4 ITEMS: U-CBPM 'SPECIALS MEDICINES' (SCHEDULE 2)

The term 'unlicensed medicine' can describe either: (1) a medicine that is licensed for use in the UK but used outside the terms of that license ("off-label"); or (2) a medicine which has no license for use in the UK but which may be prescribed to meet an individual patient's special clinical need (unlicensed "specials" medicines – as applies to this Category).[406]

For the legal definition of a specials medicine, see Annex A: §3.4. For the legal definition of a CBPM, see Annex A: § 3.1. Access to Category 4 items is described in Chapter 1: §1.2.

The 2018 rescheduling amendment defined CBPM, moved them from Schedule 1 to Schedule 2, and provided the conditions under which they could be ordered and supplied (*see Annex A: §3.2*). The order and supply of Category 4 items through the specials route can only be initiated in accordance with a prescription or direction from a physician on the GMC's Specialist Register who has clinical competency in the condition and patient group being treated.

All 'specials' medicines and their ingredients should be produced to GMP standards and distributed to GDP standards (though in practice, this is not always possible).[407] Category 4 cannabis-based specials medicines are finished products for medicinal use containing cannabis, cannabis resin or controlled (CBN-type) cannabinoids. Category 4 items do not have market authorisation, are variable in composition and quality, and typically do not have robust clinical evidence on safety or efficacy in humans.

Category 4 items may either be manufactured in the UK from Category 5 items (with or without Category 13 items) or imported from overseas. For more details, see Chapter 1: §1.2.

Examples of imported Category 4 CBPM specials include those manufactured by Bedrocan (a range of standardised cannabis products for medicinal use with different ratios of THC:CBD, available as dried floral cannabis, 'flos,' or in granular form) and by Tilray (a range of standardised cannabis oil extracts with different ratios of THC:CBD).

Table 18. Examples of U-CBPM products available for prescription as specials medicines in the UK

CBPM Formulation	Supplier	Country
Bedrocan Flos, 22% THC <1% CBD	Bedrocan	Netherlands
Bedrobinol Flos, 13.5% THC <1% CBD		
Bediol Flos, 6.3% THC 8% CBD		
Bedica Flos, 14% THC <1% CBD		
Bedrolite Flos, <1% THC 9% CBD		
Oil, 10% THC	Tilray	Canada
Oil, 25% THC		
Oil, 10% THC 10% CBD		
Oil, 25% THC 25% CBD		
Cannabis Flower, 22% THC		
Cannabis Flower, 10% THC 10% CBD		
Bedrocan Oil, 2% THC	Transvaal Apotheek	Netherlands
Bediol Oil, 1.3% THC 2% CBD		
Bedrocan / Bedrolite Oil 10% THC 5% CBD		

4.5. CATEGORY 5 ITEMS: U-CBPM 'API' (SCHEDULE 2)

Active Pharmaceutical Ingredients (API) are substances or preparations used as an ingredient of, or in the production of an ingredient of, a medicinal product. Category 5 items are API that contain cannabis, cannabis resin or CBN-type cannabinoids and are used to produce Category 4 medicinal products. Category 5 items were rescheduled in November 2018 from Schedule 1 to Schedule 2 of the MDRegs 2001 by SI 2018/1055.

We have seen correspondence to a specials manufacturer from the Home Office in which it is advised that cannabis-based ingredients are only controlled under Schedule 2 when the conditions controlling the order and supply of CBPM are met, (e.g. those ingredients have been ordered in accordance with the direction of a specialist physician; *see Annex A: § 3.2*). The definition of a CBPM in the 2001 Regulations is not dependent on the existence of a prescription from a specialist physician, but the correspondence from the Home Office suggests that API is being treated as if controlled under Schedule 1.

Category 5 items are not finished products and cannot be prescribed to a patient, but may be used in the preparation of a Category 4 medicinal product by any pharmacy or wholesaler who holds an MHRA Manufacturer's license.Manufacturing sites of API and finished products must be in receipt of Good Manufacturing Practice (GMP) certification. Importers and distributors must be in receipt of Good Distribution Practice (GDP) certification. MHRA guidance concedes that it may not always be possible to guarantee GMP quality, but that material from uncertified sources should be used only in exceptional circumstances and under conditions of strict record keeping.[408]

Finished Drug Product manufacturers are required to carry out complete reviews of supply chain traceability of active substances, from the production of the Registered Starting Materials onwards through manufacture and distribution. These reviews must include checks that all parties in the supply chain have the correct registration for all activities they perform.[409] A list of companies who are registered in EEA countries for operations involving a number of cannabis-based APIs, and listed on the EudraGMDP database, is provided in Table 19. This list is not an exhaustive description of companies with high quality cannabis-based

Table 19. Cannabis-based API registrations on the EudraGMDP database

API name	Registration holder	Operation	City	Country
Cannabis	Tilray Portugal	Manufacturing	Cantanhede	Portugal
	CannaXan	Distribution	Bayern	Germany
	Apurano Pharmaceuticals	Manufacturing	Bayern	Germany
Cannabis flower	Lenis Pharmaceutics	Distribution	Ljubljana	Slovenia
	Salus Wholesalers	Distribution	Ljubljana	Slovenia
	Farmakem Services	Distribution	Maribor	Slovenia
		Distribution	Ljubljana	Slovenia
Hemp	Kemofarmacija	Distribution	Ljubljana	Slovenia
Dronabinol (THC)	Sigmapharm Drugs	Distribution	Wien	Austria
	Kemofarmacija Wholesalers	Distribution	Ljubljana	Slovenia
	Mikro+Polo	Distribution	Maribor	Slovenia
	Salus Wholesalers	Distribution	Ljubljana	Slovenia
	Medis Pharmaceuticals	Distribution	Ljubljana	Slovenia

API products – some manufacturers may have product ranges that satisfy EU-GMP standards for which the company has not received API registration. API registration is preferable, but not mandatory.

4.6. CATEGORY 6 ITEMS: U-CBPM 'IMP' (SCHEDULE 2)

For the legal definition of an investigational medicinal product (IMP), see Chapter 1: The Medicines for Human Use (Clinical Trials) Regulations 2004. Access to Category 6 items is described in Chapter 2: Route 3: Unlicensed cannabis-based investigational medicinal products.

Investigational medical products (IMP) do not have marketing authorisation but are registered for use in clinical trials in humans. They typically have a limited evidence base developed during preclinical studies but do not yet have robust evidence for their safety, quality or efficacy in humans. The 2018 rescheduling of CBPM provides a route of access to cannabis-based IMPs as part of a clinical trial, under Schedule 2 controls, and states that cannabis-based IMPs cannot also be supplied as a special medicinal product (Category 4).

4.7. CATEGORY 7 ITEMS: SYNTHETIC L-CBM (SCHEDULE 2)

Medicinal products require a marketing authorisation (or 'product license') from the MHRA or the European Medicines Agency (EMA) before they can be marketed in the UK.[410] This license determines the medical conditions and patient groups for which the product can be prescribed, and for which medical claims may be made. New medicinal products must meet rigorous standards of evidence on safety, quality and efficacy to achieve a product licence, and consequently it is only licensed products on which medical claims can lawfully be made.

Applications for a medicinal product license must provide a risk management plan including existing safety data, missing safety data (e.g. patient populations not included in the clinical trials to date), additional pharmacovigilance research required to inform potential product harms after marketing authorisation, and a risk minimisation strategy to limit potential harms.[411]

As of the time of writing, there is one licensed synthetic cannabinoid-based medicine listed

in Schedule 2 of the MDRegs 2001. Nabilone, a capsule containing a synthetic cannabinoid that mimics the activity of THC, was approved for marketing by the Medicines and Healthcare products Regulatory Agency (MHRA) in August 2007 and rescheduled to Schedule 2 in 2009.[412] There is a robust clinical evidence base on quality, safety, and efficacy in humans.

Nabilone is listed as a prescription-only medicine (POM). Any doctor can prescribe Nabilone for its licensed indication, chemotherapy-induced nausea and vomiting, though the British National Formulary states that prescribing should preferably occur in a hospital setting under close medical supervision.[413] It may also be prescribed off-label in clinical situations where the prescriber judges it to be in the best interest of the patient. Access to Nabilone is described in Chapter 1: §1.1.

4.8. CATEGORY 8 ITEMS: SYNTHETIC CBM WITHOUT MARKET AUTHORISATION IN THE UK (SCHEDULE 2)

Dronabinol is licensed as a medicine in the US, Canada, Germany, Australia and New Zealand, but it does not have market authorisation from the MHRA in the UK. In this context, 'Dronabinol' refers to a synthetic THC formulation, although the term is also used sometimes to refer to naturally-derived THC (e.g. the British National Formulary lists the ingredients of Sativex as 'dronabinol' and 'cannabidiol'). There is a robust clinical evidence base on quality, safety, and efficacy in humans. It was not affected by SI 2018/1055, since it was listed in its synthetic form under Schedule 2 when the MDRegs 2001 came into effect. As with other U-CBPM, it can theoretically be prescribed as a specials medicine (*see Category 4 for a summary of prescribing restrictions on specials medicines, and Chapter 1: §1.2.2.2. 'Specials' medicines are not licensed*). Unlike other U-CBPM, there is no requirement for prescriptions of dronabinol through the specials route to be initiated by a doctor on the GMC's specialist register, since it is not covered by SI 2018/1055.

4.9. CATEGORY 9 ITEMS: PLANT-DERIVED L-CBM (SCHEDULE 4)

There is presently one licensed cannabis-based medicine listed in Schedule 4 of the MDRegs 2001. Sativex (also known as Nabiximols), an oromucosal spray containing THC and CBD in a 1:1 ratio, was approved for marketing in June 2016 and rescheduled to Schedule 4 of the 2001 Regulations in 2013.[414] It is licensed for the treatment of spasticity in multiple sclerosis. There is a robust clinical evidence base on quality, safety, and efficacy in humans. See Category 7 for a summary of market authorisation ('licensing') of medicinal products.

Sativex is listed as a prescription-only medicine (POM). NICE state that treatment should be initiated and supervised by a physician with specialist expertise in treating multiple sclerosis, in line with its marketing authorisation.[415] [416] Access to Sativex is described in Chapter 1: §1.1.

4.10. CATEGORY 10 ITEMS: PLANT-DERIVED L-CBM (SCHEDULE UNCLEAR)

There is one licensed cannabis-based medicine containing no significant level of controlled constituents. Epidyolex, an oral solution containing 100mg/ml CBD in sesame oil and alcohol, achieved Market Authorisation from the European Medicines Agency (EMA) in September 2019.[417] It is licensed for the treatment of seizures in Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS). There is a robust clinical evidence base on quality, safety, and efficacy in humans. See Category 7 for a summary of market authorisation ('licensing') of medicinal products.

CBD in its pure form is not a controlled cannabinoid under the MDA 1971 or the MDRegs 2001, although it might be controlled under the Psychoactive Substances Act 2016. Epidyolex contains trace amounts of THC, but less than 1mg per container, and it is consequently considered an exempt product (*see Annex A: §3.2*).[418] The current scheduling status of Epidyolex is under review; an ACMD dossier has recommended that it be moved to Schedule 5. Access to Epidyolex is described in Chapter 1: §1.1.

4.11. CATEGORY 11 ITEMS: PURE UNCONTROLLED CANNABIS-DERIVED COMPOUNDS (NO SCHEDULE)

Cannabis is known to contain over 540 phytochemicals (plant-based compounds, including cannabinoids, flavonoids and terpenes), many of which are believed to contribute to the medicinal value of the plant, and only a few of which are controlled under the MDA 1971 (*see Category 2*).[419] [420] However, some might be controlled under the Psychoactive Substances Act 2016. Category 11 items are pure, non-controlled, cannabis-derived phytochemicals and are the basis of various subsequent categories. If Category 11 items are prepared at a GMP-certified site as APIs, they are described as Category 13 items. Products containing Category 11 items which are sold commercially to the public are described as Category 12 items.

As many as 144 cannabinoids have been identified in Cannabis samples, of which only 12 are controlled drugs (*see Annex A: §3.1*). Non-controlled cannabinoid classes include: Cannabigerol (CBG)-type compounds; Cannabichromene (CBC)-type compounds; Cannabidiol (CBD)-type compounds; Cannabinodiol (CBDL)- type compounds; Cannabifuran (CBF) type compounds; Cannabicyclol (CBL)-type compounds; Cannabielsoin (CBE)-type compounds; the acid precursors of these classes; and the acid precursors of the controlled compounds THC and CBN, namely, tetrahydrocannabinolic acid (THCA) and cannabinolic acid (CBNA).[421] THCA and CBNA are not controlled drugs in their pure form, but since both readily degrade to form controlled cannabinoids, any products containing these compounds would be presumed by the Home Office to be controlled drugs.[422]

There is limited evidence that some uncontrolled phytocannabinoids affect physiological functions and may have potential medicinal value, summarised by Baron (2018).[423] Cannabinoids and cannabinoid acids identified in that review as having potential medicinal value include CBG, CBC, CBD, CBDV, CBDA and THCA. Some of the data on the medicinal value of CBD derives from clinical trials in Epidyolex, a CBD-based medicine. The results of these trials should not be extrapolated to pure CBD, or other CBD-containing products, without caution.

At least 200 terpenes and 20 flavonoids have been identified in cannabis samples.[424] [425] Neither family of compound is controlled under the MDA 1971 or the MDRegs 2001. For many of these substances, there is some limited preclinical evidence that they may produce physiological effects with potential medicinal value.

Cannabis-based terpenes identified as having potential medicinal value include β-caryophyllene, myrcene, α-pinene, humulene, linalool, limonene, terpinolene, terpineol, ocimene, valencene, geraniol, α-bisabolol, nerolidol, caryophyllene oxide, phytol, borneol, δ-3-carene, terpinene, camphene, sabinene, cineole (eucalyptol), phellandrene, guaiol, isoborneol, cedrene, geranyl acetate, fenchol, camphor, menthol, isopulegol, cymene, citral, and citronellol. Flavonoids found in cannabis that have been shown to have potentially medicinal effects include apigenin, cannflavin A and cannflavin B.[426]

4.12. CATEGORY 12 ITEMS: NON-MEDICINAL, NON-CONTROLLED CBP (NO SCHEDULE)

Category 11 phytocannabinoid items that are prepared and sold for human consumption, most commonly on the so-called 'wellness market,' are classified in this report as Category 12 items. The most popular products in this category are those containing (or claiming to contain) CBD. These products are not prepared for medicinal use and cannot be advertised as having medicinal value. Nonetheless, they are used with medicinal intent by an increasingly large number of people in the UK.

CBD products, now widely available for purchase online and on the high street, are generally assumed by vendors and consumers to be lawful to supply and possess. However, it is difficult to isolate pure CBD without trace contamination of controlled cannabinoids and any product with more than 1 milligram of a controlled drug per container cannot be sold or possessed lawfully without a licence.[427] Any product that exceeds this threshold would be considered a Class B, Schedule 1 substance. Numerous laboratory analyses of products allegedly containing pure CBD have identified concentrations of cannabinoids that differ from the amounts advertised – in many cases involving unlawfully high levels of THC.[428]

[429] [430] [431] [432] High-CBD cannabis flowers are also being sold by vendors in the UK without a licence. However, all cannabis flowers are considered Class B, Schedule 1 controlled drugs, regardless of cannabinoid content, unless produced and supplied as a Category 4 medicinal product or Category 5 API. The unlicensed supply of Class B drugs carries a maximum criminal penalty of 14 years imprisonment (*see Annex A: §3.1*).

As with all other Categories defined in this chapter as 'uncontrolled,' the production, supply and use of Category 12 items will still be subject to certain legal and regulatory controls depending on the end use of the product. Notably, the European Commission added CBD to its catalogue of 'novel foods' in 2019. This designation denotes products intended for human consumption that have no recognised history of use as a food in the EU prior to May 1997. Novel foods must have a safety assessment and authorisation before they can be sold in the EU.[433] The UK Food Standards Agency have accepted the recommendation of the EU in regard to food supplements containing CBD and have stated that they are "committed to finding a proportionate way forward by working with local authorities, businesses and consumers to clarify how to achieve compliance in the marketplace in a proportionate manner."[434] For an overview, see Chapter 1: §1.4. Novel foods status will not affect CBD products that are not produced for human consumption, including cosmetics.

4.13. CATEGORY 13 ITEMS: NON-CONTROLLED API (NO SCHEDULE)

APIs are substances or preparations used as an ingredient of, or in the production of an ingredient of, a medicinal product. Category 13 items are APIs that are constituted from wholly pure Category 11 cannabis-based compounds and contain: (1) no trace of controlled substances, or (2) traces so low as to consider the product exempt from control (*see Annex A: §3.1*). Category 13 API may be used in the production of Category 14 specials medicines or, in combination with Category 5 API, in the production of Category 4 specials medicines.

Table 20. CBD API registrations on the EudraGMDP database

API name	Registration holder	Operation	City	Country
Cannabidiol (CBD)	BSPG Laboratories	Manufacturing, Distribution	Sandwich	UK
	Sterling Pharma Solutions	Manufacturing	Dudley	
	Active Pharma Supplies	Distribution	Leyland	
	GW Pharma	Manufacturing	Sittingbourne	
	Aesica Pharmaceuticals	Manufacturing, Distribution	Cramlington	
	Chiracon	Manufacturing	Luckenwalde	Germany
	Alpha-Cannabis Pharma	Distribution	Bad Nenndorf	
	Arevipharma	Manufacturing	Radebeul	
	Fagron Hrvatska	Distribution	Donja Zelina	Croatia
	Farmabios	Manufacturing	Gropello Cairoli	Italy
	Farmalabor	Manufacturing	Canosa di Puglia	
	F.L. Group	Distribution	Vado Ligure	
	Galeno	Manufacturing	Carmignano	

The EudraGMDP database lists 13 companies registered in the EEA to manufacture or distribute cannabidiol (CBD) as an API. No API registrations were found for CBDV, CBG, CBC, CBDL, CBF, CBL, CBE, nor any of the terpenes or flavonoids identified in Category 11. However, several companies are known to be developing a range of Category 13 APIs, and it is expected that registrations for more non-controlled cannabinoids will be approved in the coming year. Other manufacturers may have, or be developing, Category 13 product ranges that satisfy EU-GMP standards for which the company has not received API registration.

4.14. CATEGORY 14 ITEMS: NON-CONTROLLED CANNABIS-BASED 'SPECIALS' (NO SCHEDULE)

For the legal definition of a specials medicine, see Annex A: §3.4. Access to Category 14 items is described in Chapter 1: §1.2. For a review of prescribing specials medicines to meet a patient's needs, see Chapter 1: §1.2.2.2. *'Specials' medicines are not licensed.*

Category 14 items are medicinal products, ordered and supplied through the specials route, that contain only non-controlled cannabis-based constituents (Category 13 APIs). Since Category 13 and 14 items are exempt from control under the MDRegs 2001, the production, supply and administration of Category 14 specials would not be bound by the statutory limitations provided by SI 2018/1055. In theory, these items could be ordered by any authorised prescriber as per the ordinary regulations on specials medicines (i.e. a doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber). As specials medicines, Category 14 items would not have market authorisation, nor would they be expected to have robust clinical evidence on safety or efficacy in humans.

4.15. CATEGORY 15 ITEMS: NON-CONTROLLED IMP (NO SCHEDULE)

For the legal definition of an investigational medicinal product (IMP), see Annex A:§3.3.

Investigational medical products (IMP) do not have marketing authorisation but are registered for use in clinical trials in humans. They typically have a limited evidence base developed during preclinical studies but do not yet have robust evidence for their safety, quality or efficacy in humans. Category 15 items are produced exclusively from Category 13 APIs and are assumed to contain: (1) no trace of controlled substances, or (2) traces so low as to consider the product exempt from control (*see Annex A: §3.2*).

4.16. CATEGORY 16 ITEMS: SEPARATED CANNABIS SEEDS, STALK AND FIBRE (NO SCHEDULE)

Hemp plants are varieties of cannabis grown from seeds that are registered in the EU's 'Common Catalogue of Varieties of Agricultural Plant Species,' in which the tetrahydrocannabinol (THC) content do not exceed 0.2 % (w/w). Hemp may be lawfully grown from approved seed types under a Home Office low-THC cultivation license. Once the non-controlled parts of the plant (i.e. the seeds, stalk and fibre) have been separated, they cease to be considered controlled substances under the MDA 1971 or MDRegs 2001. These non-controlled hemp and hemp-derived products may be supplied and possessed without a Home Office license.

The Hemp (Third Country Imports) Regulations 2002 require that hemp from 'third countries' be imported under license and, in the case of hemp seeds other than for sowing, under authorisation. After the UK's exit from the EU, licenses may be required to import seeds from Europe.

4.17. CATEGORY 17 ITEMS: CANNABIS-BASED FOOD AND FIBRE PRODUCTS (NO SCHEDULE)

Hemp-based materials are used in the production of a wide range of commercial product, including textiles and paper derived from plant fibre; and edible hemp oil, flour and animal feed derived from the processed seeds. These products are not considered to be controlled under the MDA 1971 or MDRegs 2001, but are subject to food, cosmetic and agricultural regulations according to their end use.

The EFSA novel foods catalogue entry for Cannabis sativa states, "some products derived from the Cannabis sativa plant or plant parts such as seeds, seed oil, hemp seed flour, [and] defatted hemp seed, have a history of consumption in the EU and therefore, are not novel."[435] However, the entry for cannabinoids states that "any products to which [cannabinoid extracts] are added as an ingredient (such as hemp seed oil)" would be considered novel foods.[436]

The stalk and seeds of cannabis plants contain relatively few resinous glands and, accordingly, low levels of cannabinoids. Nonetheless, laboratory analyses of food oils produced from the pressed seeds of low-THC hemp strains have found detectable amounts of controlled cannabinoids.[437] [438] These findings make the legal status of hemp seed oils rather ambiguous, particularly as large volumes are increasingly likely to breach the 1 mg threshold laid out in the third limb of the definition of exempt products (*see Annex A: §3.2*). There have been no known seizures of legitimate hemp food or fibre products in the UK, nor criminal investigations into products found to exceed the exempt limit.

Table 21. Cannabis products controlled under MDA 1971 and subsequent regulations

			Legislative Classification					Regulatory Controls	
#	Category Description	Example	MDA 1971 (as amended), Class	MDRegs 2001 (as amended), Schedule	Rescheduled by SI 2018/1055?	MHRA Market Authorisation	May be prescribed (outside of research)	Circumstances under which authorized actions may occur (MDRegs, 2001)	Criminal penalties for unauthorized actions (MDA, 1971)
1	Cannabis or cannabis resin (unless exempt and in Categories 4, 5, 6, or 16)	Cannabis items not authorized for medical use	B	1	✗	✗	✗	May be produced with a Home Office high-THC cultivation license; see also controls on Categories 2-3.	Unauthorized actions (i.e. production, importation, exportation, supply, or possession without authorisation, or provision of premises for unauthorized actions) may incur penalties including up to 14 years imprisonment.
2	Controlled cannabinoids and -containing products (unless exempt and in Categories 4, 5, or 6)	CBN-type compounds, including THC-type compounds	B	1	✗	✗	✗	May be used for research purposes with a Home Office Schedule 1 license.	
3	Synthetic cannabinoids (unless exempt and in Categories 7 or 8)	JWH-018, AM-2201, UR-144, XLR-11, PB-22, 5F-PB-22, APICA	B	1	✗	✗	✗	May be used for research purposes with a Home Office Schedule 1 license.	
4	CBPM 'specials' containing Category 1 or 2 items	Product ranges by Bedrocan, Tilray, Aurora, etc.	B	2	✓	✗	✓	May be produced, procured and prescribed as 'specials medicines,' subject to Schedule 2 & specials regulations with statutory restrictions.	
5	API containing Category 1 or 2 items	GxP-grade raw cannabis flowers or extracts for use as medicinal ingredients	B	2	✓	✗	✗	May be produced, procured and used in the manufacture of a Category 4 item, subject to Schedule 1 or 2 regulations with statutory restrictions.	
6	IMP containing Category 1 or 2 item	GxP-grade medicinal products administered in an authorized clinical trial	B	2	✓	✗	✗	May be produced, procured and administered as part of a clinical trial, subject to Schedule 2 regulations with statutory restrictions. Must have an IMP dossier & Clinical Trials Authorisation (CTA).	
7	Synthetic L-CBM with market authorisation	Nabilone (THC-type)	B	2	✗	✓	✓	May be procured and prescribed, subject to terms of licensing, Schedule 2 and CD regulations.	
8	Synthetic CBM without market authorisation in the UK	Dronabinol (THC)	B	2	✗	✗	✓	May be procured and prescribed as a 'specials medicine,' subject to Schedule 2 and Specials regulations.	
9	Plant-derived L-CBM with market authorisation (Schedule 4)	Sativex (CBD:THC)	B	4	✗	✓	✓	May be procured and prescribed, subject to terms of licensing, & Schedule 4 regulations.	
10	Plant-derived L-CBM with market authorisation (Schedule 5?)	Epidyolex (CBD with trace amounts of THC)	B	?	✓	✓	✓	May be procured and prescribed, subject to terms of licensing. Current scheduling status of Epidyolex is under review.	

Table 22. Cannabis products not controlled under MDA 1971 and subsequent regulations

			Legislative Classification					Regulatory Controls	
#	Category Description	Example	MDA 1971 (as amended), Class	MDRegs 2001 (as amended), Schedule	Rescheduled by SI 2018/1055?	MHRA Market Authorisation	May be prescribed (outside of research)	Circumstances under which authorized actions may occur (MDRegs, 2001)	Criminal penalties for unauthorized actions (MDA, 1971)
11	Pure non-controlled cannabinoids	CBG-, CBC-, CBD-, CBF-, CBDL-, CBL-, CBE- and CBT-type compounds	N/A	N/A	✗	✗	✗	May be prepared, supplied and possessed without a license. No medical claims can be made.	Unauthorized actions (i.e. production, importation, exportation, supply, or possession without authorisation, or provision of premises for unauthorized actions) may incur penalties including up to 14 years imprisonment.
12	Non-medical, non-controlled products containing Category 11 items	CBD-containing products on the 'wellness market'	N/A	N/A	✗	✗	✗	May be prepared, supplied and possessed without a license. No medical claims can be made. Must meet all three limbs of an exempt product under MDRegs 2001. CBD be subject to Novel Foods Regulations.	
13	Non-controlled API containing Category 11 items	Isolates of Category 11 items for use as medicinal ingredients	N/A	N/A	✗	✗	✗	May be produced, procured and used in the manufacture of a Category 14 item, subject to Specials regulations. Must meet all three limbs of an exempt product under MDRegs 2001.	
14	Non-controlled 'specials' medicines containing Category 11 items.	GxP-grade product ranges manufactured from Category 13 items	N/A	N/A	✗	✗	✓	May be prescribed as 'specials' medicines, subject to Specials regulations. Must meet all three limbs of an exempt product under MDRegs 2001.	
15	Non-controlled IMP containing Category 11 items.	GWP42006 (CBDV) administered in a clinical trial	N/A	N/A	✗	✗	✗	May be produced, procured and administered as part of a clinical trial. Must have Clinical Trials Authorisation (CTA). Must meet all three limbs of an exempt product under MDRegs 2001.	
16	Non-controlled parts of the Cannabis plant after separation.	Hemp	N/A	N/A	✗	✗	✗	May be removed from plants cultivated or imported under a Home Office license. May be supplied and possessed within the UK without a license.	
17	Commercial products derived from Category 16 items.	Hemp seed oil	N/A	N/A	✗	✗	✗	May be prepared and supplied from Category 16 items, subject to food regulations. May be supplied and possessed without a license.	

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Conservative Drug Policy Reform Group
Suite 15.17, Citibase
15th Floor Millbank Tower
21-24 Millbank
London, SW1P 4QP

www.cdprg.co.uk