A CLINICIAN’S GUIDE TO CBD

UNDERSTANDING CANNABIDIOL - VERSION 2

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THE MEDICAL CANNABIS CLINICIANS SOCIETY

Medical Cannabis Clinicians Society
# Table of Contents

| 01 | Introduction |
| 02 | The Endocannabinoid System |
| 03 | What is CBD? |
| 07 | Key differences between Hemp, CBD and cannabis oils |
| 08 | Indicated uses of CBD |
| 09 | In what forms do patients consume CBD? |
| 11 | Dosing CBD |
| 12 | Discussing CBD with patients |
| 14 | Drug interactions |
| 16 | Side effects |
| 18 | Legalities of CBD products in the UK |
| 20 | What should consumers look for in CBD products? (COAs) |
| 23 | Checklist for CBD products |
| 24 | References |
Over the past few years, over the counter Cannabidiol (CBD) products have gained popularity in the UK and across the world. We have seen unprecedented growth in the quantity and range of CBD products available for purchase on the high street and from online retailers.

CBD appears to have caught the imagination of the general public, who are using it for a number of health conditions ranging from pain and anxiety to depression and sleep. According to the Centre for Medical Cannabis, surveys conducted in 2019 by Dynata and YouGov indicates that between 8-11% of UK adults respectively - approximately 4-6 million people - have tried CBD products.

Currently, doctors report receiving mixed messages as to whether these products are legal, safe and effective and clinicians are largely unfamiliar with what patients are using. Given this widespread use of CBD, it is crucial that doctors are confident in understanding the properties of CBD and how it may affect our patients - including therapeutic effects, dosing, side effects and potential drug interactions.

This guide provides an overview of CBD for clinicians, including its modes of action and therapeutic effects, pharmacodynamics and dosing. We also summarise the current legal status of CBD in the UK.

We hope that the information contained in this publication will help doctors understand CBD and help guide their patients to the safest and most effective and evidence-based products available.
The endocannabinoid system (ECS) is a complex cell-signalling system and is universal to all vertebrates.

The ECS consists of endocannabinoids, cannabinoid receptors, and enzymes that regulate biosynthesis and degradation of endocannabinoids.

The ECS has been implicated in a variety of disease states and important regulatory functions, including:

- Anxiety
- Appetite
- Autonomic functions
- Bladder function
- Cancer control
- Energy balance
- Female reproductive function
- GI function
- Homeostasis
- Inflammation
- Memory
- Metabolic functions
- Motor control
- Neurogenesis
- Neuroplasticity
- Neurotransmission
- Regulation of pain
- Sleep
- Social behaviour
- Stress response
- Thermoregulation

CB1 and CB2 are the two main cannabinoid receptors found within our bodies which we know most about so far, although there are likely others involved to a lesser degree.

They are both G-protein coupled receptors located on presynaptic membranes that detect molecules outside the cell and activate internal signal transduction pathways and cellular response.

- CB1 is primarily located in the central nervous system with some expression in peripheral tissues.
- CB2 receptors are found in the periphery on cells with immune function, in the gastrointestinal tract and at low densities in the central nervous system.

Anandamide and 2-Arachidonoylglycerol (2AG) are our two main endogenous endocannabinoids, which act as neurotransmitters/ligands binding to CB1 and CB2 receptors.

They are both synthesised on demand to maintain homeostasis.
The cannabis plant *Cannabis sativa* contains over 500 natural compounds including terpenes, flavonoids and 113 known phytocannabinoids.

Phytocannabinoids are lipophilic molecules, synthesised in the glandular trichomes of the unfertilised female cannabis flower and are able to modulate our endocannabinoid system due to molecular similarities to anandamide and 2AG.

The best-known and most widely studied of these phytocannabinoids are CBD and THC (Tetrahydrocannabinol).

CBD is a non-psychomimetic or non-psychotropic cannabinoid and is of great research interest due to its multi-modal properties in various medical conditions.

Tetrahydrocannabinol (THC) is responsible for the main psychotropic effect of cannabis.

Over the counter CBD which can be bought without a prescription is primarily extracted from the dried female flower tops of hemp or from the leaves and stems – a fast growing strain of *Cannabis sativa* that has been selectively bred over time for its industrial properties.

Hemp strains of cannabis contain substantially less THC and higher levels of CBD than other cannabis strains and the trace percentages of THC have almost zero chance of causing a psychomimetic effect.
WHAT IS CBD? Continued

CBD OIL VS HEMP SEED OIL

CBD is sometimes confused with hemp seed oil but there are distinct differences.

Hemp oil is extracted from cannabis seeds and has only trace amounts of CBD of the hemp plant, whereas CBD is produced in glandular trichomes of female flowers and to a lesser extent from the leaves and stems.

Hemp oil is similar to olive oils and vegetable oils and contains a rich source of nutrients including fatty acids, omega 3 and 6, vitamins and minerals.

Hemp oil is widely used as an addition to cosmetics, balms and skin creams and in its refined form has a number of useful industrial applications.

CANNABIS BASED MEDICAL PRODUCTS (MEDICAL CANNABIS)

Chemovars, also known as chemotypes, refer to the breakdown of a plant species according to chemical composition.

Cannabis chemovars have been selectively bred over centuries to produce active compounds such as THC, CBD and other lesser known minor cannabinoids and terpinoids in different but much smaller concentrations and proportions.

All Cannabis sativa chemovars produce active compounds, but each variety produces these compounds in different concentrations and proportions.

The major difference between over-the-counter CBD oils and cannabis based medical products is that the latter can contain varying concentrations of THC, above the 1mg amount allowed in OTC products.

In November 2018, cannabis-based products for medical use (CBMP) were moved from Schedule I to Schedule 2 classification of Misuse of Drug Regulations. The re-scheduling meant that CBMP could be prescribed medicinally by any doctor on the GMC specialist register for an unmet clinical need.

GPs can continue to prescribe CBMPs under shared care arrangements.

The Government has defined a CBMP in humans as a product which:

1. is or contains cannabis, cannabis resin, cannabinoil or a cannabinol derivative (not being dronabinol or its stereoisomers);
2. is produced for medicinal use in humans; and
3. 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 (1).

Home Office and MHRA approvals require the content and ratio of THC/CBD to be declared, a certificate of analysis, a valid GMP certificate from the site of manufacture, a justification for special clinical need and prescription by a doctor registered on the GMC Specialist register.

All CBMP are Schedule 2 controlled drugs and are subject to the full controlled drug requirements of any other Schedule 2 drug which includes strict rules around labelling, storage and prescriptions.

Continued...
A CBD oil is comprised of a CBD extract mixed with a carrier oil such as hemp seed oil, MCT oil or olive oil. Some CBD oil will benefit from the “entourage effect” which is the synergy of the various bioactive molecules working together to enhance effectiveness.

- Whole plant & Full-spectrum = Full entourage effect (CBMP only)
- Broad-spectrum = Broad entourage effect (Over-the-counter (OTC))
- Narrow-spectrum = Narrow entourage effect (OTC)
- No-spectrum (isolate) = No entourage effect (OTC)

**Whole-plant (crude) CBD oil** uses an unrefined CBD extract. It contains the key compounds from the cannabis flower such as cannabinoids, terpenes and flavonoids, plus undesirable compounds such as fats, lipids, waxes and chlorophyll. The undesirable compounds are considered contaminants in CBD extracts. The more undesirable compounds present in an extract, the lower the quality of the CBD oil. It fully benefits from the entourage effect and will contain controlled cannabinoids such as THC, CBN or THCV. If the combined total amount of the controlled cannabinoids is over 1mg per container, the product is classed as a Schedule 1 drug under the MDR 2001.

**Full-spectrum CBD oil** uses a refined CBD extract. The key compounds of cannabinoids and terpenes will be present along with some flavonoids. The undesirable compounds of fats, lipids, waxes and chlorophyll have been removed resulting in a very high-quality CBD oil. Full-Spectrum CBD oil does fully benefit from the entourage effect. By definition, it will contain controlled cannabinoids such as THC, CBN or THCV. If the combined total amount of controlled cannabinoids is over 1mg per container the product is classed as a Schedule 1 drug under the MDR 2001.

**Broad-spectrum CBD oil** uses a further refined CBD extract. The key compounds of cannabinoids and terpenes will be present with trace amounts of flavonoids. The undesirable compounds of fats, lipids, waxes and chlorophyll have been removed. Controlled cannabinoids such as THC, CBN and THCV have also been removed, classifying it as a legal, high quality CBD Oil. Broad-spectrum CBD oil benefits from the entourage effect, although not as much as Full-spectrum due to the loss of direct receptor binding cannabinoids such as THC, CBN or THCV. It does not contain controlled cannabinoids like THC, CBN or THCV. It is not classed as a Schedule 1 drug and may be sold as a food supplement.

**Narrow-spectrum CBD oil** uses an over refined CBD extract. The number of cannabinoids and terpenes present has been significantly reduced through over refinement. The undesirable compounds of fats, lipids, waxes and chlorophyll have been removed along with controlled cannabinoids such as THC, CBN and THCV. It does not fully benefit from the entourage effect. The over refinement results in a loss of minor cannabinoids and terpenes which reduces the entourage effect. It does not contain controlled cannabinoids like THC, CBN or THCV. It is not classed as a schedule 1 drug and may be sold as a food supplement.

**No-spectrum CBD oil** uses a CBD isolate extract. There is only CBD present, the isolated extract is usually 99% pure CBD. There are no additional cannabinoids, there are no terpenes or flavonoids. It does not benefit from the entourage effect and the effectiveness is biphasic; once hitting optimal dosage, effects begin to reverse or diminish even when dosages are increased. It just isolated CBD, it does not contain controlled cannabinoids like THC, CBN or THCV. It is not classed as a schedule 1 drug and may be sold as a food supplement. The advantage that CBD isolate has it that it is approved by WADA for professional athletes. WADA does not approve the use of any other cannabinoids in competition, whether controlled or not.
Licenced Cannabis Based Products

A drug company must have a product licence to advertise and sell a medicine.

Obtaining a licence for a medication is both timely and costly and involves running clinical trials for a specific illness or condition.

In the UK, the MHRA assess data from clinical trials and licences are only granted if strict safety and quality standards are met.

There are currently two licenced cannabis based medical products available in the UK - Sativex and Epidyolex.

Sativex is a schedule 4 medication licenced for spasticity in MS and is composed of a 1:1 ratio of THC to CBD.

Epidyolex is a 98% pure CBD preparation, schedule 5 drug and has been approved for the treatment of severe epilepsy in Dravet and Lennox- Gastaut syndromes.

Nabilone is a synthetic cannabinoid with antiemetic properties with a licence in the UK to treat nausea and vomiting caused by chemotherapy unresponsive to conventional antiemetics.

Is CBD safe?

An extensive report by the WHO found CBD to be generally well tolerated with a good safety profile with no evidence that CBD causes intoxication, psychotic symptoms or impairments of motor or psychomotor performance in humans. To date there is no evidence of recreational use, no effects indicative of any abuse or dependence potential of CBD or any public health issue (2).
# Key Differences Between Hemp, CBD and Cannabis Oils in the UK

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>Hemp Seed Oils</th>
<th>Hemp/CBD Oils</th>
<th>Cannabis Oils</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Part of Plant Extracted</strong></td>
<td>Seeds</td>
<td>Flowers and leaves of hemp plant</td>
<td>Flowers and leaves of cannabis plant</td>
</tr>
<tr>
<td><strong>Main Components</strong></td>
<td>Omega-6 and omega-3 fatty acids</td>
<td>Mostly CBD and B-caryophyllene with other smaller quantity phytocannabinoids and terpeneoids</td>
<td>Mostly THC with some CBD and other phytocannabinoids and terpeneoids</td>
</tr>
<tr>
<td><strong>THC Levels</strong></td>
<td>None</td>
<td>Less than 1 mg per container. Seeds used must produce less than 0.2% THC</td>
<td>Variable – can be up to 30% dry weight) No upper limit</td>
</tr>
<tr>
<td><strong>CBD Levels</strong></td>
<td>Little to none</td>
<td>Up to 20% dry weight</td>
<td>Variable - up to 20% dry weight</td>
</tr>
<tr>
<td><strong>Uses</strong></td>
<td>Nutritional supplements</td>
<td>General health and wellbeing supplement</td>
<td>Medical use for conditions such as epilepsy and pain</td>
</tr>
</tbody>
</table>

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Doctors should be aware that CBD is often promoted for a broad range of health benefits, yet the evidence base remains at large confined to pre-clinical studies or animal models.

CBD is however known to have a wide range of useful therapeutic modes of actions which include the following properties:

- anticonvulsant
- analgesic
- anti-inflammatory
- anti-anxiety
- antipsychotic
- neuroprotective
- immunosuppressive

There has been rapid acceleration into CBD research over recent years. The strongest evidence for CBD exists for treatment resistant epilepsies (3-4).

For most other indications, there is only pre-clinical evidence, while for some there is a combination of pre-clinical and limited clinical evidence.

Phase 2 and 3 clinical trials are currently underway in diverse areas including schizophrenia, drug dependency, tumour reduction, pain conditions, and PTSD (5).
CBD is available for use in a wide variety of forms and the pharmacokinetics and pharmacodynamics of CBD and other cannabinoids vary as a function of the route of administration.

**Oral**

CBD is a highly lipophilic molecule with low oral bioavailability. Oral and gastrointestinal tract absorption is therefore slow, erratic and leads to variable pharmacokinetics.

Bioavailability from oral delivery has been estimated at 6% due to low water solubility and significant first-pass metabolism in the liver. Maximal plasma concentrations are usually achieved after 60–120 min and may be up to 6 hours for oral ingestion.

Oils with graduated demarcated pipettes and capsules allow for convenient and more accurate dosing in terms of the amount consumed but do not account for individual differences in likely absorption and bioavailability.

CBD products infused into food and beverages will cause the CBD to be digested and metabolized. The amounts in these products tends to vary but generally are quite low per serving.

**Sublingual / transmucosal**

This route of administration allows direct uptake into the blood which eliminates first pass metabolism.

CBD tinctures generally are created by mixing a CBD extract with a carrier oil such as hemp seed oil, MCT oil or olive oil. They can be directly absorbed under the tongue or on mucosal surfaces.

CBD suppositories may be suitable for those who are unable to swallow CBD capsules or take CBD oils orally. CBD tampons are also being utilised to help with painful menstrual cramps although the human data is lacking currently in this area.
In what forms do patients consume CBD?

**Intranasal route**

By-passing the oral route may be of benefit to patient patients who experience nausea, vomiting, oral mucositis or impaired gastrointestinal function.

**Vaping / inhalation**

Vaporizing CBD (in both oil or dried flower form) has become a popular method of use. CBD cartridges are heated to the point of vaporization which results in rapid onset as cannabinoids are absorbed through the lungs into the bloodstream.

Vaping results in fast onset of action and high systemic bioavailability. Cannabis-related effects generally begin within a few minutes of the first inhalation. Peak plasma levels after 10 mins and remain active for 3-5 hours.

CBD oils are viscous and are commonly mixed with a thinning agent to allow the cartridge to function as intended.

Consumers must be cautious concerning the safety of the products they purchase and should avoid products containing propylene glycol (PG), polyethylene glycol 400 (PEG 400), or other such additives as there is evidence they produce noxious compounds when they are heated past a certain temperature.

Smoking - which involves direct combustion of CBD/dried hemp flowers - can produce harmful toxins which are damaging to the lungs and should be actively discouraged.

**Topical / transdermal**

Topical application through creams and transdermal patches provides a pathway for local rather than systemic absorption of CBD.

The avoidance of the first-pass metabolism effect improves drug bioavailability.

Transdermal applications allow a steady infusion of a drug to be delivered over a prolonged period of time, while also minimising the adverse effects of higher drug peak concentrations, which can improve patient adherence.

There may be low skin penetration of drugs with a hydrophilic structure. There are many over-the-counter patch products available but many are not formulated to deliver active ingredient (CBD) transdermally and will have variable bioavailability depending on the product.

Research into cannabinoid delivery systems is growing and it is expected that recent developments in pharmacological, pharmaceutical and technological sciences will result in new therapeutic strategies.
We must emphasise that doctors must treat over the counter CBD products in the same way as any other general health or food supplement.

Claims that these non-medical products can treat, mitigate, cure or prevent disease can result in legal consequences. Doctors should exercise extreme caution around giving advice on specific dosing for over the counter CBD products.

However, we also recognise the widespread use of CBD amongst the general public for health purposes and patients may understandably ask their doctors for their opinion or advice around efficacy, safety and interactions with other prescribed medications.

Holistic and compassionate medical care goes beyond just knowing about prescribed medications and keeping up-to-date with advances in medicine and science is a professional duty and also forms part of the GMC Good Medical Practice Guidelines.

Gaining knowledge in CBD and cannabis-based medicines are no exception, as this duty applies to all evidence-based therapies appropriate to a patient's care.

Doctors must ensure they are able to have informed conversations with patients around this subject matter. They should also explore further why CBD is being used or considered for use as this may highlight an unaddressed clinical need.

With this in mind, we have prepared a guide which continues on the next page.
DISCUSSING CBD WITH PATIENTS

Every living mammal has an endocannabinoid system; however, the tone of an individual’s endocannabinoid system will vary from one person to the next. This means dosage should be tailored to the individual to suit their personal endocannabinoid tone.

No person’s endocannabinoid tone is the same and many factors determine the tone such as age, tolerance, body fat percentage, genetics and metabolism.

A person’s endocannabinoid tone is dictated by 3 main factors; endocannabinoids, receptors and enzymes.

1. **Endocannabinoids**: The ability for a person’s body to produce enough endocannabinoids when needed for inter-cell signalling (on-demand messages).
2. **Receptors**: The number of active cannabinoid receptors available in the body (message receivers).
3. **Enzymes**: Enzyme activity levels will determine the break down rate of endocannabinoids (post message recycling).

A person’s endocannabinoid tone will determine the dosage of CBD they require to balance their endocannabinoid system and subsequently alleviate their medical issue.
KEY POINTS FOR DISCUSSION

A CLINICIAN’S GUIDE TO CBD

- It may be useful to discuss CBD as a supplement to a diet which can help maintain general health and well being due to its wide range of physiological effects and multiple potential sites of action both centrally and peripherally within the body.

- It can be useful to explain how CBD works in a similar way to anandamide and 2AG, modulating our own endogenous endocannabinoid system and affecting a wide range of physiological functions such as mood, sleep, inflammation and pain.

- Different types of CBD products will impact dosing requirements.

- CBD products and other cannabinoids will show a typical individualised and variable drug response which will be affected by age, tolerance, body fat percentage, genetics and metabolism) – i.e. something that works well for one person may not produce the same effect for someone else.

- CBD is excreted by the kidneys and moderate to severe impairment of kidney or liver function may theoretically reduce its clearance. Patients with reduced eGFR or liver impairment may therefore be advised to take caution and start on a lower dose of CBD.

- Typical starting regime should start with slow titration.

- For CBD naive patients we recommend a starting dose of 10mgs daily which can be built up gradually over about 4 weeks to around 60mgs and reassess. A few people are very sensitive (about 10%) hence the importance of starting at a low dose.

- Patients may need guidance on how to accurately work out mg per ml from the container.

- It may be useful for patients to keep a journal and track usage, dosage and effect.
There is a general lack of data on the types of drug-drug interactions that may occur between CBD and other pharmaceutical drugs in terms of published evidence of clinically significant interactions at the doses being used by consumers via over-the-counter CBD products.

Generally, at doses of CBD below 50mg or even 100mg a day, the chance of a clinically significant drug/herb interaction is probably quite low.

However, if the patient is taking certain medications such as antiepileptics, immunosuppressive agents post-transplant or cancer immunotherapy drugs or anticoagulantins, it is best practice to be especially careful and to ensure that specialists involved in a patient’s care and prescribing are made aware of any CBD use.

The main considerations are as follows:

CBD is known to act as an inhibitor of P450 isozymes. Patients should talk to their doctors about whether any of the medications they are taking are metabolized by the cytochrome P450 system before taking CBD.

CBD is a potent inhibitor of CYP2C19 and CYP3A4 and caution should be taken when cannabis-based medicines are co-administered with any medications that are CYP inhibitors or inducers (6).

Common examples of P450 inducers include Carbamazepine, Rifampicin and Phenytoin.

Common inhibitors include:

- Sodium valporate
- Ciprofloxacin
- St John’s Wort
- Sulphonamide
- Cimetidine
- Omeprazole
- Antifungals
- Amiodarone
- Isoniazid
- Erythromycin
- Clarithromycin

Broad spectrum CBD products may increase the actions of warfarin and other anticoagulants leading to increased risk of bleeding and for such patients the INR should be monitored closely (7).
A rise in liver function tests and serum concentration of some anticonvulsants has been observed with Epidyolex. In a small study of 39 adults and 42 children, raised drug levels were all within therapeutic range and AST/ALT levels were significantly increased in patients concurrently prescribed valproate and CBD (8).

In another small study in children with refractory epilepsy (n13), CBD was demonstrated to increase clobazam and norclobazam concentrations (9).
Information regarding CBD safety is limited to a few short-term human studies and information should be interpreted cautiously. Further study is needed on larger cohorts of CBD patients, and evaluation of CBD effects following long-term exposure.

To date, CBD has been found to have relatively low toxicity and multiple small studies have demonstrated that it is well tolerated across a wide dosage range. CBD exhibits no effects indicative of any abuse or dependence potential and there is no evidence of recreational use or any public health related problems associated with the use of pure CBD (2).

In a meta-analysis of studies involving 550 patients with Lennox-Gastaut or Dravet syndrome taking Epidyolex, adverse effects associated with CBD included somnolence, decreased appetite, diarrhoea and increased serum aminotransferases. Reports of somnolence were more frequent in patients also receiving the antiepileptic clobazam (10).

CBD differs to THC by lacking any intoxicating features. Patients may need to be reassured that CBD will not make them feel “high”.

Two of the most common adverse effects after CBD administration are somnolence and sedation but generally these are seen at high doses of hundreds of milligrams.

Other factors such as the chemovar including those high in myrcene (a terpene with potentially sedating properties), may also be involved in this response in some people based on preclinical and case report/clinical observation but no large studies exist to confirm this.
POTENTIAL SIDE EFFECTS OF CBD BASED PRODUCTS

These effects are dose-related and may be potentiated by co-administration of the anti-epileptic drugs clobazam and valproate, and other CNS depressants (including alcohol).

Patients should be advised that their ability to drive or operate machinery could be impaired while under CBD treatment.

The pharmacokinetics and toxicity of CBD in children is not well understood as in adults and therefore we do not recommend that children should be using over the CBD products.

It is recommended that any significant side effects/ adverse reactions are reported via the yellow card scheme.
In the UK, CBD falls into a novel food category which allows it to be purchased legally without a prescription. A novel food is defined as a type of food that does not have a significant history of consumption or is produced by a method that has not previously been used for food. Novel foods are subject to Food Standards Agency regulations.

CBD is legal to sell over the counter in the UK as long as the product meets certain criteria. It can contain very small amounts of a controlled drug (like THC) as long as:

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 (11).

One milligram of the controlled drug (mainly THC but also THCV and CBN) is allowed per container regardless of the size of the container.

At present there are twelve controlled cannabinoids.

1. Trans-delta-9-tetrahydrocannabinol-C5
2. Cis-delta-9-tetrahydrocannabinol-C5
3. Delta-9-tetrahydrocannabinol-C4
4. Delta-9-tetrahydrocannabinol-C3
5. Delta-9-tetrahydrocannabinol-C1
6. Delta-8-tetrahydrocannabinol
7. Cannabinol-C1
8. Cannabinol-C2
9. Cannabinol-C3
10. Cannabinol-C4
11. Cannabinol-C5
12. Cannabinol methyl ether-C5

These cannabinoids can be grouped into Δ9-THC, Δ9-THCV, Δ8-THC, CBN & CBNM-C5. Simplified as THC, CBN & THCV.

Current legislation is unclear when it comes to the 1mg rule per container. Does it apply to each controlled cannabinoid individually or the total sum of the controlled cannabinoids?

Assume the worst-case scenario to be safe and assume the total sum of controlled cannabinoids is the rule to avoid offering a CBD product classified as a schedule 1 drug.
LEGALITIES OF CBD PRODUCTS IN THE UK

It is widely thought that the limit of THC in legal CBD products is 0.2% but this refers to the permitted seed type which must have a maximum THC content of 0.2%.

Over the counter CBD products have not been through the rigorous processes that medicines are require to be put through to gain market entry by the MHRA and as such cannot be advertised as having medicinal properties.

Advertising or promoting CBD wellness supplements products that claim to prevent, treat or cure human disease is not permitted.

As a result of a lack of regulatory enforcement and rapid growth in the CBD sector over the past few years, the overall safety and quality of products cannot be guaranteed.

A number of laboratory analyses of CBD products have identified concentrations of cannabinoids that differ from the amounts advertised – in some cases involving unlawfully high levels of controlled substances, other phytocannabinoids and harmful chemicals including solvents and heavy metals.

In a recently published study, 29 different CBD products available in the UK were tested. The study found that only 38% products were within 10% of the advertised CBD content. 55% of products had measurable levels of controlled substances and detectable levels of heavy metals were found in many CBD products (12).

The Foods Standards Agency (FSA) announced a deadline of 31 March 2021 for the CBD industry to submit valid novel food authorisation applications to ensure products meet legal standards on safety and content. After this time only products with a valid application will be allowed to remain on the market to be sold directly to consumers.

This application process is both expensive and time consuming and this may result in a reduced range of products available to consumers as only larger companies can afford to take the necessary regulatory steps.

The FSA has also issued further guidance recommending a daily dose of CBD as 70mg unless under medical direction, and that CBD should not be taken by pregnant women nor taken with any other medications.

The MCCS is not aware of any scientific evidence that doses above 70mgs daily are unsafe.

The usual dose range for adults with anxiety and pain, for example, is 60-100mgs daily. Children with epilepsy take much higher doses – up to 12mgs/kg is common.
Due to the largely unregulated CBD market in the UK, consumers need to take extra caution on deciding about which type of CBD product to use. With such a wide variety of products available, some people will naturally feel confused on what constitutes an effective and high quality and safe CBD product. One of the most important considerations is ensuring the product has what is called a COA, or certificate of analysis, which should be available for any reputable supplier or brand.

Each batch of CBD oil should have a full panel Certificate of Analysis with it. This ensures safe and accurate consumption for your patient.

This document is proof that the batch has been tested by an approved third party laboratory and contains the stated amount of CBD on the label as well as being free from contaminants, THC above trace limits and free from heavy metals, pesticides, residual solvents, mycotoxins and microbials.

A full panel certificate of analysis should include:
- Cannabinoid Potency
- Terpene test
- Flavonoid Test
- Heavy Metals Test
- Pesticides Test
- Microbiological Test
- Residual Solvents Test
- Mycotoxins Test

Each is explored in depth below.

**Cannabinoid Potency**
Accurate determination of cannabinoid concentrations in CBD supplements is one of the most important components of testing. A potency test will display the levels of cannabinoids present within the product.
- Does the CBD content match what’s stated on the label?
- Are there additional minor cannabinoids present (these contribute to the entourage effect)?
- Are there any controlled cannabinoids present?
Cannabinoid Potency continued
Example: A 10ml bottle of CBD oil should not contain more than 1mg total of controlled cannabinoids. This is expressed as no more than a combined percentage of 0.01%.

Limit of Quantification (LOQ) is important to ensure that the lowest concentration of a cannabinoid can be determined. If a certificate of analysis only has an LOQ of 0.05%, controlled cannabinoids could be displayed as non-detect when in fact they are present.

Terpene test
Terpenoids (terpenes) are produced in the trichomes of the cannabis flower along with cannabinoids like CBD. Terpenes/terpenoids give cannabis its individual profile of flavour and aroma.

Identifying natural cannabis terpenes present in a CBD supplement will determine which type of spectrum the CBD supplement is.

“Terpenoids (terpenes) alter the effects of the cannabinoids in a way that often is synergistic. Synergy is a boosting of effect. So, it would be the idea that 2 + 2, instead to equalling 4, it gives you an 8 in terms of the benefit.” Dr. Ethan Russo

Flavonoid Test
Flavonoids are phytonutrients, they are found in the leaves, the flowers and the trichomes of the cannabis plant. They play a role in plant pigments, flower coloration, taste, smell and an overall sensory experience. Along with cannabinoids and terpenoids, flavonoids can also bind with cannabinoid receptors and thus they too contribute to the entourage effect (synergy boosting).

Although not crucial to a CBD supplement like a sublingual oil (preference is ingestion), they do help to determine the type of extract used in a CBD supplement.

Heavy Metals Test
Cannabis (hemp) loves to collect heavy metals. It absorbs heavy metals from the soil, water and air. These toxic elements can be passed from the plant into a CBD extract and then into a consumer’s body where they would pose a health risk. It is important for CBD supplements to be free from heavy metals.

Note: organic certification does not require any screening for heavy metals.

Pesticides Test
Pesticides are used in many forms of commercial farming all across the world; they are carcinogenic and mutagenic, causing serious harm to consumers - the most vulnerable being those who are already immunocompromised.

Testing CBD supplements for pesticides ensures the product is clean and free from residual pesticides.

Microbiological Test
According to the United Nations, 1 in 10 people world wide get ill from consuming a microbiologically contaminated food. Microbiological contamination can lead to serious illness and health issues.

Common pathogenic screening, tests for the presence of Shiga toxin E. coli, salmonella, and Listeria. CBD supplements should be free from microbials.

Residual Solvents Test
Residual solvents can be chemicals left over from the process used to extract cannabinoids, terpenoids and flavonoids from the cannabis plant. Solvents can also be used in the filtration process too. Cannabis supplements should be free from any residual solvents or below the legal required amount determined as safe.
Mycotoxins Test
Mycotoxins are contaminants that naturally occur in moulds and fungi, which will decompose organic matter. You can find moulds that contain mycotoxins in a variety of crops such as nuts, spices, apples and coffee beans. You can also find mycotoxins in cannabis (hemp) flower and then its subsequent extract whether that be in oils, edibles, tinctures or creams.

Mycotoxins contain carcinogenic and mutagenic properties that can cause the development of cancerous cells and damage to the structure of your DNA and as such can be very harmful to humans, especially in cases of long-term exposure. CBD supplements should be free from mycotoxins.
CHECKLIST FOR CBD PRODUCTS

- Is there a batch, lot, or control number?
- Is there a production date or expiration date?
- Is there GMP certification?
- Are there appropriate warnings for use, including any individuals for whom the product is contraindicated, as appropriate; and instructions for use and appropriate storage?
- Is the CBD product Whole-plant, Full-spectrum, Broad-spectrum, Narrow-spectrum or No-Spectrum (isolate)?
- Is there a Certificate of Analysis available that displays a cannabinoid potency test? Does it display terpene and flavonoid analysis?
- Does it pass for heavy metals, pesticides, mycotoxins, microbials and residual solvents?
- Does it contain any controlled cannabinoids (THC, CBN or THCV) in total above 1mg?
- Does the company have an independent adverse event reporting programme?
- Is there accurate labelling which ensure that consumers understand what they are buying?
- Does the product make any medical claims?
- Is it in compliance with EU food safety laws?
REFERENCES
A CLINICIAN’S GUIDE TO CBD

THE MEDICAL CANNABIS CLINICIANS SOCIETY
INDEPENDENT, EXPERT SUPPORT FOR CLINICIANS

The Medical Cannabis Clinicians Society is an independent community of medical cannabis pioneers – the first prescribers of this treatment in the UK.

We believe that every patient who could benefit from medical cannabis should have access to it.

We provide the medical and scientific community interested in supporting patients with medical cannabis with high-quality training and expert support.

Membership is open to those with a professional interest in medical cannabis, including clinicians, nurses, GPs, allied health professionals (AHPs), medical students, healthcare scientists, pharmacists and those working across acute, primary and community healthcare.

As part of the UK’s leading group of medical cannabis experts, members have access to information to inform treatment decisions, up-to-date product guidance and support to ensure clinicians can become as confident in prescribing medical cannabis as they are with first line treatments.

With the most respected medical cannabis clinicians in the country providing support, members are better able to help their patients.

Annual membership is £90 for consultants, GPs and others and £45 for nurses and AHPs. Membership is free for medical students and we welcome international members.

Join online at www.ukmccs.org.

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