

ACMD

Advisory Council on the Misuse of Drugs

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Victoria Atkins MP
Parliamentary Under Secretary of State for Crime, Safeguarding and Vulnerability
2 Marsham Street
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22 December 2017

Dear Minister,

RE: Legitimate use of controlled drugs: research and healthcare

In July 2017, the Home Secretary wrote to the Advisory Council on the Misuse of Drugs (ACMD), outlining the Council's work programme for the next three years. This programme included a commission for the ACMD to determine whether there was more the Home Office could do to facilitate legitimate research involving compounds which are in Schedule 1 to the Misuse of Drugs Regulations 2001 (MDR).

It is the ACMD's aim to provide advice to the Home Office with respect to the harms caused by dangerous drugs whilst avoiding unnecessary restrictions to legitimate research.

The ACMD has undertaken an initial consultation with research community representatives (Annex 1) and the Home Office and we are now in a position to inform you of our progress. As this is a complex area, this advice will require additional work and consultation by the ACMD to scope the benefits and risks across the entire supply chain, potential unintended consequences and international obligations before we can provide our final advice. This is our interim advice; at the moment these are proposed solutions for the Home Office to consider. We would welcome your feedback on the feasibility of these options, after which we will consult and develop our final recommendations next year.

Considering the breadth of research and the stages in the supply chain, it is unlikely there will be a 'one size fits all' solution. It has been suggested by research

community representatives that a blanket research exemption, similar to that in the Psychoactive Substances Act 2016 (PSA) is desirable. However, the ACMD understands that this may not be feasible due to the narrowly defined offences of the PSA, the known harms of substances covered under the Misuse of Drugs Act (MDA) and the potential to create loopholes but we will consult further to fully evaluate this option.

Requirements under the Misuse of Drugs Regulations 2001

The MDR sets out the different requirements for the legitimate handling of compounds controlled under the MDA. Substances are classified into five schedules according to their medicinal value and perceived risk: Schedule 1 contains those of no medicinal value, Schedule 2 contains those of medicinal value but with high abuse potential and Schedules 3/4/5 contain those with widespread medicinal use. The additional requirements for work with Schedule 1 substances involve obtaining a Home Office Schedule 1 licence, following safe custody regulations and record keeping.

Within the five schedules of the MDR, compounds are either listed individually by name or are captured under a generic definition replicated from the MDA. Generic definitions have been developed to capture groups of compounds that are closely related in structure to potential "designer drugs" that are often created to circumvent those named in the MDA.

The research supply chain

The ACMD has examined the three broad areas within the research supply chain conducted in industry, academia and other research organisations:

- Discovery research (drug and non-drug related)
- Development activity
- Clinical studies.

A number of different sites may be involved during the development of a medicine and as research can involve the movement of compounds between different countries, these sites will need to obtain import and export licences for Schedule 1 controlled compounds.

Discovery research (drug and non-drug)

Discovery research can cover both drug-discovery research, for example, by pharmaceutical companies, biotech companies and academic units, and non drug-discovery research, for example, by academic institutions and industry.

A typical programme in the drug-discovery phase for medicinal development can begin with a library of ~2 million compounds at the screening stage, stored in plates at low volumes and concentrations in a non-recoverable form. Once the properties of

the library are characterised, the compound optimisation work can involve synthesis of hundreds of compounds either in-house or by Contract Research Organisations (CROs) at a global level, at various amounts of material varying from milligrams to kilograms (*submission received from ABPI et al*).

Discovery research compounds which are in Schedule 1 of the MDR and are moved between collaborative partners or research sites would be subject to licences and controls, including import and export licences.

Research organisations in industry and academia keep libraries of compounds and testing is usually carried out on screening plates, involving small amounts of substances in non-recoverable form. Schedule 1 compounds, which are used in drug development, need to be kept in locked cabinets, which can be problematic for library compounds stored in multi-well plates in a computerised repository.

There appears to be a lack of clarity on the restrictions on the use and movement of small amounts of Schedule 1 compounds. The ACMD is not aware of specific guidance for the research community around Schedule 1 requirements.

There is already an 'exempt product' definition in Section 2 of the Misuse of Drugs Regulations for small quantities of controlled substances which are in a non-recoverable form and not for human consumption. This was originally intended to facilitate the use of test kits for testing biological samples for traces of controlled drugs. There should be guidance which clarifies whether this exemption can be utilised or further developed to cover multi-well screening plates such as those used for drug discovery. If such an exemption is enabled, we would expect screening activities within the pharmaceutical and biotechnology industries and in academic drug discovery groups to be able to proceed without undue restriction.

Feedback received from the research community was that it would be helpful to provide academic institutions with a single organisational licence to exempt the institution from the requirements of Schedule 1. After an initial review, the ACMD does not feel that a blanket exemption is workable as there is considerable potential for unintended consequences and thus we propose to consult further before giving advice on the matter.

Development activity

The current challenges for the research community during the development stage include the variable amounts of compounds used in development and the need to keep samples in locked cabinets.

Feedback received from research community representatives included the need to be able to identify potential drugs without barriers, perhaps by way of an organisational licence, to cover all those institutions working with a particular substance, or an all institution exemption from Schedule 1 requirements (as

mentioned above), but even if this is feasible, further work will be needed to adequately define a research group or organisation.

The most workable solution that has arisen so far is to allow industry to claim an exemption for a compound by stating it does not have activity that would bring it under the requirements of Schedule 1, notwithstanding it being covered by a generic, on the understanding that they have the supporting data and structure on file even though they may not be able to reveal this for reasons of confidentiality and may only be able to provide the company number for the compound in question. Establishing whether this is legally practicable requires further work and consultation.

Clinical studies

This stage involves active clinical research trials, which often use multiple sites, which may not all have Schedule 1 licences. The clinical trials area is already a heavily regulated space with requirements imposed by Health Research Authority (HRA) research ethics committees.

There are potential delays to clinical research as compounds within the scope of the MDR which move into trials in humans need to obtain appropriate licences and put practical arrangements in place for clinical trial sites (e.g. storage of compounds).

For Schedule 1 compounds proceeding into clinical trials, provided that the sponsor can send a detailed investigator's brochure and ethical committee approval to the Home Office, which establishes that the compound can be safely tested in humans, the ACMD proposes that the Home Office should allow such compounds to be expeditiously moved to a temporary 'research schedule' with reduced requirements for the purpose of clinical evaluation. If clinical trials continue, this status can be maintained but if trials fail then the compound would revert to Schedule 1. Should a compound get as far as product registration then the legal status of the resulting marketed medicine would be determined in the usual manner.

Case study: 3rd generation synthetic cannabinoids

The ACMD published advice on the third generation of synthetic cannabinoids in December 2014. This advice recommended a generic definition under the MDA, placing these compounds under Class B of the MDA due to the harms and widespread availability and under Schedule 1 of the MDR, as the ACMD could not confirm any medicinal uses identified at the time.

Following the implementation of the advice, representatives of the research community informed the ACMD that the broad scope of the generic definition had captured a large number of research compounds and a limited number of potential medicinal drugs, some of which are not likely to be CB1 agonists.

By capturing a larger number of compounds, the research institutions are now in a position where they must ensure compliance with the additional requirements of the

Schedule 1 Misuse of Drugs Regulations for these now controlled compounds. Unintended consequences reported by the research community have included:

- Many more compounds now under the scope of the MDR
- Additional regulatory and logistical burden on industry
- Lack of awareness and difficulties with enforcement

In addition, the ACMD is considering the possibility of a **‘self-policing’ approach** whereby a research body or “sponsor” would apply to the Home Office for a compound-specific exemption in the MDA without disclosing the chemical structure but using a unique identifier from the sponsor. This might allow compounds that were covered by the generic but which were of interest because of, for example, novel non-cannabinoid activity to progress through the drug discovery and development pipeline without hindrance. However, this option may render the UK unable to meet the International Narcotics Control Board (INCB) requirements to monitor and report on UN-listed Schedule 1 materials.

Proposed solutions (longer term)

The ACMD proposes the following solutions below, on which we will welcome the Home Office’s feedback before we begin further necessary work:

1. The Home Office to consider a ‘self-policing’ approach to allow drug-discovery researchers to apply to the Home Office for a compound-specific exemption using a unique identifier from the sponsor. Industry is used to professional regulation of, for example, its promotional activities and the imposition of sanctions for non-adherence so a similar regimen may be applicable to drug discovery.
2. That Schedule 1 compounds with a complete investigator’s brochure and HRA-ethical committee approval be temporarily moved to a ‘research schedule’ for the purpose of clinical evaluation. It is our understanding that the risk of diversion and misuse in a research setting is likely to be minimal.
3. The ACMD is mindful of the concerns of some pre-clinical researchers with respect to the psychopharmacological and neuroscientific research in the UK with Schedule 1 drugs. A proposed measure may be the extension of the import/ export licence validity period. We would like to consider this area of research further in our future discussions.

Recommendations (to cover the shorter term)

1. The Home Office to produce detailed guidance aimed at the research community to clarify the Schedule 1 licensing requirements, in particular, those concerning small volumes of compounds on screening plates. If needed a specific screening exemption should be written into the MDR.

2. The ACMD recommends a revision of the generic definition for synthetic cannabinoids in order to reduce the scope.

The ACMD considers that a revision of the generic definition is necessary to reduce the scope of the definition (Annex 2). Although this revision will be part of a broader solution, the ACMD considers that replacing the term “univalent” with a defined number of substituents will reduce the number of compounds unintentionally captured by the generic definition while retaining those compounds that have been found to cause harms. Owing to the continued harms posed by 3rd Generation Synthetic Cannabinoids, the ACMD does not recommend a repeal of the generic definition.

Next Steps

Subject to receiving feedback from the Home Office on the above proposals, the ACMD’s Technical Committee will continue dialogue with the Home Office and stakeholders and would aim to provide further advice by April 2018.

I look forward to hearing from you.

Yours sincerely,

A handwritten signature in black ink, appearing to read "Owen Bowden-Jones". The signature is fluid and cursive, with the first name "Owen" being the most prominent.

Dr Owen Bowden-Jones
Chair of the ACMD

Rt Hon. Amber Rudd MP, (Home Secretary)
Rt Hon. Jeremy Hunt MP, (Secretary of State for Health)
Steve Brine MP (Minister for Public Health and Primary Care)

Annex 1: Research community representatives and Government Departments/ Agencies Consulted

The Academy of Medical Sciences
Pistoia Alliance
Association of the British Pharmaceutical Industry
Academy of Medical Sciences
Academy/Royal Society Fellow
British Pharmacological Society
Royal Pharmaceutical Society
DrugScience
Home Office
Department of Health
Public Health England
Health Research Authority
Medical Research Council
Office for Life Sciences
Medicines and Healthcare Regulatory Products Agency
Representative of Contract Research Organisations
Representative of Biotech Community
Royal Society of Chemistry

Annex 2: Revised Generic Definition

A review of the chemical structures of more than 130 3rd generation synthetic cannabinoids found that alkyl, halide, phenyl and halophenyl groups were the most frequently encountered univalent substituents. Other less frequently encountered substituents included cyano (as in AM2232, 4-cyano CUMYL-BUTINACA and Cumyl-4CN-BINACA), alkoxy (MN-25 and 2-Me MN-25) and benzyl (5-fluoro BEPIRAPIM) groups. Alkyl groups can also be replaced by alkenyl or haloalkyl groups without significantly changing the structure-activity relationship. Likewise a halophenyl substituent can be replaced by a phenyl group bearing other small substituents and a benzyl substituent can be replaced by a similarly substituted benzyl group.

There are a few active compounds with unusual substituents, e.g. N,N-diethylcarboxamide (MCHB-1), although this compound has high selectivity for CB₂ over CB₁ (K_i = 3.7 and 110 nM, respectively), and hydroxyethyl (Pfizer Compound 171). The earlier generations of synthetic cannabinoids also included a few compounds with hydroxy and nitro substituents, so these might also be incorporated into new synthetic cannabinoids structures.

Two options were therefore considered for reducing the scope of the generic definition whilst retaining control of the vast majority of existing 3rd generation synthetic cannabinoids together with some ‘future proofing’ of the legislation. The first option specified which univalent substituents are included in the generic definition, whilst the second option attempted to define the univalent substituents in terms of which types of atoms they can contain and a maximum permitted number of carbon atoms. The latter approach has not previously been used in the Misuse of Drugs Act 1971 and, when applied, was found to be not very effective in excluding the licensed medicines which are currently excluded by name.

The first option restricted the type of univalent substituents to alkyl, alkenyl, halide, haloalkyl, alkoxy, cyano, phenyl, benzyl and substituted phenyl and benzyl groups. The importance of including the cyano group is highlighted by a recent EU Early Warning System alert regarding deaths associated with Cumyl-4CN-BINACA.

The reduced scope of this option excludes all of the licensed medicines and the two Class A drugs currently excluded by name and will exclude many materials of potential pharmaceutical interest .

The suggested wording for a revised version of the current generic control is therefore:

“Any compound (not being a compound for the time being specified in sub-paragraph (c) above) structurally related to 1-pentyl-3-(1-naphthoyl)indole (JWH-018), in that the four substructures, that is to say the indole ring, the pentyl substituent, the methanone linking group and the naphthyl ring, are linked together in a similar manner, whether or not any of the sub-structures have been modified, and whether or not substituted in any of the linked sub-structures with a benzyl or phenyl group and whether or not such compound is further substituted to any extent with alkyl, alkenyl, alkoxy, halide, haloalkyl or cyano substituents and, where any of the sub-structures have been modified, the modifications of the sub-structures are limited to any of the following, that is to say—

- (i) replacement of the indole ring with indane, indene, indazole, pyrrole, pyrazole, imidazole, benzimidazole, pyrrolo[2,3-b]pyridine, pyrrolo[3,2-c]pyridine or pyrazolo[3,4-b]pyridine;*
- (ii) replacement of the pentyl substituent with alkyl, alkenyl, benzyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl, 2-(4-morpholinyl)ethyl or (tetrahydropyran-4-yl)methyl;*
- (iii) replacement of the methanone linking group with an ethanone, carboxamide, carboxylate, methylene bridge or methine group;*
- (iv) replacement of the 1-naphthyl ring with 2-naphthyl, phenyl, benzyl, adamantyl, cycloalkyl, cycloalkylmethyl, cycloalkylethyl, bicyclo[2.2.1]heptanyl, 1,2,3,4-tetrahydronaphthyl, quinolinyl, isoquinolinyl, 1-amino-1-oxopropan-2-yl, 1-hydroxy-1-oxopropan-2-yl, piperidinyl, morpholinyl, pyrrolidinyl, tetrahydropyranyl or piperazinyl.”*