ACMD

Advisory Council on the Misuse of Drugs

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11 September 2018

Dear Home Secretary and Secretary of State for Health and Social Care,

Re: Consultation on *Cannabis*-derived medicinal products

Thank you (Home Secretary) for your letter of 26 July 2018, in which you accepted the Advisory Council on the Misuse of Drugs' (ACMD's) recommendations from our initial short-term review on *Cannabis*-derived medicinal products (CDMPs).

On 15th August 2018, further to the ACMD's initial short-term review, the ACMD's CDMP Working Group met with representatives of the Home Office, the Department of Health and Social Care (DHSC) and the Medicines and Healthcare products Regulatory Agency (MHRA). This meeting considered the Government's proposed interim approach for the rescheduling of CDMPs, which included three components, designed to work together:

- *Component 1: An interim definition of a CDMP;*
- *Component 2: Three access routes for prescribing CDMPs; and*
- *Component 3: Guidance to support practitioners.*

The ACMD is now providing advice on this interim approach, as well as a number of additional recommendations intended to strengthen the proposed approach. Given our conclusions and recommendations we believe it to be advisable to address our response to both of you.

Component 1: Interim definition of CDMPs

The ACMD reiterates its previous advice that CDMPs should meet defined safety and quality assurance standards to ensure that they do not put patients at risk of harm. As an interim measure, only products meeting these standards were recommended to be rescheduled to Schedule 2 of the Misuse of Drugs Regulations 2001. Any products not meeting these safety and quality assurance standards should remain in Schedule 1. To achieve this, the formulation of a clear definition of a CDMP was recommended.

The Government has now proposed an interim definition of a CDMP for medicinal use in humans, which includes the following three elements.

1) *It contains Cannabis, Cannabis resin, cannabinol or a cannabinol derivative.*
2) *It is produced for medicinal use in humans.*
3) *It is:*
    i. *a medicinal product; or*
    ii. *a substance or preparation for use as an ingredient of a medicinal product; or*
    iii. *a substance for use in the preparation or manufacture of an ingredient of a medicinal product.*

The ACMD has reviewed this definition and has reached the following conclusions.

The interim definition does not include safety and quality assurance standards, as the ACMD previously recommended. Without explicitly setting these standards or referring to defined standards, it is impossible for prescribers to determine which products should be made available to patients as prescription medications.

The ACMD concluded that element 1 of the interim definition, as currently drafted, is too broad. The ACMD is concerned that element 1 could potentially encompass a wide range of products not appropriate for medicinal use and these would be available to be prescribed with no information about their quality or safety. Examples include products of known acute harm, such as very high-*tetrahydrocannabinol* (THC) containing solid and edible products, liquid extracts, and products with impurities which have not undergone any quality control.

Elements 2 and 3 lack clarity regarding the term ‘medicinal product’. Without further detail, elements 2 and 3 will not assist in identifying products specifically manufactured to an acceptable medicinal standard.

As is described in the Government's interim proposal, prescribers will take sole responsibility for ensuring the safety, quality and efficacy of unlicensed CDMPs. However, the current lack of UK pharmacopoeial standards on CDMPs and the relative paucity of high quality clinical evidence at present means that on a practical level, prescribers will be unable to judge safety, quality and efficacy of CDMPs when using the proposed CDMP definition. This potentially puts patients at risk and is exactly the situation the ACMD expressed concern about in our letter of 19 July 2018.[1]

In addition, the lack of a clear definition for CDMPs is regarded by the ACMD as a significant risk to their successful adoption and therapeutic use by clinicians and could lead to wider harms, including misuse and diversion.

In view of these concerns, the ACMD recommends that the Home Office, DHSC and MHRA continue working on refining the definition of CDMPs to include appropriate standards so that only those products which meet those standards are available to be prescribed. The ACMD will further examine the definition in the longer-term review.

Any definition of CDMPs should be underpinned by existing regulations [The Misuse of Drugs Regulations 2001, The Human Medicines Regulations 2012, and The Controlled Drugs (Supervision and Management and Use) Regulations 2013] and clinical guidance specific to CDMP prescribing.

Conclusion 1: The ACMD notes that the proposed interim definition of a CDMP is currently extremely broad, with no reference to safety or quality. The lack of clarity in the definition significantly increases the risk of unintended consequences.

Recommendation 1: The Home Office, DHSC and MHRA to refine the definition of a CDMP as a priority.

Component 2: Three access routes for prescribing CDMPs

The ACMD previously recommended the development of additional frameworks and clinical guidance for 'checks and balances' to maintain safe prescribing of CDMPs to avoid harm to patients and others. The three access routes that shall enable CDMPs to be made available are:

1. *a 'special' unlicensed medicinal product that is for use in accordance with a prescription or direction of a specialist medical practitioner, or*

[1] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/727333/ACMD_advice_on_scheduling_of_cannabis_derived_medicinal_products.pdf

2. *an investigational medicinal product without a marketing authorisation that is for use in a clinical trial, or*

3. *a medicinal product with a marketing authorisation.*

The ACMD has reviewed and agreed the three proposed access routes by which a CDMP can be prescribed in the UK to ensure patient safety.

Conclusion 2: The ACMD supports the availability of CDMPs by the three proposed access routes for prescribing to ensure patient safety.

Designation order

To enable the prescription of CDMPs by specified routes and by specialist clinicians, CDMPs should be removed, as part of their rescheduling, from the Misuse of Drugs (Designation) Order 2015.

Recommendation 2: CDMPs meeting appropriate safety and quality standards under Schedule 2 should be exempted from the general designation of *Cannabis*, *Cannabis* resin, cannabinol and cannabinol derivatives under the Misuse of Drugs (Designation) Order 2015.

Licence fees

The ACMD agrees to the proposed amendment of the licence fees regulations to clarify the Secretary of State's discretionary power to waive licence fees where appropriate.

Component 3: Guidance to support practitioners

The ACMD recommends that any guidance to support practitioners in prescribing CDMP should address both unlicensed products and those with marketing authorisation. In the proposal, the responsibility for prescribing an unlicensed CDMP falls within the existing framework for the prescription of unlicensed medications. The ACMD agrees that unlicensed CDMPs should be considered as a product of last resort and used only when no other drug with MHRA marketing authorisation meets the clinical need.

Given the currently limited evidence base, and the unfamiliarity UK clinicians have with CDMPs, it is insufficient to make clinicians solely responsible for the safety, quality and efficacy of unlicensed 'special' CDMPs. In view of this, the ACMD supports the development of interim guidance by the DHSC and NHS-England (and its equivalents in Scotland, Wales and Northern Ireland) for those prescribing CDMPs (both unlicensed and those with MHRA marketing authorisation). Guidance should be applicable to both public and private sectors. The ACMD anticipates that the interim

guidance will address the medical conditions for which CDMP should be used and will help prescribers to make appropriate clinical decisions around patient safety.

The ACMD agrees with the involvement of the National Institute for Clinical Excellence (NICE) to develop substantial guidance to replace the interim guidance in due course. The substantial guidance should also address formulations, covering aspects such as high/low THC products, THC/cannabidiol (CBD) ratios and inhalable and edible products.

Conclusion 3: The emphasis on the prescriber to ensure the safety, quality and efficacy of unlicensed 'special' CDMPs means that clear interim guidance should be developed as a matter of urgency and be ready by the time of implementation to assist in clinical decision making.

Recommendation 3: The DHSC and NHS England (and their equivalents in Scotland, Wales and Northern Ireland) to lead the development of interim guidance for clinicians considering prescribing a CDMP and pharmacists who will be required to source and dispense CDMPs (including unlicensed 'special medicinal products' and products with MHRA marketing authorisation). The ACMD supports the involvement of NICE in developing substantial guidance to replace the interim guidance in due course.

Competency framework for prescribers

The ACMD agrees with the proposed initial restriction of CDMP prescribing to clinicians on the specialist register of the General Medical Council (GMC) and suggests that this does not impede research on CDMPs from taking place. To prevent the prescribing of CDMPs outside clinicians' specialist areas, the proposed restriction to clinicians on the specialist register should include the relevant specialist registration. Doctors authorised on study delegation logs should be considered as eligible to prescribe within their research setting.

The ACMD stresses that a clear training pathway and competency framework should be developed to:

- define safe, effective and ethical prescribing.
- ensure the competence of prescribers of CDMPs.

Recommendation 4: The DHSC (and its equivalent in Scotland, Wales and Northern Ireland) to develop, with stakeholders, a competency framework and training pathway for the prescribing of CDMPs to support safe and effective prescribing.

Additional ACMD recommendations on interim proposals

Content description

Prescribers will need to know the content of a CDMP when making a clinical decision. The ACMD re-iterates that prescribers must have confidence in the composition and consistency of CDMPs to ensure patient safety. Labelling of CDMPs will support prescribers in clinical decision making and help to develop the clinical evidence base.

Cannabis contains many different compounds, of which THC and CBD have been the most studied.[2,3,4] The understanding of the precise therapeutic action of THC and CBD, acting independently or together, is still developing.[5,6,7,8,9,10,11,12,13] Other compounds commonly present in *Cannabis* may potentiate or attenuate the clinical effects of THC and CBD. As a minimum, the actual amounts of THC and CBD in the product (in mg per unit dose or volume) should be a mandated part of the labelling of all CDMPs.

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[2] **Russo, E. B. and Marcu, J.** (2017) 'Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads', *Adv. Pharmacol*., 80, pp 67–134.

[3] **Ligresti. A., De Petrocellis, L. and Di Marzo, V.** (2016) 'From Phytocannabinoids to Cannabinoid Receptors and Endocannabinoids: Pleiotropic Physiological and Pathological Roles Through Complex Pharmacology', *Physiol. Rev*., 96, pp 1593–659.

[4] **Izzo, A. A., Borrelli, F., Capasso, R., Di Marzo, V. and Mechoulam, R.** (2009) 'Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb', *Trends Pharmacol*. *Sci*., 30, pp 515–27.

[5] **Allan, G. M., Ton, J. and Perry, D.** (2018) 'Evidence for THC versus CBD in cannabinoids. Pain, nausea and vomiting, spasticity, and harms', *Can. Fam. Physician*, 64, p 519.

[6] **Russo, E. and Guy, G. W.** (2006) 'A tale of two cannabinoids: The therapeutic rationale for combining tetrahydrocannabinol and cannabidiol', *Medical Hypotheses*, 66, pp 234–246.

[7] **Johnson, J. R., Burnell-Nugent, M., Lossignol, D., Ganae-Motan, E. D., Potts, R. and Fallon, M. T.** (2010) 'Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain', *J. Pain Symptom Manage*., 39 (2), pp 167–79.

[8] **Bonomo, Y., Souza, J. D., Jackson, A, Crippa, J. A. S. and Solowij, N.** (2018) 'Clinical issues in cannabis use', *Br. J. Clin. Pharmacol*.

[9] **Lucas, C. J., Galettis, P. and Schneider, J.** (2018) 'The pharmacokinetics and the pharmacodynamics of cannabinoids', *Br. J. Clin. Pharmacol.*

[10] **Schleider, L. B., Abuhasira, R. and Novack, V.** (2018) 'Medical cannabis: aligning use to evidence-based medicine approach', *Br. J. Clin. Pharmacol.*

[11] **Abrams, D. I.** (2018) 'The therapeutic effects of Cannabis and cannabinoids: An update from the National Academies of Sciences, Engineering and Medicine report', *Eur. J. Intern. Med.,* 49, pp 7–11.

[12] **Allan, G. M., Finley, C. R., Ton, J., Perry, D., Ramji, J., Crawford, K., Lindblad, A. J., Korownyk, C. and Kolber, M. R.** (2018) 'Systematic review of systematic reviews for medical cannabinoids: Pain, nausea and vomiting, spasticity, and harms', *Can. Fam. Physician,* 64, pp e78–e94.

[13] **Gaston, T. E. and Friedman, D.** (2017) 'Pharmacology of cannabinoids in the treatment of epilepsy', *Epilepsy Behav.,* 70, pp 313–318.

Some CDMPs will contain, in addition to THC and CBD, a number of other compounds derived from *Cannabis*. At present, the evidence is unclear as to the therapeutic benefit or harms of these other compounds. As scientific understanding improves, the labelling of CDMPs with other compounds should be indicated.

In the development of guidance, consideration should also be given to the following.

- The acidic forms of some of the cannabinoids that exist in *Cannabis*. For example, tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA) can be converted to THC and CBD respectively by the action of heat. Specific methodology to ensure consistency of values on analysis could be stipulated. Alternatively, the total THC and total CBD amounts could be required to include both THC and CBD and their acids.
- Ratios of the compounds present may be included on a label to help to reduce clinical errors.
- An indication of variability of the compounds should be included, as CDMP materials will be derived from natural ingredients.

Recommendation 5: The ACMD recommends that all CDMPs should have a clear content description. The description should, as a minimum requirement, state the content of CBD and THC (in mg per unit dose or volume) in a manner that would inform the prescriber when making a clinical decision. Consideration should be given to what additional information would be helpful to prescribers.

Route of administration

The ACMD previously identified potential risks related to inappropriate prescribing and diversion of CDMPs. In addition to providing a clear content description, the form and specific dosing instructions should, as with any other prescription, be clearly stated on the prescription. The ACMD recommends that the route of administration be included as an additional prescription requirement for CDMPs. The ACMD does not anticipate that smoking will be a permissible route of administration of a CDMP as there is evidence of harms associated with smoking *Cannabis*. [14]

Recommendation 6 The DHSC and NHS England (and their equivalents in Scotland, Wales and Northern Ireland) to ensure that the route of administration is stated on prescriptions to help to ensure patient safety and reduce diversion. Producers of CDMPs should be required to state the appropriate route of consumption of their product. CDMPs should not be administered by smoking.

Capturing clinical outcomes

Expanding upon the Government's intention to establish a national registry to capture levels of prescribing, the ACMD recommends that mechanisms should be set in place

[14] **Lee, M. and Hancox, R. J.** (2011) 'Effects of smoking cannabis on lung function', *Expert Review of Respiratory Medicine*, 5:4, pp 537–547.

to collect, collate and publish the clinical outcomes of the prescription and use of CDMPs, as this will help to build understanding of their benefits and harms.

Recommendation 7: The ACMD recommends that the DHSC (and its equivalents in Scotland, Wales and Northern Ireland) establishes mechanisms to capture and publish the clinical outcomes of the prescription and use of CDMPs.

Clinical trials

A programme of clinical trials should be co-ordinated:

- to establish a credible evidence base to understand the short- and long-term safety of using CDMPs;
- to identify specific clinical conditions and indications; and
- to enhance clinical decision making.

Recommendation 8: The National Institute for Health Research (NIHR) to work with DHSC and NHS England (and their equivalents in Scotland, Wales and Northern Ireland) to co-ordinate and support a programme of clinical trials to establish a credible evidence base for short and long-term safety and clinical indications.

Implementation and review of interim proposals

Communications strategy

At present the demand for CDMPs is unknown. However, judging from other countries that have made CDMPs available, the demand could potentially be high. The ACMD advises that the Government carefully considers the likely demand in the UK. It is critical that there is clear information disseminated regarding the introduction of CDMPs prior to the implementation of the proposed approach. The potential benefits and limitations of prescribing CDMPs should be clearly described for clinicians, patients and their relatives prior to the introduction of CDMPs. Those responsible for law enforcement will also require information specific to these products.

Recommendation 9: The Home Office, DHSC (and its equivalents in Scotland, Wales and Northern Ireland) and MHRA to develop a robust communications strategy for the public, clinicians and law enforcement to ensure that coherent messages are conveyed prior to and following the proposed rescheduling. This should clarify when these products are likely to be prescribed and the route by which they can be prescribed.

Encouraging licensed products in an emerging CDMPs market

The ACMD notes that the supply of unlicensed CDMPs will initially be largely through importation. It is however likely that the UK market will develop. As the UK market matures, it is desirable that CDMPs with MHRA marketing authorisation and

associated safety and quality checks become more widely available. To expedite the transition from the use of 'specials' to the use of licensed medicinal products, the Government should encourage pharmaceutical companies developing CDMPs to apply for MHRA marketing authorisation.

Recommendation 10: The DHSC and MHRA to consider methods to encourage pharmaceutical companies to apply for MHRA marketing authorisation for CDMPs.

Review of interim proposals

The time interval between the proposed interim guidance and the development of the NICE guidance will provide an opportunity for the Government to explore international models on the clinical use of CDMPs. In addition to the ongoing ACMD work, the Government should review the outcomes and consequences of the proposed interim approach, including any changes in legislation.

Recommendation 11: The Home Office and DHSC (and its equivalents in Scotland, Wales and Northern Ireland) to commit to undertaking an evidence-based review of the proposed interim approach. The ACMD looks forward to the findings of this review being made available to inform our longer-term work.

We would welcome the opportunity to discuss our conclusions and recommendations.

Yours sincerely,

Dr Owen Bowden-Jones
Chair of the ACMD