DMC0047

Written evidence from the British Pharmacological Society

About us
The British Pharmacological Society (BPS) is the primary UK learned society concerned with research into drugs and the way they work. The Society has around 4,000 members working in academia, industry, regulatory agencies and the health services, and many are medically qualified. The Society covers the whole spectrum of pharmacology, including laboratory, clinical, and toxicological aspects. Pharmacology is a key knowledge and skills base for developments in the pharmaceutical and biotech industries, and is therefore fundamental to a thriving UK industry and R&D. The Society publishes three scientific journals: the British Journal of Pharmacology, the British Journal of Clinical Pharmacology, and Pharmacology Research and Perspectives.

Summary of key points:
1. The Society would like to raise a number of concerns regarding the usage of 'Cannabis plant-derived medicinal products' (CDMPs) in medicine and research. In summary:
    - There needs to be more clarity about which products are covered by the CDMP re-scheduling decision. For example, cannabidiol (CBD) is a CDMP but is not a controlled drug in the UK - but there are other issues with access and prescribing (see paragraph 2).
    - There needs to be more clarity regarding which CDMP products are now considered to be Schedule 2 preparations for pre-clinical researchers. Use of Schedule 1 drugs entails a much greater burden of licensing and administration for researchers and institutions than those in Schedule 2, and this burden presents a barrier to legitimate research.
    - There should be a formal process for reviewing scheduling decisions using current scientific evidence.
    - Currently available CDMPs are unlicensed medicines or "specials", with the exception of Sativex, which is licenced in the UK for the treatment of spasticity associated with multiple sclerosis in adults. Unlicensed medicines usually require approvals on a named patient basis within hospital Drug and Therapeutics systems.
    - Few of the available CDMPs are produced to the quality standards expected of a licenced medicine—ie, quality-controlled and in adherence to Good Manufacturing Practice (GMP) standards. It is important that only products of defined composition and standard are prescribed and/or used in a research setting.
    - There has been little lead time to produce guidance in time for the changes in legislation. Therefore, we believe there are few specialists who will be confident to prescribe these products. A clear prescribing framework and safeguards for CDMPs that would manage risks to health is not yet available. Current prescribing rules are cautious, but this is appropriate until further guidance has been released.
    - There is insufficient public and patient awareness of the prescribing rules, including the rule that only doctors on the GMC Specialist Register are allowed to prescribe CDMPs. This has led to a mismatch between public/patient expectation and the reality that CDMPs are currently unlikely to be prescribed.
    - It is likely that difficult situations between patients and prescribers will continue, at least until further NICE guidance is published later this year.
    - We are concerned that the restricted availability of Epidiolex (via a compassionate access scheme) could lead to treatment inequity should more patients be considered eligible, and the scheme becomes full. The Society recommends rapid consideration of whether Epidiolex should be granted UK authorisation.

What does the current evidence base tell us about the efficacy of medicinal cannabis?

2. Regarding the Committee's question about the current evidence base, we would like to note the recent review on this matter by Chief Medical Officer, Professor Dame Sally Davies[1]. Guidance issued by the British Paediatric Neurology Association[2] discusses further evidence for the use of cannabidiol (CBD) in the treatment of certain complex epilepsies in children. CBD is not a controlled drug in the UK.

Do practitioners have the knowledge and products available to them to confidently prescribe medicinal cannabis?

3. Statutory Instrument No. 1055[3] allows doctors on the GMC Specialist Register to "issue prescriptions for cannabis-based medicines when they agree that their patients could benefit from this treatment"[4]. The legislation does not affect the classification of Cannabis as a Class B drug as defined by the Misuse of Drugs Act (1971)[5] and so does not affect penalties for unlawful possession, supply and production. The Statutory Instrument moves 'Cannabis plant-derived medicinal products' (CDMPs) to Schedule 2 from Schedule 1. Scheduling defines the circumstances in which it is lawful to possess, supply, produce, export and import controlled drugs, as set out by the 2001 Regulations associated with the Act. CDMPs are defined by the legislation as:

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

4. There needs to be more clarity about which products are covered by the CDMP definition with regards to rescheduling. The cannabis plant contains many active ingredients. For example, cannabidiol (CBD), although a CDMP, is not currently controlled by UK law due to its lack of activity at cannabinoid receptors. However, it has received media attention as 'medicinal cannabis' particularly relating to its use in cases of intractable epilepsy in children. The British Paediatric Neurology Association highlights that current evidence of benefit is restricted to cannabidiol (CBD)[2]. CBD is available in pure form as Epidiolex, which is not currently a licenced medicine in the UK, but is authorised in the USA and is undergoing authorisation processes in Europe. CBD is also available as 'cannabis oil' (from suppliers such as Bedrocan in the Netherlands), but levels of tetrahydrocannabinol (THC), although intended to be low, are not guaranteed. The latter products are therefore treated as controlled substances because they may contain THC. Further, the BPNA "caution against using THC-containing products in children because of concerns about the effect of exposure to

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[1] Davies S. (2018). Cannabis Scheduling Review Part 1 The therapeutic and medicinal benefits of Cannabis based products – a review of recent evidence. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/722010/CMO_Report_Cannabis_Products_Web_Accessible.pdf

[2] British Paediatric Neurology Association (2018). Guidance on the use of cannabis-based products for medicinal use for children and young people. Available online: https://www.bpna.org.uk/userfiles/BPNA_CBPM_Guidance_Oct2018.pdf

[3] UK Government. (2018). Dangerous drugs, England and Wales dangerous drugs, Scotland. The Misuse of Drugs (Amendments) (Cannabis and Licence Fees) (England, Wales and Scotland) Regulations 2018. Available online: http://www.legislation.gov.uk/uksi/2018/1055/pdfs/uksi_20181055_en.pdf (last accessed 6 February, 2019)

[4] Home Office. (2018). Government announces that medicinal cannabis is legal. Available online: https://www.gov.uk/government/news/government-announces-that-medicinal-cannabis-is-legal (last accessed 6 February, 2019)

[5] UK Government. Drugs penalties. Available online: https://www.gov.uk/penalties-drug-possession-dealing (last accessed 6 February, 2019)

THC on the developing brain". A related concern is that Epidiolex is available on a limited basis in the UK via a compassionate access scheme. Therefore, the issue of using CBD in intractable childhood epilepsies appears to be primarily related to the lack of availability of high-quality, licenced products and a need for more research – not scheduling. The issue of drug control appears to arise only when the absence of THC cannot be guaranteed. Further, Sativex (also known as nabiximols elsewhere) contains both CBD and THC and is licenced in the UK for patients who have not responded to other treatments for spasticity associated with Multiple Sclerosis. However, this medicine is already in Schedule 4 (part 1), and licences are no longer required for its medical or research use[6]. In our view, Epidiolex and Sativex are the only available CDMP products that meet the standards expected of a prescribed medicine in the UK. We are unclear about whether the CDMP definition will capture medicinal products that are authorised in other countries.

5. Regarding other non-licenced preparations, it is unclear which products are within the scope of this definition. Some of the manufacturers of these products (e.g. Bedrocan in the Netherlands) focus on medicinal use and claim to work to GMP standards. Others will not be manufactured to GMP standards and will be of unknown and inconsistent composition. Further, there is limited guidance as to which particular preparation (in terms of dose, route of administration, frequency of administration) might be beneficial for any particular individual with a specified disease/disorder. Further, what constitutes (and will be required of) an approved supplier must be clarified. It is the Society's view that only quality-controlled products made to GMP standards should be used in research and healthcare settings. Standardisation will be important to enable robust assessments of efficacy and safety.

6. Whilst we recognise that only prescribers on the Specialist Register can prescribe CDMPs (even once they are properly defined), we believe there will be few specialists confident enough to prescribe these products. There is no clear prescribing framework, or safeguards to manage the risk to health and there is genuine concern over the risk of drug diversion. Clinical pharmacologists are experts in the safe and effective use of medicines. However, they are unlikely to be the prescribers of these products, rather they are more likely to be involved in governance systems relating to CDMPs e.g. via NICE and the MHRA. There has been not been enough time to allow for the production of guidance in time for the changes in legislation. We hope there will be rapid assessments for the licensing of CDMPs - the lack of availability of licensed products and the reliance on unlicensed products ("specials") is a problem.

7. Further, within paediatrics all consultant paediatricians are classified as being on the Specialist Register. However, the BPNA recommends[2] that the ability to prescribe CDMPs should be limited to specialists with paediatric neurology expertise e.g. in tertiary care by a Consultant Paediatric Neurologist.

Is the current guidance around prescribing CDMPs fit for purpose?

8. Current prescribing guidance has been developed by the Royal College of Physicians (London) and the Royal College of Radiologists, with input from the Faculty of Pain Medicine of the Royal College of Anaesthetists[7]. Additional guidance has been provided by the British Paediatric Neurology Association[2] and is helpful for certain conditions (such as rare epilepsy syndromes), but the lack of clear guidance with the full evidence base is lacking in most other areas. Specialists await further guidance from NICE but this is not expected until October 2019[8]. Generally, the guidance is

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[6] Home Office. Scheduling of the cannabis-based medicine 'Sativex'. Available online: https://www.gov.uk/government/publications/scheduling-of-the-cannabis-based-medicine-sativex (last accessed 6 February, 2019)

[7] RCP (London). (2018). Recommendations on cannabis-based products for medicinal use. Available online: https://www.rcplondon.ac.uk/projects/outputs/recommendations-cannabis-based-products-medicinal-use

[8] NICE. (2018) Cannabis-based products for medicinal use. Available online: https://www.nice.org.uk/guidance/indevelopment/gid-ng10124/documents (last accessed 6 February, 2019)

most helpful in those indications where CDMPs are currently going through licensing applications in Europe, the main example being Epidiolex.

What plans are there for research into the medicinal use of cannabis, and what challenges are faced by that research?

9. The possibility of drug-drug interactions needs to be carefully evaluated particularly in patients with complex diseases, such as epilepsy, who may already be on other medicines. There is some indication that THC and/or CBD may interact with other medicines (e.g. levels of benzodiazepines) but many of these effects may not be fully identifiable without reliable data derived from a large number of patients. It will also be important for any adverse events to be immediately reported to the MHRA via the Yellow Card scheme. It will also be important to understand whether long-term safety issues arise with CDMP use. It is our understanding that CDMPs previously in Schedule 1 will be classed as Schedule 2 for use in healthcare and clinical research settings.

10. We would also welcome clarification about what is usable in a pre-clinical research setting. Pre-clinical research is fundamental to understanding mechanism of drug action and disease. We note section 4.4 of Statutory Instrument No. 1055 (page 3), which says:

    > *"Nothing in this regulation shall have effect in relation to the order or supply of a cannabis-based product for medicinal use in humans for administration to animals for research purposes."*

    Therefore, it is not clear to us whether a compound meeting the definition of a CDMP would be available to pre-clinical researchers as a Schedule 2 drug. This is important because of the requirement to hold a Schedule 1 licence appears to present a barrier to legitimate research (see paragraph 12). We also have doubts about whether it would be practical to use the type of research (clinical or pre-clinical) as the basis for CDMP scheduling decisions: this would be a highly unusual use of the scheduling system. The Society's view is that CDMPs previously in Schedule 1 should be classed as Schedule 2 for use in healthcare, clinical research and pre-clinical research settings.

11. Compounds within Schedule 2 are defined as "drugs of medicinal value but with high abuse potential" e.g. heroin and cocaine. These compounds can be prescribed and therefore legally possessed and supplied by pharmacists and doctors and possessed with prescription. Further, under current guidance issued by the Home Office, University research departments do not generally require a licence to possess drugs in Schedules 2, 3, 4 (parts I and II) and Schedule 5. Drugs in Schedule 2 are subject to safe storage requirements and record keeping, in addition to any local rules. The 2001 Regulations make provisions for legitimate use and research for drugs of medicinal value. We would value clarification on whether any CDMP that has been moved to Schedule 2 would be available to researchers in the same way as other Schedule 2 drugs. We are concerned that if the intention is to treat CDMPs differently for medicinal versus research use, then a potential barrier to legitimate research may persist.

12. We hope that the intended definition of CDMPs and the scope for medicinal and research use will be clarified. However, we also anticipate that CDMPs as defined by the legislation will not capture all compounds with CB_1 cannabinoid receptor activity that are of interest to researchers because of their potential medicinal value. We anticipate that a number of these compounds will remain in Schedule 1. Compounds within Schedule 1 are defined as "drugs of no medicinal value". This includes drugs such as Lysergic acid diethylamide (LSD) and 3,4-Methylenedioxymethamphetamine (MDMA, commonly known as ecstasy) that are of research interest. Compounds in Schedule 1 may be used for research only under a Home Office licence – but this

requirement appears to be preventing researchers from studying these drugs. Members of the Society tell us that this is because the process is hard to navigate, puts an unrealistic burden on individual researchers, is too expensive and takes too long to organise:

12.1 "We have some really interesting new methods for depression research and would like to study cannabinoid and psychedelic compounds given their potential for clinical use, but the Schedule 1 status makes this difficult and costly and so is not something we have been able to progress." – BPS Member

12.2 "I was not able to apply for a Schedule 1 Licence until I had grant funding in place to pay the costs – likely to be £3000 inspection/application fee and £1500 per annum. I now have funding but my University Safety Officer says it will take another 3-6 months before a licence can be obtained. I cannot apply for an import licence (my drugs come from NIH USA) until I have a Schedule 1 holding licence. Therefore, there will be another delay to import the drugs after we have a Schedule 1 holding licence. This means we will lose a significant part of the first year of a 3-year grant project." – BPS Member

12.3 "I have been unable to purchase THC for my research on cellular models of disease for a number of years. In order to obtain THC, considerable administrative work is involved and the Schedule 1 licence is prohibitively expensive. I have found it difficult to understand the pathway to obtain the license from information on the Home Office website and have found it difficult to get the answers I need by email. I also think there is uncertainty about what a CDMP is and if it contains THC, which many of them do. When do I need a licence? I have utilised collaborators at other University sites that do have a licence, which is one way around the problem, but it limits the scope of the experimental plan since different expertise exists in each lab. Small companies in other countries extract cannabinoids from plants and formulate them into products, but there is considerable administrative work to be done around export and import licences, which has meant that this avenue hasn't worked for me either." – BPS Member

13. In section 1.5 of her review[1], Professor Dame Sally Davies summarises her view that *"the whole class of cannabis based medicinal products [should be moved] out of Schedule 1, [which] will allow the evidence base on the therapeutic benefits associated with using this class of drugs to be improved through research, maximising benefits to patients".* Schedule 2 is intended to support legitimate possession for medicinal use and research, but it is not being used to its full potential. Part of the reason for this is that once a drug is placed into Schedule 1, there is no formal process for reviewing this decision based on the current scientific evidence, research value and potential medicinal value.

14. We understand that the Advisory Council on the Misuse of Drugs (ACMD) is undertaking a longer-term review of the scheduling of cannabinoids and hope this work will include consideration of the value of research that explores the potential medicinal value and mechanism of action of these drugs. We would also like to recommend a broader review of scheduling decisions, based on current scientific evidence. Put simply, a scheduling decision stating a drug has no medicinal use can put up barriers to legitimate research. If this research is never carried out as a result, there is a danger of this becoming a self-fulfilling prophecy.

Have recent changes in the scheduling and availability of CDMP, and media attention around this, affected public opinion and behaviours in the UK?

15. The rescheduling of CDMPs is not currently accompanied by suitable licensed medicinal products in the UK, but this is not widely known. The media attention concentrated on the ability to now prescribe CDMPs and not the availability of them. There is public interest around whether CDMPs are effective and appropriate treatments for indications such as pain conditions (such as fibromyalgia), neurological conditions and cancer amongst other indications. BPS members who work in medicines management roles in hospitals have had to deal with requests for prescriptions of CDMPs from patients and colleagues. These are for a wide variety of indications far beyond the original media cases relating to paediatric patients with certain forms of severe epilepsy. Given that the currently available CDMPs are unlicensed medicines or "specials", these usually do require approvals on a named patient basis within hospital Drug and Therapeutics systems. The public perception is that any doctor (including GPs) can prescribe these products as the awareness of the required checks and balances (e.g. unlicensed risk assessments) have not been made clear. This has created many difficult situations between patients and prescribers and within healthcare systems who have been unprepared for the rescheduling of CDMPs. This is likely to remain a problem until better evidence-based guidance and licensed medicinal products are available in the UK. As described in paragraph 4, we are also concerned that the restricted availability of Epidiolex in the UK (via a compassionate access scheme) could lead to treatment inequity should more patients be considered eligible, and the scheme becomes full. The Society recommends rapid consideration of whether Epidiolex should be granted UK authorisation.