ACMD

Advisory Council on the Misuse of Drugs

Considerations of barriers to research

Part 1: Synthetic cannabinoid receptor agonists (SCRA)

30th July 2021

Contents

1. Introduction

1.1. Synthetic cannabinoid receptor agonists (SCRA) are chemicals that stimulate the endogenous cannabinoid receptors (CB_1 and CB_2) within the body. The over-activation at the CB_1 receptor produces the intoxicating effects sought by users. The SCRA entering the novel psychoactive substances (NPS) market are those with structures that target the CB_1 receptor [ACMD, 2014; Antonides *et al*, 2016; Banister *et al*, 2016].

1.2. In July 2009 the Advisory Council on the Misuse of Drugs (ACMD) advised that SCRA should be put in Class B under the Misuse of Drugs Act 1971 (MDA) and Schedule 1 in the Misuse of Drugs Regulations 2001 (MDR) [ACMD, 2009]. This was adopted in late 2009 [UK Legislation, 1971, SI 2009/3209; 2001, SI 2009/3136].

1.3. Instead of controlling a compound by name some regulations control a compound through a description of a chemical structure, which provides broad coverage to cover multiple chemicals; this is called a generic definition. In the MDA, SCRA have been controlled using both generic definitions and by naming individual compounds [UK Legislation, 1971, SI 2009/3209, 2013/239, 2016/1109, 2019/1373; 2001, 2009/3136, 2013/176, 2016/1125, 2019/1362].

1.4. Within SCRA a relatively small change to the chemical structure can produce a vast number of chemicals with similar effects. These chemicals are easy to synthesise and so producers could modify the chemical structure to be uncontrolled whilst maintaining psychoactive effects. The generic definition was introduced to try and anticipate this.

1.5. In December 2016 the MDA and the MDR were amended to include a generic definition for third generation synthetic cannabinoids [UK Legislation, 1971, SI 2016/1109; 2001, p. SI 2016/1125]. This amendment, however, inadvertently also controlled a large number of compounds that had no CB_1 activity, and thus are not SCRA compounds. In July 2017 the then Home Secretary wrote to the ACMD asking the Council to review the barriers to research caused by the inadvertent control of non-SCRA compounds.

1.6. The ACMD's initial advice of December 2017 included potential short- and long-term solutions [ACMD, 2017]. In January 2019 the short-term advice was accepted; this included revising the third generation generic definition [UK Legislation, 1971, SI 2019/1373; 2001 SI 2019/1362], but the long-term suggestions were all deemed unfeasible. The scope of the generic definition was revised to better capture the compounds known to cause harms while reducing the number of compounds unintentionally described. The number of individual potential structures included by the revised definition is still extremely large, and will cover potentially harmful SCRA as well as inadvertently some compounds with little or no CB_1 activity, some of which may have potential legitimate uses.

1.7. The objective of this report is to facilitate high quality research in the UK. The ACMD has formulated recommendations to reduce the barriers to research caused by the generic third generation SCRA definition following a call for evidence, consideration

of international approaches and additional representations from the research community.

1.8. Further recommendations (in a future ACMD report) will provide advice on barriers to research with controlled drugs more generally, not specific to compounds controlled by the generic third generation SCRA definition.

1.9. A summary of the types of research can be found in *Legitimate use of controlled drugs in research and healthcare* [ACMD, 2017] and in Annex H I of this report.

1.10. As SCRA are in Schedule 1 under the MDR they require a domestic licence to produce/possess/supply/offer to supply within the UK and an import/export licence to take compounds across the UK border. Annex B provides a summary of the drug licensing process in the Home Office.

2. Barriers to research experienced under current regulations

2.1. In February 2020 the Advisory Council on the Misuse of Drugs (ACMD) invited submissions for written evidence [ACMD, 2020] from researchers regarding barriers to legitimate research with controlled drugs, specific to synthetic cannabinoid receptor agonists (SCRA). The following section summarised the findings of this call for evidence. A summary of the quantitative information received can be found in Annex E but as the sample size was small this might not be representative.

2.2. The evidence takes into account submissions provided to the ACMD from the research community since the 2017 report.

2.3. Respondents to the ACMD's call for evidence included UK contract research organisations (CROs), companies from the pharmaceutical industry, royal societies, non-profit organisations, individual university researchers and other stakeholders. These different types of organisations highlighted varying problems.

Barriers to research relating to SCRA

Academia

2.4. Academic research can involve substances that are known to be SCRA as well as unintentionally covering non-SCRA compounds that happen to be within the scope of the generic control covering SCRA (but are not SCRA as they are not a cannabinoid receptor [CB_1] agonist). As identified in the call for evidence, three out of eight universities used SCRA and two out of eight universities used compounds controlled as SCRA (see Case Study 5) with written and verbal input from the research community.

2.5. Academic research is funded by grants, which are paid by a third party with conditions on how the money is spent and over what time period.

2.6. There was no evidence submitted to the ACMD about the risk of diversion that academic research presents. However, the risk of diversion is likely to vary depending on the type of research and compound being used.

The following are themes that emerged from the call for evidence.

2.7. **Awareness of controlled drug status:** The call for evidence identified that there was some lack of awareness of the legislation and regulations around controlled drugs (as evidenced by Case Study 5). This has worsened as the software used to identify controlled compounds, including those described under the third generation generic definition of SCRA, is expensive therefore use is not widespread in academia. Only one out of nine university respondents to the call for evidence reported having computer software to identify compounds that are controlled. The generic definitions are also considered more complicated to follow in comparison to individually named compounds.

2.8. **Time:** The process to obtain a domestic licence is reported to take roughly one year, with some reports of this process taking longer. This was compounded by ignorance of the legislation and regulations, which might cause a delay to start a licence application. As grants are usually time limited, this can be a substantial proportion of a three-year grant (as evidenced by Case Study 1 and Case Study 2).

2.9. **Cost:** The cost of licences, the Disclosure and Barring Service (DBS) checks and installing storage that fulfil safe custody requirements (when using compounds in higher schedules the compounds must be kept within a safe of a certain standard, this is set out by the safe custody requirements) were highlighted as substantial in comparison to the size of a grant. This was especially the case when compared against other substances that do not have these requirements.

2.10. **Bureaucracy:** The process of obtaining a licence was considered highly bureaucratic by academic researchers, with multiple steps of evaluation (see Annex B). Navigating this process was viewed as unclear by academics.

2.11. **Opportunity loss:** With it being more difficult to undertake research with these compounds in comparison to ones not described by the third generation generic definition, it is less likely that the evidence to support reclassification and control under the Misuse of Drugs Regulations 2001 (MDR) will be conducted.

2.12. **Collaboration:** The restriction of licences to one building does not permit collaboration between departments of universities, which may use multiple buildings for research involving these compounds (as evidenced by Case Study 2). Academics usually belong to international communities and compounds are regularly sent over borders. This means that there is a need to be aware of legislative requirements in other countries.

Conclusion 1

Academic researchers use both SCRA and compounds without CB_1 activity that are unintentionally described by the third generation generic definition. The barriers to research mainly stem from limited resources, be it time or money caused by the structure of academic grants. It takes roughly a year for a new research project to obtain a domestic licence at a substantial cost in comparison to the total grant. These barriers can cause a loss of opportunity as it is harder for the UK to participate in a global research community.

Pharmaceutical companies

2.13. Pharmaceutical companies are unlikely to take compounds with significant CB_1 activation into drug development and clinical trials. Therefore they are mainly concerned with the compounds without CB_1 activity, which include those compounds that are unintentionally described by the third generation SCRA definition.

2.14. These companies will usually keep these compounds in small plates that contain multiple (96, 384 or 1,536) ‘wells’, each with a different compound in.

2.15. Companies usually operate across multiple countries so may need to transfer compounds across borders. They have access to large funds to apply the most stringent regulations, and have access to status-finding software. However, they are adversely affected by the number of compounds that are controlled.

2.16. In the call for evidence, all three respondents from pharmaceutical companies reported that the compounds tested in their institution's drug discovery programmes were in practice not recoverable in quantities that would pose a threat to public health, after dissolution and dilution in organic solvents such as dimethyl sulfoxide (DMSO). Therefore risk of diversion is low.

2.17. The December 2016 third generation generic definition was reported to have increased the number of compounds controlled in their libraries by between 8.5 and 150 fold. The November 2019 revision reduced the number of compounds affected considerably (by up to between 60 and 91%). However, there were still many controlled compounds described by the generic definition within their libraries.

2.18. **Time:** Companies have to spend a lot of time applying for licences for multiple sites (as each licence applies only to one building) rather than having a whole legal entity licence.

2.19. **Cost:** Compliance software is essential for finding compounds using generic definitions. However, there are other generic definitions than just for SCRA, which is a significant cost even for larger companies. Safeguarding and record keeping controlled compounds is considered costly (this is not specific to industry), especially as they are regularly in plates with multiple wells that contain some compounds that are controlled and some that are not. Normally these organisations have compliance teams for controlled compounds.

2.20. **Time:** Controlled substances that require to be moved between sites are regularly delayed due to the time taken to get an import/export licence (as evidenced by Case Study 4).

2.21. **Opportunity loss:** As a result of the introduction of the generic definition for third generation SCRA, some companies are restructuring so that they do not investigate controlled compounds in the UK, as well as using non-UK based CROs for testing (as evidenced by Case Study 4). As pharmaceutical companies stored between 6,000 and 13,000 compounds that were controlled as SCRA, this will lead to a loss of knowledge and research being undertaken in the UK (as evidenced by Case Study 6). This research will be carried out in other countries (as evidenced by Case Study 4).

Conclusion 2

Pharmaceutical companies have reported using non-SCRA compounds that are described by the third generation generic definition. The main reported barriers to research stem from the number of controlled compounds, i.e. having to apply for multiple licences, safe storage, record keeping and moving substances across borders. This is causing international pharmaceutical companies to consider moving operations to countries with fewer restrictions.

Contract research organisations

2.22. CROs are contracted to undertake research on certain compounds, such as assessment of CB_1 activity on behalf of a pharmaceutical company. They will regularly be sent large libraries of compounds and they usually have access to a status-finding software. In the call for evidence two out of three CROs said they were using such software.

2.23. Similarly to pharmaceutical companies, compounds are regularly diluted in DMSO. Therefore they are in a form that would require specialist equipment to recover the original compounds. The quantities involved are small and are associated with a low risk of diversion. Regularly clients will provide plates with multiple wells, some containing controlled compounds.

2.24. **Cost:** Safeguarding controlled compounds is costly, especially as they are mixed with non-controlled examples and are hard to separate.

2.25. **Collaboration**: CROs find it hard to interact with international pharmaceutical companies due to import/export restrictions.

2.26. **Time:** The time lost in negotiations having to inform international clients about the UK scheduling of compounds that are not controlled in other territories.

Conclusion 3

CROs commonly investigate compounds controlled in the UK as SCRA. The main barriers to research for CROs are moving compounds across borders and international collaboration. This is caused by the regulations requiring safe keeping, record keeping and paperwork for moving compounds. This is causing a loss of opportunity as companies look to countries where it is easier to carry out this research.

De minimis limit

2.27. The call for evidence sought information on the quantity of samples required for research. This section details the findings of this. The '*de minimis* limit' comes from the exempt product definition in the MDR. If under 1mg (with the exception of LSD) is used for scientific or diagnostic purposes, as specified by the exempt product definition, no controls apply to it.

2.28. To anchor this discussion for a medium potency SCRA, JWH-018, a study demonstrated that doses as low as 2mg can induce unpredictable psychological effects in humans that vary from weak to moderate [Theunissen *et al*, 2019]. The minimum dose to elicit a pharmacological response will vary with the potency of the SCRA on the CB_1 receptor.

2.29. Whilst some *in vitro* tests (tests that are performed outside the usual biological context, such as in a test tube) can be carried out on 1mg samples, quantities of up

to 10mg can be required for a single test. A 100mg quantity is typically required for all tests required in academic research or drug discovery stage research.

2.30. The following table contains the typical quantities of compounds used in the different stages of drug discovery provided in evidence submission.

Table 1: Typical quantities for drug discovery testing provided in research submission

Assay type	Purpose	Typical amount of product consumed
Quality control	Quality, identity, purity	2–10mg
Activity testing	Confirmation and assessment of action on biological target	2–10mg
Physico-chemical assessment of absorption, distribution, metabolism and excretion (ADME) selectivity	Solubility, factors that may determine route of administration or formulation challenges	2–10mg
	In vitro assessment of potential for drug uptake, routes of administration, enzyme responses, delivery to target disease area and potential toxicology	1–5mg per assay per screen type. Total 5–25mg
	Assessment that drug targets only the disease vector	1–5mg per assay
Allowance for repeat assays		10–50mg
Total		100mg

2.31. **Academic settings**: In conversation with the research community and through the call for evidence usually no more than 100mg of a compound will be required to carry out most research activities. However, it might be stored in forms where the controlled compound is recoverable.

2.32. **Pharmaceutical companies and CROs**: The respondents to the call for evidence and research submissions report 50 to 100mg of a compound would be sufficient for testing and initial drug discovery. However, larger quantities would be required for further drug development (250mg to 10g, equalling 10,000mg).

Conclusion 4

Typically 100mg of a compound or less is needed for the initial stages of drug research in industry and academia. Within industry it is usually stored in a format where the compound is unrecoverable whereas this is not necessarily the case in academic settings.

3. Analysis

3.1. This report has highlighted that there are perceived barriers to the research with compounds controlled as synthetic cannabinoid receptor agonists (SCRA). However, these must be balanced against the need to minimise the risk of diversion and to control substances that have been found to be harmful, as presented in previous Advisory Council on the Misuse of Drugs (ACMD) reports on SCRA.

3.2. Before formulating the following recommendations, seven options were considered by the ACMD, with their potential benefits and drawbacks listed in Annex G. The four main proposals were:

- to maintain the status quo;
- control compounds by their endogenous cannabinoid receptor (CB_1) activity;
- repeal the third generation SCRA definition; and
- define research organisations to allow different rules for these.

3.3. Making no changes was considered. The current system functions with a cost to the user in both time and money; however, this should be considered proportional to the risk that some of the compounds controlled under the third generation SCRA definition pose. A balance between the risk of diversion within the policy adopted has to be weighed against this cost and the associated risks of research not being undertaken, or being carried out in other countries.

3.4. It is difficult to quantify the risk of diversion that a change in policy provides. However, an international comparison (in Annex C) highlighted how lighter touch regulations appear to provide no additional risk of diversion. Consequently, the ACMD decided to recommend a change in policy to lower these barriers, with monitoring undertaken.

3.5. Removing the controls on compounds that have been proven to have no CB_1 activity would reduce the number of compounds inadvertently described by the third generation generic definition. However, the practicalities of defining this in law, and wanting to make rules simple to follow made this option infeasible.

3.6. Repealing the third generation SCRA definition and going back to naming compounds would stop all barriers to research with the compounds controlled as third generation SCRA. However, this would rely on the Psychoactive Substances Act 2016 (PSA) to stop the sale of these compounds and would require the Government to consider all new compounds that prove to have psychoactive effects. Individually naming compounds removes a level of future-proofing provided by the generic definition and would increase the legislative burden, making this option infeasible.

3.7. The last option considered was defining ‘research organisations’ and setting different rules for these organisations. These rules would be different for the *de minimis* limit for all third generation SCRA and would not require import/export licences for most third generation SCRA. The main downside to this will be the need to define a research organisation and how to check this definition with no licensing required.

3.8. The definition of a research organisation needs to be clearly defined so as to minimise misuse of these compounds. There are examples of such definitions in other legislation, such as the PSA (see Annex H). However, the ACMD's understanding of this is that it cannot be applied to the MDA as it only covers research on humans. Therefore, a bespoke definition for the MDA is required.

3.9. When defining 'research organisation' (Recommendation 1) it is essential that it covers research in following locations:

- academic research institutions;
- contract research organisations; and
- pharmaceutical companies.

The definition should not be so broad to risk diversion to illicit markets. When the definition used in the PSA was formulated, officials consulted with the research community. This should once again be considered in the development of the definition of 'research organisation'.

3.10. The new *de minimis* limit of 100mg was supported by the call for evidence and would facilitate drug discovery by removing the need for a licence in most cases (Conclusion 4). The ACMD also agreed it was sufficiently low as to minimise the risk of diversion, although there are some SCRA that are sufficiently potent to cause psychoactivity at doses significantly below 100mg. The proposed *de minimis* limit does not provide sufficient amounts for later stage drug development or clinical trials, but the numbers of compounds being tested in later stages of development are sufficiently small to cause minimal barriers to industry.

3.11. The amendment, similar to the exempt product definition, should allow the utilisation of 100mg per site or preparation, rather than per organisation.

3.12. To facilitate cross-border collaborative research the ACMD recommends 'research organisations' do not require import/export licences for amounts below the *de minimis* limit. This would apply to all compounds described by third generation generic SCRA definition with the exclusion of 'green list' compounds. This is to exclude those compounds already recognised as used in illegal markets internationally and to keep the UK compliant with its obligations in international law.

3.13. The lack of import/export licences could have workload implications for the Border Force. They would need to determine if:

- the compound weighed less than 100mg;
- the compound was controlled under the generic third generation SCRA definition; and
- the intended recipient was a legitimate research organisation.

The rules surrounding this would need to be clear-cut and not open to interpretation. Similar schemes are in effect such as the Raw Tobacco Approval Scheme [Home Office, 2016].

3.14. This will still require researchers to obtain a Letter of No Objection (LoNO), at no cost to the user, from the Home Office's Drugs and Firearms Licensing Unit (DFLU)

if compounds were imported or exported to/from a country in which the compounds were controlled. It is likely that these proposed changes will have financial and workload implications for the DFLU as more research organisations move from the charged import/export licence to the free LoNO.

3.15. Changing the existing exempt product recommendation was not considered as the proposals should only apply to research organisations and should not require the compound to be unrecoverable.

4. Recommendations

4.1. The Advisory Council on the Misuse of Drugs (ACMD) proposes the recommendations below to encourage legitimate research whilst ensuring that the correct checks and balances apply. All proposed recommendations ensure that the UK remains compliant to the United Nations Office of Drugs and Crime (UNODC) Convention on Psychotropic Substances [UNODC, 1971] whilst lowering the administrative burden on all legitimate research organisations. See Annex C for an explanation of the international controls and Annex D for a list of controlled compounds.

Recommendation 1

To ensure that proposed changes only apply to legitimate research, the ACMD recommends that the Home Office defines the term ‘research organisation’.

Lead organisations: Home Office.

Measure of impact: This will have been implemented by a change to the Misuse of Drugs Regulations 2001 (MDR).

Recommendation 2

The ACMD recommends that the MDR should be amended to permit such ‘research organisations’ to produce/possess/supply/offer to supply a 100mg *de minimis* limit for compounds described under the synthetic cannabinoid generic definition of the Misuse of Drugs Act 1971 (MDA) and the MDR.

Lead organisations: Home Office.

Measure of impact: This will have been implemented by a change to the MDR.

Recommendation 3

The ACMD recommends that the MDR should also be amended to permit ‘research organisations’ defined in recommendation 1 to import/export up to 100mg of synthetic cannabinoids, except those that come under international control.

Lead organisations: Home Office.

Measure of impact: This will have been implemented by a change to the MDR.

Annex A List of abbreviations used in this report

Abbreviation	Name
ACMD	Advisory Council on the Misuse of Drugs
ADME	Absorption, distribution, metabolism and excretion
CB_1/CB_2	Endogenous Cannabinoid Receptors
CoPS	Convention on Psychotropic Substances
CPS	Crown Prosecution Service
CRO	Contract research organisation
CSA	Controlled Substances Act 1970
DBS	Disclosure and Barring Service
DEA	United States Drug Enforcement Agency
DFLU	Drugs and Firearms Licensing Unit at the Home Office
DMSO	Dimethyl sulfoxide
INCB	International Narcotics Control Board
LoNO	Letter of No Objection
mg	Milligram
MDA	Misuse of Drugs Act 1971
MDR	Misuse of Drugs Regulations 2001
MDSCR	Misuse of Drugs (Safe Custody) Regulations 1973
MHRA	Medicines and Healthcare products Regulatory Agency
NDS	National Drugs control System
NPS	Novel psychoactive substance
PO	Purchase order
PSA	Psychoactive Substances Act 2016
SCRA	Synthetic cannabinoid receptor agonists
UN	United Nations

UNODC	United Nations Office of Drugs and Crime

Annex B Licence flow charts

The Home Office's Drugs and Firearms Licensing Unit (DFLU) provided the following steps to explain the controlled drug licensing process:

- applying for an import/export licence; and
- applying for a domestic licence.

Import/export licence

Step 1: Register on National Drugs control System (NDS)

- Companies must register on the NDS (online) before they can apply for any import or export licence. The registration is free.
- If the registration is accepted the company can apply for a drugs licence.
- If the registration is refused the company can apply again when they can address the reasons for refusing their account application (i.e. no domestic licence). Each registration received is considered carefully on its merits, taking account of the ability of the applicant to comply with regulatory standards and their ability to satisfy the requirements of other relevant regulatory bodies in order to be issued with a licence under the terms of the Misuse of Drugs Regulations 2001 (MDR).
- The processing of the registration is reliant on the information provided by the applicant and validation with internal domestic licensing records. Where all relevant information is in place the registration can be approved within two to five working days of receipt.

Step 2: Add trading establishments

- Companies must apply to add their 'trading establishments' to their NDS account.
- Trading establishments are commercially sensitive to many companies and the list is not public or visible to all NDS users.
- This only needs doing once for each 'trading establishment'.
- If the 'establishment' already exists on the NDS (i.e. another licensee trades with it) it can be added by the DFLU, otherwise the licensee must submit an electronic portal request to add the establishment.
- The processing of a trading establishment request is reliant on the information provided by the applicant and validation of this, potentially with overseas competent authorities; two to five working days should be allowed for this process.

Step 3: Add 'preparations' to account

- Companies must apply to add their 'preparations' to their NDS account.
- Preparations can be commercially sensitive and/or unique to companies and the list is not public or visible to all NDS users.
- This only needs doing once for each 'preparation'.
- If the 'preparation' already exists on NDS (i.e. another licensee trades in it) it can be added by the DFLU, otherwise the licensee must submit electronic portal request to add the preparation.

- The processing of the preparation request is reliant on the information provided by the applicant and validation of base-drug content (internally, against the International Narcotics Control Board's [INCB's] conversion factors and medicines compendia). Two to five working days should be allowed for this process.

Step 4: Apply for import or export licence

- All applications are made online.
- Supporting documentation – such as import authorisations, copies of purchase orders or declarations – may need to be uploaded with the application.
- The applicant can apply for up to four different 'products' of the same type (narcotic or psychotropic) on one permit (though all compounds controlled as 3rd generation SCRA by the generic definition count only as one compound).
- Applications are typically processed next working day.

Step 5: Decision

- Each application is considered against international drug estimates for the UK and the other importing/exporting competent authority estimates.
- Checks are made that the stated drug content is correct (base drug), drug details match import permits and permits/documents are genuine.
- Validation of applications may be required with other agencies or authorities.
- If an application is refused, reasons are given – it cannot be re-opened or 'held over' – the company must re-apply.
- All licences are issued electronically, typically the next working day. The service standard time is up to seven to ten working days.
- They are single use only – imports are valid for up to three months from the date pf issue of the licence, exports are valid for up to two months from issue.

Step 6: Fees

- Each licence costs £24 – the size of shipment (one box/one vial/one pallet) does not matter.
- Invoices are issued monthly in arrears.
- Non-payment leads to account suspension.

Domestic licence

Step 1: Register online

- As for the import/export licence above, companies must register on the NDS (online) for free before they can apply for a domestic drugs licence.
- If the registration is accepted they can apply for a drugs licence, otherwise the company can submit another registration but must address the points for the reason for refusal.
- Each registration received is considered on the ability of the applicant to comply with regulatory standards and to satisfy the requirements of other relevant regulatory bodies in order to be issued with a licence under the terms of the MDR.

- The processing of the registration is reliant on the information provided by the applicant. Where all relevant information is in place the registration can be approved within two working days of receipt.

Step 2: Disclosure and Barring Service (DBS)

- Before submitting an application form those named on the application must obtain a DBS check:
    - the person in charge;
    - the person in charge of regulator compliance;
    - the person in charge of security; and
    - authorised witness(es).
- This is done by an online application and requires documentation.
- It costs £56.09 per person to get an enhanced DBS check.

Step 3: Licence application

- A new domestic licence costs between £3,133 and £4,700 depending on the use of the substance. Renewal applications cost £1,371 or £326, depending on whether a compliance visit is required.
- The Licence application can be done online but it will require an inspection of the single building it applies to.
- A drugs activity list and supporting documentation must be submitted with the application. These include:
    - protocols;
    - Medicines and Healthcare products Regulatory Agency (MHRA) and ethic approvals;
    - Maps; and
    - business proposals.

Step 4: Triage

- All applications undergo a triage to establish the licensing history (if applicable) and whether:
    - the correct application has been submitted against the policy;
    - the company holds other regulatory licences/registrations and valid DBS checks; and
    - the company has submitted the relevant supporting documentation.
- All new licensees, new sites, changes in legal entity and upgrades are signposted for a compliance visit. Renewal cases are visited every three to five years on a rolling basis.
- Renewal cases, downgrades, change in company name and change in authorised witness will be assigned to a paper-based desk decision where a visit is not required.
- Applications can be rejected at this stage.

Step 5: Paper-based consideration

- All applications are considered on a case-by-case basis.

- The licensing history, DBS checks, application and supporting documentation is reviewed and considered.
- A proposed decision on whether to grant or refuse a licence is made and sent to a senior manager to review.

Step 6: Compliance visit preparation

- All applications are considered on a case-by-case basis. Before a compliance visit can be arranged the applicant must have submitted all relevant information and have a realistic prospect of being granted a licence.
- The applicant must have obtained any applicable other regulatory licences/registrations.

Step 7: Compliance visit

- This is an arranged visit that audits and assesses the applicant's premises, security, procedures and operations in accordance with the Misuse of Drugs Act 1971 and associated MDR regulations.
- There is generally a 12 to 16 week lead-in time for a visit, and this depends on the applicant submitting all the relevant information.

Step 8: Compliance visit consideration

- All applications are considered on a case-by-case basis.
- The information gathered from the compliance visit, the licensing history, DBS checks, the application and supporting documentation is reviewed and considered.
- A proposed decision on whether to grant or refuse a visit is made and sent to a senior manager to review.

Step 9: Decision review

- The application is reviewed by a senior manager.
- If the application is refused the applicant would be notified in writing.
- If the application is granted an invoice will be raised and the relevant fee levied.

Step 10: Fees

- Invoices are raised against the details provided within the application form.
- Delays often occur at this stage if the applicant has failed to provide a purchase order number.

Step 11: Licence issued

- Controlled drug licences are valid for one year.
- Industrial hemp licences are generally valid for three growing seasons.
- Licences are issued electronically.

Annex C International perspective

Convention on Psychotropic Substances, 1971

All signatories (the UK is one) have agreed to abide by the United Nations Office of Drugs and Crime (UNODC) Convention on Psychotropic Substances, 1971 (CoPS) [UNODC,1971].

The convention establishes an international control system for psychotropic substances. It responded to the diversification and expansion of the spectrum of drugs of abuse and introduced controls over a number of synthetic drugs according to their abuse potential on the one hand and their therapeutic value on the other.

Approximately 20 individual compounds (Annex D), currently defined (as at June 2021) as synthetic cannabinoid receptor agonists (SCRA) in UK law, are contained in Schedule 2 of the International Narcotics Control Board (INCB) 'green list' [INBC, 2020]. These are controlled by the CoPS.

For these Schedule 2 compounds the CoPS holds the UK to the following.

a) Require a licence for the industrial use of these. However, "*The provisions ... of this article relating to licensing or other similar control measures need not apply to persons duly authorized to perform and while performing therapeutic or scientific functions.*" (Article 4)

b) "... *require a separate import or export authorization, on a form to be established by the Commission, to be obtained for each such export or import whether it consists of one or more substances*." Moreover, "*The Government of the importing country or region, when the importation has been effected, shall return the export authorization with an endorsement certifying the amount actually imported, to the Government of the exporting country or region*." (Article 12)

c) "... *provide to the United Nations (UN) annual statistical reports ... In regard to each substance ... on quantities manufactured, exported to and imported from each country or region as well as on stocks held by manufacturers*." (Article 16)

The SCRA controlled by the CoPS are known to be endogenous cannabinoid receptor (CB_1) agonists and therefore are likely to have little industrial interest to the research community. However, they may still be of interest to academics.

Currently the Home Office licensing procedures ensure compliance with the CoPS and provide the data for the Home Office to report to the UNODC. Any new rules must also allow for this.

China

Chemical factories in China are considered the main producers and exporters of SCRA. As a signatory of the UN drug conventions, materials under UN controls are controlled within

China. In addition, China has brought an extensive range of other novel psychoactive substances (NPSs), including 48 more individually named SCRA, under national control.

As part of an expansion of its controls on NPS, and in response to the continuing appearance of novel SCRA not yet individually listed for control, China has recently introduced a set of generic controls on SCRAs, covering a very wide range of core structures and modifications. This change is intended to impose a blanket ban on the production of SCRA within China. The new generic controls are broad and include '4th generation' SCRA core structures not yet controlled by the UK's Misuse of Drugs Act. Controlling SCRA production within China can be expected significantly to influence the types and quantities of such materials encountered in other parts of the world, including the UK.

The Chinese drug control regulations include a process for exemption from control should materials be found to have application in medicine, industry, scientific research or in other lawful purposes as set out in paragraph 2 of Article 3 of the "Measures for the listing of non-medicinal narcotic and psychotropic drugs". Paragraph 1 of Article 3 sets out the state bodies which can make adjustments to which materials are subject to control. [NNCC, 2021]

USA

The USA's system of drug control is built around two key elements:

- the Controlled Substances Act 1970 (CSA), which individually lists controlled materials; and
- the Controlled Substance Analogue Enforcement Act 1986 ('the Analogue Act'), which extends control to cover materials that are substantially similar both in structure and effect to materials listed in Schedules I or II of the CSA.

The profusion of novel structures encountered as NPS, and particularly as SCRA, and the requirement of the Analogue Act to be able to demonstrate similarity of structure to an already-controlled material, has meant that a series of additions to the CSA have been made, which provide points of comparison for the many SCRA variants being identified within the NPS market in the USA.

The Synthetic Drug Abuse Prevention Act 2012 (SDAPA), in force since July 2012, amended the CSA by the legislative placing of 'cannabimimetic agents' (cannabinoids) and 26 substances (including 15 cannabimimetic agents, 9 phenethylamines and 2 cathinones) in Schedule I. The amendment introduced for the first time a broad definition of 'cannabimimetic agents' and provided an administrative mechanism to the Attorney General (delegated to the United States Drug Enforcement Agency [DEA] administrator) to administratively schedule substances meeting the cannabimimetic agents' definition. A number of synthetic cannabinoid substances are reported to be currently under assessment in an effort to demonstrate that the substances meet the two-pronged cannabimimetic agents requirements:

- substance binds to the CB_1 receptor; and
- substance has CB_1 activity in a functional assay.

There are no general exemptions for research within the US system. The DEA routinely grants exemptions for specific chemical preparations if they are:

- formulated in such a way that they do not present significant potential for abuse;
- intended for laboratory, industrial, educational or special research purposes; and
- not for general administration to a human being or animal.

The DEA has found relatively few barriers to research.

Germany

Germany lists an extensive range of individual SCRA (more than 60) within Schedule II of their Federal Narcotics Act [Betaubungsmittelgesetz, 2020].

In addition, it has recently adopted generic controls on several types of NPS, including SCRA, as part of its New Psychoactive Substances Act (NpSG). The German SCRA generic is similar to the UK's, but is broader in scope as it reflects some recently reported structural variants that are outside the UK's current generic definition. Even so limitations are placed on the maximum size or mass of some components, which serve to limit the coverage of their control.

Section 3 of the NpSG is stated below (non-official translation).

"It is prohibited to traffic a NPS, to put it into circulation, to manufacture it, bring it into, outside or through the territory to which this Act applies, acquire it, own it or administer it to others. The following uses are excluded from the prohibition:

- *uses of a NPS recognized to be in line with the state of the art in science and technology for commercial, industrial or scientific purposes; and*
- *uses of a NPS by federal or state authorities for their official business and by authorities appointed by them to investigate NPS."* [Bundesministerium, 2020].

The NpSG provides a research exception within it. In this regard, companies and facilities do not need any official permit or exemptional approval for recognised uses of NPS. The German Government is not aware of any barriers to research and never heard any complaints from stakeholders in Germany. So far there are no known cases that illicit drug suppliers/producers attempted to defend themselves by claiming that they were doing scientific research in line with the state of the art in science and technology. It is also noted that it would first of all be the duty of the investigating authorities and the public prosecutor´s office to show and prove that the defendants have committed the accused actions. If the defendants claimed that they had been doing scientific research, investigating authorities and the prosecutor would have to prove that this had not been the case. The judge/court would have a very close look at the individual case and would consider and examine the circumstances, if needed with the support of experts.

Switzerland

Switzerland makes exemptions for certain low dose substances in Article 4 of their drug control legislation. An unofficial translation of this exemption follows [Fedlex, 2013].

"1. The provisions of this Regulation do not apply to:

A. homeopathic preparations that contain controlled substances but whose dilution is more than D8/C4;

B. Precursors and auxiliary chemicals in pharmaceutical preparations or mixtures that cannot be easily recovered from them.

2. The supply and use of small quantities of controlled substances for analytical purposes by authorities or by direct agents of them shall be excluded from this Regulation.

3. The supply and use of controlled substances in solution and in a concentration of up to 1mg per 1ml for analytical purposes are excluded from Chapter 6 (Control) of this Regulation."

As paragraphs 2 and 3 specify *"for analytical purposes"*, these clauses appear intended to exempt chemical reference materials for use by, for example, forensic and toxicology laboratories. They also specify the end users who can take advantage of this exemption.

Belgium

Similarly, in Section 5 of Article 31 of the Royal Decree of 2017, Belgium makes exceptions from import/export controls for certain materials intended for analytical use by certain organisations, subject to a 1mg/ml concentration and a maximum volume of 1ml.

"An import or export authorisation is not required for the following products, insofar as these are used for analytical purposes:

1. *preparations with a concentration not exceeding 1 mg/ml and a maximum content of 1 ml per preparation on condition that the laboratories concerned report to the Belgian Early Warning System on Drugs;* [and]
2. *small quantities of products, which exclusively contain substances referred to in Annex IV** [*Annex IV lists the materials controlled under Belgian law, including generic controls on amphetamines, cathinones, fentanyls, SCRAs, tryptamines and piperazines].

Should a foreign government still require a Belgian import authorisation, then the FAMHP will supply a 'letter of no objection' (LoNO)." [FAMHP, 2017].

Guernsey

Guernsey has adopted the UK's three-legged 'exempt product clause' (found in the MDR), but has extended and clarified this by adding a further specification that the exemption only applies to analytical reference materials, and also specifies the end user.

The additional requirement is worded as follows:

"(b) the preparation or other product is used, or intended to be used, only as analytical reference material by an authorised analyst." [Guernsey Legal Resources, 1997, Section 1]

Annex D List of controlled compounds under UNODC Convention on Psychotropic Substances, 1971

At the international level, synthetic cannabinoid receptor agonists (SCRA) are being controlled under Schedule II of the 1971 United Nations Office of Drugs and Crime (UNODC) Convention on Psychotropic Substances [UNODC, 1971]. Materials controlled under this convention are set out in the annually updated 'List of Psychotropic Substances under International Control' (the 'green list'), issued by the International Narcotics Control Board [INCB,2020]. The April 2021 green list includes 20 SCRA, of which 2 (indicated by *) were added during 2021:

- AB-CHMINACA;
- ADB-CHMINACA;
- 5F-ADB (5F-MDMB-PINACA);
- AB-PINACA;
- AM-2201;
- 5F-APINACA (5F-AKB-48);
- CUMYL-4CN-BINACA;
- FUB-AMB (MMB-FUBINACA);
- ADB-FUBINACA;
- JWH-018;
- MDMB-CHMICA;
- 5F-PB-22;
- UR-144;
- XLR-11 (5F-UR-144);
- AB-FUBINACA;
- 5F-AMB PINACA (5F-AMB, 5F-MMB-PINACA);
- 5F-MDMB-PICA;
- 4F-MDMB-BINACA;
- *MDMB-4en-PINACA; and
- *CUMYL PEGACLONE.

The UNODC placed the latest two additional SCRA (MDMB-4en-PINACA and Cumyl-PeGaClone) onto the green list at its 64th session in April 2021. Signatories to the convention, including the UK, have up to six months to bring these materials under their national controls.

MDMB-4en-PINACA is already controlled by the generic control on SCRA within the UK's Misuse of Drugs Act 1971. However, CUMYL-PEGACLONE is a 'fourth generation' SCRA and is outside the scope of the UK's current generic control on SCRA.

Annex E Quantitative data from call for evidence

The table below contains all the quantitative data from the call for evidence.

Table *AE.1*: Quantitative answers to call for evidence

Questions	Academic		Industrial			Joint
	Other	University	CRO	Other	Pharma	Society
Number of responses	**1**	**8**	**3**	**2**	**3**	**2**
Q4: Barriers from individually named compounds	0	7 (88%)	2	0	1	1
Q4: Barriers from generic definition	0	3 (38%)	3	1	3	2
Q5: Access to computational software	0	1 (13%)	2	1	2	0
Q6: Research on SCRA	0	2 (25%)	2	0	1	1
Q6: Research other compounds classed as SCRA	0	3	3	1	2	2
Q7: Organisation has regulatory burdens	0	7	3	1	3	2
Q7: Organisation has financial burdens	0	8 (100%)	3	1	1	2
Q7: Organisation has time burdens	0	6 (75%)	2	1	3	2
Q8: Direction is affected by these burdens	0	6	2	1	2	2

Notes*: CRO = contract research organisation; SCRA = synthetic cannabinoid receptor agonists.*

Although some organisations did not use compounds controlled as SCRA, other barriers related to Schedule 1 compounds. These responses have been omitted in the following table.

Table AE.2: Quantitative answers to call for evidence from organisations that use compounds controlled as SCRA

Questions	Academic	Industrial			Joint
	University	CRO	Other	Pharma	Society
Number of responses	**5**	**3**	**1**	**3**	**2**
Q4: Barriers from individually named compounds	4	2	0	1	1
Q4: Barriers from generic definition	3	3	1	3	2
Q5: Access to computational software	0	2	1	2	0
Q6: Research on SCRA	2	2	0	1	1
Q6: Research other compounds classed as SCRA	3	3	1	2	2
Q7: Organisation has regulatory burdens	4	3	1	3	2
Q7: Organisation has financial burdens	5	3	1	1	2
Q7: Organisation has time burdens	5	2	1	3	2
Q8: Direction is affected by these burdens	4	2	1	2	2

Notes: CRO = contract research organisation; SCRA = synthetic cannabinoid receptor agonists

When reading this the limitations of the data received should be considered. With low responses there is high uncertainty. Also organisations that experience few barriers to research or are ignorant of the regulation have little motivation to respond. Please note the societies represent multiple organisations in one combined response to the call for evidence.

Annex F Case studies from call for evidence

This section presents case studies provided by the call for evidence. This is qualitative evidence demonstrating typical problems confronted.

Case Study 1. *"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 £3,000 inspection/application fee and £1,500 per annum. I now have funding but my university safety officer says it will take another three to six months before a licence can be obtained. I cannot apply for an import licence (my drugs come from National Institutes of Health 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 three-year grant project."*

Case Study 2. *"We had to wait one year to obtain our controlled drugs licence to investigate effects of cannabinoids in rats. This is an enormous delay! The form requires work, the holder must have a Disclosure and Barring Service check from Security Watchdog costing £56.09, which further adds to the delay. We must store the drugs in an alarmed and locked cabinet. We cannot move the drugs outside of our building. This means that a colleague working on the same project in another building could not work under the permission of our controlled drugs licence. To have one licence for each building within an institution is very restrictive, expensive and time-consuming (for us and the Home Office) and does not enable academic collaboration, which is essential for the success of research.*

It cost us £3,133.00 to obtain the licence to possess controlled drugs and it now costs £326 each year to maintain it. If a visit from a controlled drugs licensing inspector is required for renewal of the licence then a fee of £1,371 needs to be paid. We also had to buy lockable fridge-freezer, for storage in the controlled drugs designated room, costing £600. This is absolutely prohibitive for most academics. As our work is funded by a pharmaceutical company we can pay this fee, but most academics do not have that luxury. I have asked other academics about this (animal researchers like myself) and most say they cannot do this work because they do not have the funding available and their university won't fund it."

Case Study 3. *"A second major impact with the scheduling system is that there are now very few suppliers willing to synthesise the products, which has resulted in a marked increase in the cost of many of these products. We experienced this with mephedrone, which we were originally able to secure from a small commercial company; I think they decided it was not worthwhile them holding the appropriate licences to synthesise the product so it was discontinued. I also believe (but would need to check this) that many companies only keep small stocks of Schedule 1 drugs in the country and many compounds often have to be imported before they can be supplied in the UK, which results in often very significant delay to the supply to universities, and extra cost."*

Case Study 4. *"Synthesis, compound management and testing facilities are distributed globally and are totally reliant on fast and efficient shipment of compounds across borders to the appropriate testing facilities. Research is carried out not only in pharmaceutical institutes, but also at several UK-based and global*

contract research organisations. With thousands of compounds now in the scope of the new legislation, obtaining the necessary export and import licences delays movement of samples so as to render our research timelines unworkable. This had led to research programs being moved out of the UK."

Case Study 5. *"We heard from an academic whose PhD student was researching molecular probes to identify new cancer therapies. The compounds they were investigating, substituted benzimidazoles, were captured by the third generation generic definition. They became aware of the issue only when purchasing chemicals for the synthesis and asked to produce a Schedule 1 licence. These compounds, made via a complex synthesis, were not expected to be* [endogenous cannabinoid receptors] *CB_1 agonists and therefore would not be expected to exhibit psychoactive activity. The university did not have a Schedule 1 licence and as it would have taken nine months to obtain a licence at an expensive cost, not covered by the research grant, the student was unable to continue researching in this area. The impact of this was that the student had to change the direction of research and relocate to the company sponsoring the research, which held a Schedule 1 licence, slowing down the development of new therapies."*

Case Study 6. *"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."*

Annex G Options considered

Option	Benefits	Drawbacks
<u>Option 1:</u> Permit research organisations (which should be defined in legislation) to possess/supply a 100mg *de minimis* limit for compounds described by the synthetic cannabinoid generic definition of the Misuse of Drugs Act 1971/Misuse of Drugs Regulations 2001 (MDA/MDR), to facilitate the initial stages of drug discovery.	• This option would facilitate the initial stages of drug discovery, as evidence suggests that the quantity of compounds required for the relevant assays is roughly 100mg. • The research community had previously noted that the initial stages of drug discovery would be the appropriate point to introduce a *de minimis* limit. • With the *de minimis* limit only applying to synthetic cannabinoids, ultra-potent compounds (e.g. fentanyls) would not be exempt from control via this mechanism. • Defining 'research organisation' in legislation would ensure that only bona fide organisations can access the 100mg *de minimis* exemption • A 100mg *de minimis* limit applicable to synthetic cannabinoids would allow a research organisation to legally utilise a sufficient quantity of compound to run assay(s) to test for endogenous cannabinoid receptors (CB_1) agonism. • Research organisations have submitted evidence to note that only negligible quantities of compound would be recoverable after the initial stages of drug discovery (usually in dimethyl sulfoxide [DMSO] solvent).	• A number of synthetic cannabinoids will be harmfully potent at sub-100mg levels (i.e. it is not just fentanyls that are a concern in this respect). • Option 1 could be perceived as a missed opportunity to extend such a mechanism wider (i.e. beyond synthetic cannabinoids). • If 'research organisations' are not precisely defined in legislation, illegitimate bodies may attempt to utilise the *de minimis* limit. • Could be challenging to define 'research organisations' in legislation – the definition would need to cover academia, pharmaceutical organisations, contract research organisations (CROs), etc. If the definition was not precisely set, some bona fide organisations may fall outside of that definition. It could arguably be preferable not to strictly define 'research organisations' in legislation, and simply to allow the prosecution to pursue any instances where it appears that illegitimate bodies are attempting to utilise the *de minimis* limit – as has been done in German legislation. The definition

	• Option 1 would to allow the UK to remain in line with its international obligations – paragraph 2 of Article 3 of the United Nations Office of Drugs and Crime (UNODC) 1971 Psychotropic Convention (which says that substances that are compounded in such a way to present no or negligible risk of abuse – and which cannot be recovered by readily applicable means in a quantity liable to abuse so that the preparation does not give rise to a public health and social problem – may be exempted).	would also have to allow the utilisation of 100mg <u>per site</u>, rather than <u>per organisation</u>. • To utilise this exemption, research organisations would have to make sure that only 100mg of a compound is held at any one time – there could not be any overlap, e.g. if a laboratory had 20mg of a compound remaining after running a number of assays, it would be unlawful for a postal order of another 100mg to arrive until the remaining 20mg was destroyed/used. • Need to ensure that chemical suppliers are protected from prosecution in the event that a researcher purchases multiple samples of 100mg of a compound without first using up all 100mg of the compound that had been in their possession.
<u>Option 2</u>: (As per Option 1) Permit research organisations (which should be defined in legislation) to import/export up to 100mg of synthetic cannabinoids without requiring a Home Office licence.	• Option 2 would facilitate cross-border research. • A number of the compounds controlled as 'synthetic cannabinoids' under UK legislation will not be controlled in other countries – this option will alleviate the barriers to research with such compounds. • This option would allow the cross-border transfer of a sufficient quantity of a compound to enable the conduct of a	• A number of synthetic cannabinoids are controlled under the UN drug conventions (See Annex C for UNODC regulations and Annex D for list of controlled substances) – this option may therefore be incompatible with the UK's reporting obligations under the UN drug conventions. • Challenges (as per Option 1) in effectively defining 'research organisations' to avoid illegitimate import/export of synthetic

	range of assays in the initial stages of drug discovery. • This option could conceivably include only the synthetic cannabinoids that are not covered by the UN drug conventions (see 'drawbacks' column, see Annex C for UNODC regulations, and Annex D for list of controlled substances). • Although the financial cost of an import licence is limited (only £24), there is an administrative cost – for example, respondents to the call for evidence reported seeing delays in obtaining a Letter of No Objection from some countries to import/export something that is not controlled in those countries, but is in the UK.	cannabinoids, while extending the measure to the relevant bona fide organisations. • Import/export licences are only £24 and are issued the next working day – and import/export licences for synthetic cannabinoids (in a significant departure from the normal process, which would ordinarily require every controlled drug to be licensed for import/export to be listed by chemical name) already cover <u>all</u> synthetic cannabinoids (in recognition that some compounds may have been inadvertently captured). • The onus would be on the Border Force to determine whether an import would be legitimate or not (including whether the compound is a synthetic cannabinoid. Does it weigh more than 100mg? Was it from a legitimate research organisation?). Operationally difficult for them – e.g. the Border Force has previously mistakenly intercepted legitimate Cannabis based products for medicinal use. The alternative (i.e. not intercepting packages that they are unsure about) risks misuse if illegitimate importers attempt to disguise another compound (e.g. fentanyl) as a synthetic cannabinoid. • It is unclear whether this option would have a significant impact. Since 2017

		(when the third generation synthetic cannabinoids definition was created), only a small number of import/export licences have been issued for synthetic cannabinoids each year (approximately less than 50 a year). • If the driver of this option is mostly to facilitate cross-border research with compounds that do not display CB_1 agonism, there would be an argument that a revision of the generic definition of synthetic cannabinoids would be the more appropriate solution.
<u>Option 3</u>: Introduce an exemption into the MDR for compounds where CB_1 receptor agonist activity is not known and that are intended to be used for research purposes.	• For compounds structurally described by the synthetic cannabinoid generic definition, but where the activity at the CB_1 receptor is unknown, this option would not place a legal obligation on research organisations to screen to check whether a compound displays CB_1 agonism. • This option would facilitate research with drugs that are captured by the synthetic cannabinoid generic definition, but where a researcher has no interest in exploring the CB_1 agonism (or lack of this) of that compound.	• Would have to define in legislation what would constitute proven CB_1 receptor activity – otherwise researchers (or others) might try to exploit this option (i.e. by stating that there is not evidence that a compound that they possess displays CB_1 receptor agonism), in order to avoid being required to obtain a Home Office controlled drug licence. How would this option be enforced? How would it be proved whether or not someone knew a compound displayed CB_1 activity? • If a compound was found to be a CB_1 agonist at a later stage, what would be the process? There would have been no limit on how much of the compound they could have handled until CB_1 agonism was proven – they

		could therefore hold a significant store of a proven CB_1 agonist, which could be a large risk of misuse/diversion. • There would be an argument that, if CB_1 agonism is not known for a set of compounds, a revision of the generic definition of synthetic cannabinoids would be the more appropriate solution. • Defining drugs under the MDA with reference to their psychoactive pharmacological effect would be novel and unprecedented – it is unclear whether the power to make this amendment to the MDR is allowed. This would require an informal view from the Joint Committee on Statutory Instruments.
<u>Option 4</u>: Introduce an exemption into the MDR for compounds currently described by the synthetic cannabinoid generic definition in the event that those compounds are proven to lack CB_1 receptor agonism.	• This option could be particularly effective in combination with Option 1. Utilising a 100mg *de minimis* limit (i.e. Option 1), would allow 'research organisations' (defined in legislation) to utilise a sufficient quantity of a compound to test for CB_1 receptor agonism. • In the event that a compound is proven to lack CB_1 activity, it could then be fully exempted from control (i.e. allowing the researcher to then utilise more than 100mg of the compound). This option would therefore allow compounds fully exempted from control to be utilised in	• As with Option 3, the Advisory Council on the Misuse of Drugs (ACMD) would have to define standardised assays that would describe whether or not a compound shows CB_1 activity – and again this could be difficult to enforce. • Would need to be used in combination with Option 1 to be truly effective – otherwise researchers would have to obtain a controlled drugs licence anyway, to be able to possess to test for CB_1 agonism. • There would be an argument that, if CB_1 agonism is not known for a set of

	research beyond the initial stages of drug discovery.	compounds, a revision of the generic definition of synthetic cannabinoids would be the more appropriate solution. • Defining drugs with reference to their psychoactive pharmacological effect would be novel and unprecedented – it is unclear whether the power to make this amendment to the MDR is allowed. This would require an informal view from the JCSI.
Option 5: Controls for compliance; supplementing the pre-existing controls in place within industry with additional controls in the event that any *de minimis* limit is introduced.	• This option was suggested by a submission from the research community, which believes that these controls would provide assurance in the event that a *de minimis* limit is implemented. • It is believed that these controls can be audited and place minimal additional administrative burden on Home Office resources. • University-based researchers are obliged to conduct research within ethical guidelines and are routinely required to have processes for storage and monitoring in place. • Could help to safeguard public safety whilst preserving the fast cycle times necessary to effectively conduct the research and develop new medicines whilst safeguarding public safety.	• It may be that some of the organisations caught under the definition of a 'research organisation' (in the event that a *de minimis* limit was implemented) would not apply the 'existing controls' reported by the representatives from the research community. There would therefore be a more significant burden for these organisations to take on all of these controls. • The scale of the administrative burden of auditing on Home Office resources is currently unclear.
Option 6: Repeal the generic definition of synthetic cannabinoids from the MDA/MDR and	• This option would immediately remove the control of compounds that do not display CB_1 agonism/have not been evidenced to cause harm in the UK.	• Potentially harmful novel synthetic cannabinoids would not be controlled by the MDA/MDR – and the mechanisms of the PSA alone may

instead simply list all of the third generation synthetic cannabinoids by name that have proven harms/prevalence in the UK.	• Researchers would not require expensive software to interrogate their chemical library to establish which compounds are controlled – it would be clear to researchers which compounds are controlled. • Significantly, it would also be easier for law enforcement to know which compounds are/are not controlled. • The synthetic cannabinoid generic definition was brought in before the Psychoactive Substances Act 2016 (PSA) – which could now provide 'cover' to prevent a displacement of use from the compounds explicitly controlled under the MDA to drugs not controlled under the MDA (which would previously, before the introduction of the PSA, have been considered 'legal highs'). With this option, if evidence of harm/prevalence in the UK *did* arise for compounds not explicitly listed under the MDA/MDR, Temporary Class Drug Orders could be used in tandem with the PSA as a 'stepping stone' for control where the ACMD does not believe that the response of the PSA is sufficiently effective [ACMD, 2019]. There is an exemption within the PSA facilitating research with substances solely controlled under the PSA (i.e. and not also the MDA/MDR).	not be felt to be robust enough to deter a displacement to these novel compounds. Could see a return to the pre-PSA 'cat-and-mouse' situation of new legislation repeatedly needing to be introduced to control compounds under the MDA. • Amending the list of compounds controlled under the MDA/MDR is a lengthy process (especially for the MDA, which requires primary legislation). • The ACMD would have to provide a current list of all the synthetic cannabinoids that had been proven to cause harm in the UK – are they all known? The ACMD would have to be careful not to miss any off the list
<u>Option 7</u>: 'Status Quo'	• The legislative change in November 2019 to reduce the scope of the synthetic cannabinoid generic definition does	• Despite the reduction in scope, it does still appear that a significant number of compounds described by

	appear to have significantly reduced the number of compounds inadvertently (i.e. in that they do not display CB_1 agonism) brought under control.	the synthetic cannabinoid generic definition would not display CB_1 agonism. • Even where a compound does, or might, display CB_1 agonism, it may be that this compound would still be of research interest – it would be important to facilitate research with these compounds. With a *de minimis* limit, properly defined, it would be unlikely that a recoverable quantity of a CB_1 agonist remained in order to represent a threat to public health (and this threat would be further negated by appropriate controls to reduce diversion). • If an appropriate solution(s) can be found to alleviate barriers to research with synthetic cannabinoids, the ACMD can then consider how/if these can be applied to other controlled drugs, more widely.

Annex H Statutory Definitions of Research

Statute	Term	Definition
Human Fertilisation and Embryology (Disclosure of Information for Research Purposes) Regulations 2010/995	Research Establishment – Regulation 2	"research establishment" means a university or other body or institution that carries out medical or other research within the United Kingdom
	Research Ethics Committee – Regulation 2	"research ethics committee" means a research ethics committee recognised or established by or on behalf of the Health Research Authority under the Care Act 2014
	Research Project Regulation 2; Regulation 4(4)(c)	"research project" means "a description of the medical or other research to be undertaken by the research establishment within the United Kingdom"
Various	Research establishment	"research establishment" means an establishment carrying out research into a designated organism.
Income Tax (Earnings and Pensions) Act 2003 NB: definition only includes public funded / not for profit research.	Research Institution– s457	"In this Chapter "research institution" means- (a) any university or other institution that is a publicly funded institution as defined in section 41(2) of the Higher Education Act 2004, or (b) any institution that carries out research activities otherwise than for profit and that is neither controlled nor wholly or mainly funded by a person who carries on activities for profit

Statute	Term	Definition
Invasive Alien Species (Enforcement and Permitting) Order 2019/527 NB: Not yet in force.	Research – Article 2	"Research" means descriptive or experimental work, undertaken under regulated conditions, to obtain new scientific findings or to develop new products, including the initial phases of identification, characterisation and isolation of genetic features (other than those features which make a species invasive) or invasive alien species in so far as essential to enable the breeding of this features into non-invasive species.
Misuse of Drugs Act 1971	Research purposes –	No definition but there is a reference to research (in the context of Schedule 1 drugs): s7(4) If in the case of any controlled drug the Secretary of State is of the opinion that it is in the public interest- (a) for the production, supply and possession of that drug to be either wholly unlawful or unlawful except for purposes of research or other special purposes… he may by order designate that drug as a drug to which this subsection applies.
Misuse of Drugs Regulations 2001	Research – Regulation 7(2)(f) & 9(2)(d)	Permission to produce and supply Schedule 2 to 5 controlled drugs: 7(2) (f) a person who is in charge of a laboratory the recognised activities of which consist in, or include, the conduct of scientific education or research and which is attached to a university, university college or such a hospital aforesaid or to any other institution approved for the purpose under this sub-paragraph by the Secretary of State. Permission to produce and supply Schedule 3 to 4 drugs: 9(2)(d) a person in charge of a laboratory the recognised activities of which consist in, or include, the conduct of scientific education or research.

Statute	Term	Definition
Psychoactive Substances Act 2016 NB: Only covers ethics-approved research and not discovery or other research.	Research - Schedule 2, para 4	**4.** Any activity carried on in the course of, or in connection with, approved scientific research. In this paragraph— *"approved scientific research"* means scientific research carried out by a person who has approval from a relevant ethics review body to carry out that research; *"relevant ethics review body"* means— (a) a research ethics committee recognised or established by the Health Research Authority under Chapter 2 of Part 3 of the Care Act 2014, or (b) a body appointed by any of the following for the purpose of assessing the ethics of research involving individuals— (i) the Secretary of State, the Scottish Ministers, the Welsh Ministers, or a Northern Ireland department; (ii) a relevant NHS body; (iii) [United Kingdom Research and Innovation or] a body that is a Research Council for the purposes of the Science and Technology Act 1965; (iv) an institution that is a research institution for the purposes of Chapter 4A of Part 7 of the Income Tax (Earnings and Pensions) Act 2003 (see section 457 of that Act); (v) a charity which has as its charitable purpose (or one of its charitable purposes) the advancement of health or the saving of lives; *"charity"* means— (a) a charity as defined by section 1(1) of the Charities Act 2011, (b) a body entered in the Scottish Charity Register, or (c) a charity as defined by section 1(1) of the Charities Act (Northern Ireland) 2008; *"relevant NHS body"* means— (a) an NHS trust or NHS foundation trust in England, (b) an NHS trust or Local Health Board in Wales, (c) a Health Board or Special Health Board constituted under section 2 of the National Health Service (Scotland) Act 1978,

Statute	Term	Definition
		(d) the Common Services Agency for the Scottish Health Service, or (e) any of the health and social care bodies in Northern Ireland falling within paragraphs (a) to (d) of section 1(5) of the Health and Social Care (Reform) Act (Northern Ireland) 2009.
Care Act 2014 NB: Useful definitions of "health research" and "social care research".	Health research - s110 (3)	Health research is research into matters relating to people's physical or mental health; but a reference to health research does not include anything authorised under the Animals (Scientific procedures) Act 1986. [Context: the Health and Research Authority's functions]
	Social care research - s110 (4)	Social care research is research into matters relating to personal care or other practical assistance for individuals aged 18 or over.. (etc.) [Not relevant to drug research].
	Research ethics committee – s112(2)	"A research ethics committee is a group of persons who assess the ethics of research involving individuals, and the ways in which health or social care research might involve individuals, include, for example ---" [see provision for full extract]. Research ethics committees established under s115 CA 2014.
Science and Technology Act 1965 NB: Useful definitions of "research councils" & scientific research.	Scientific Research – s6(1)	"In this Act "scientific research" means research and development in any of the sciences (including the social sciences) or in technology.
	Research Councils – s1	The Research Councils – (1) The following bodies established or to be established by Royal Charter shall be Research councils for the purposes of this act, that is to say,--

Statute	Term	Definition
		(c) any body which is established for purposes connected with scientific research and consists of persons appointed by a Minister of the Crown and which is declared by Order in Council to be established as a Research Council for the purposes of this Act.
Human Medicines Regulations 2012	University / Higher education research – s43A(3)	"universities or other institutions concerned with higher education or research, other than healthcare institutions". Note that there are exemptions for supply of medicinal products to "universities, other institutions concerned with higher education or institutions concerned with research" – see Schedule 17, Part 1.
Animals (Scientific Procedures) Act 1986	N/A	Controls the use of animals in research. No directly applicable definitions, but references to: • Qualifying purposes - experimental or other scientific purposes, or educational purpose - s2(1) • Project licences to be issued only for – basic research, or translational or applied research with specified aims – s5C(3)
Human Tissue Act 2004	Research – s1(9)	"Research falls within this subsection if – (a) it is ethically approved in accordance with regulations made by the Secretary of State; (b) [you can't identify the living person]. [Context: permitted research on human tissue]
Human Tissue Act 2004 (Ethical Approval, Exceptions from Licensing and Supply of	Ethical approval – Regulation 2 Research ethics	"research is ethically approved …where it is approved by a research ethics authority". "Research ethics authority" means (a) a research ethics committee recognised or established by or on behalf of the Health Research Authority under the Care Act 2014, or

Statute	Term	Definition
Information about Transplants) Regulations 2006/1260	authority – Regulation 1	(b) any other group of persons which access the ethics of research involving individuals and which is recognised for that purpose by or on behalf of the Welsh Ministers or the Department of Health, Social Services and Public Safety in Northern Ireland".
Corporation Tax Act 2010 NB: This definition of SRA is relied upon in other legislation, e.g. Controlled Waste and Duty of Care Regulations (Northern Ireland) 2013/255	Charity – s202 **Scientific Research Association – s469**	Charity - "In this Chapter "charity" includes…(b) a scientific research association as defined in section 469. **Scientific Research Association:** 469 Conditions for qualifying as a scientific research association (1) For the purposes of this Part a body qualifies as a scientific research association for an accounting period if— (a) it is an association (see subsection (5)(a)), and (b) it meets conditions A and B with respect to the accounting period. (2) Condition A is that the body has as its object the undertaking of research and development which may lead to or facilitate an extension of any class or classes of trade. (3) Condition B is that the memorandum of association or other similar instrument regulating the body's functions precludes the direct or indirect payment or transfer to any of its members of any of its income or property by way of dividend, gift, division, bonus or otherwise by way of profit. (4) For the purposes of compliance with condition B it is not necessary that the memorandum of association or other similar instrument regulating the body's functions should prevent the payment to its members of— (a) reasonable remuneration for goods, labour or power supplied, or for services provided, (b) reasonable interest for money lent, or (c) reasonable rent for premises. (5) The Treasury may by regulations— (a) make provision specifying what is to be treated as being, or as not being, an association for the purposes of subsection (1)(a), or

Statute	Term	Definition
		(b) prescribe circumstances in which a body is to be treated as not meeting condition A or B with respect to an accounting period.
Income and Corporate Taxes Act 1988	Scientific Research – s508(3)	"In this section "scientific research" means any activities in the fields of natural or applied science for the extension of knowledge. NB: Guidance available on this - here (research and development for tax purposes).
Non-Legislative Definitions		
EU Communication: Framework for state aid for research and development and innovation. Link: here	Applied Research – 15(e) p8 Experimental development – 15(j) p 9 Fundamental Research – 15(m) p 9 Industrial Research – 15(q) p10 Research organisation – 15(ee) p 11	"Applied Research" means industrial research, experimental development or any combination of both. "Experimental development" means acquiring, combining, shaping and using existing scientific, technological, business and other relevant knowledge and skills with the aim of developing new or improved products, processes or services. This may also include, for example, activities aiming at the conceptual definition, planning and documentation of new products, processes or services. Experimental development may comprise prototyping, demonstrating, piloting, testing and validation of new or improved products, processes or services in environments representative of real life operating conditions where the primary objective is to make further technical improvements on products, processes or services that are not substantially set. This may include the development of a commercially usable prototype or pilot which is necessarily the final commercial product and which is too expensive to produce for it to be used only for demonstration and validation purposes. Experimental development does not include routine or periodic changes made to existing products, production lines, manufacturing processes, services and other operations in progress, even if those changes may represent improvements;

Statute	Term	Definition
		"fundamental research" means experimental or theoretical work undertaken primarily to acquire new knowledge of the underlying foundations of phenomena and observable facts, without any direct commercial application or use in view; "industrial research" means the planned research or critical investigation aimed at the acquisition of new knowledge and skills for developing new products, processes or services or for bringing about a significant improvement in existing products, processes or services. It comprises the creation of components parts of complex systems, and may include the construction of prototypes in a laboratory environment or in an environment with simulated interfaces to existing systems as well as of pilot lines, when necessary for the industrial research and notably for generic technology validation "research and knowledge dissemination organisation" or "**research organisation"** means an entity (such as universities or research institutes, technology transfer agencies, innovation intermediaries, research-oriented physical or virtual collaborative entities), irrespective of its legal status (organised under public or private law) or way of financing, whose primary goal is to independently conduct fundamental research, industrial research or experimental development or to widely disseminate the results of such activities by way of teaching, publication or knowledge transfer. Where such entity also pursues economic activities, the financing, the costs and the revenues of those economic activities must be accounted for separately. Undertakings that can exert a decisive influence upon such an entity, for example in the quality of shareholders or members, may not enjoy a preferential access to the results generated by it.
OECDs Frascati Manual NB: OECD Frascati Manual – internationally recognised methodology for collecting and using	Research and Experimental Development (p44)	"Research and experimental development (R&D) comprise creative and systematic work undertaken in order to increase the stock of knowledge – including knowledge of humankind, culture and society – and to devise new applications of available knowledge". (para 2.5, p44) "the activity must be novel, creative, uncertain, systematic, transferable and/or reproducible. All five criteria are to be met" (para 2,6 – 2.7, p 45)

Statute	Term	Definition
research and development statistics. Link: here and here.		"The term R&D covers three types of activity: basic research, applied research and experimental development. Basic research is experimental or theoretical work undertaken primarily to acquire new knowledge of the underlying foundations of phenomena and observable facts, without any particular application or use in view. Applied research is original investigation undertaken in order to acquire new knowledge. It is, however, directed primarily towards a specific, practical aim or objective. Experimental development is systematic working, drawing on knowledge gained from research and practical experience and producing additional knowledge which is directed to producing new products or processes or to improving existing products or processes." (para 2.9, p 45).

Annex I Different types of research organisation

Theoretical research

- Any academic research that does not focus on drug discovery
- Normally is carried out by smaller organisations funded by time and size-limited grants
- May find it harder to access status-finding software
- Interested in research with SCRA and compounds controlled as SCRA
- Normally part of international communities
- Usually procures compounds through larger organisations

Drug discovery research

- Testing compounds against a biological target to see viability for drug development
- Large libraries of compounds being tested all at once with a mix of controlled and uncontrolled compounds
- Compounds will normally be synthesised on site
- Normally has access to electronic testing system for controlled drug status

Drug development and clinical trials

- Tests to see the efficacy of the drugs and improve formulation
- Will have to be ethically reviewed and scrutinised by other regulatory bodies
- Compounds at this stage will have their CB_1 activity tested
- These tests can be carried out over multiple sites
- A few compounds will be developed but larger amounts of each will be used

Annex J ACMD membership, at time of publication

ACMD membership, at time of publication	
Dr Kostas Agath	Consultant Psychiatrist (addictions), Change Grow Live Southwark
Professor Judith Aldridge	Professor of Criminology, University of Manchester
Professor Owen Bowden-Jones	Chair of ACMD, Consultant Psychiatrist, Central North West London NHS Foundation Trust
Dr Anne Campbell	Lecturer in Social Work, Queens University Belfast
Mr Mohammed Fessal	Chief Pharmacist, Change Grow Live
Dr Emily Finch	Clinical Director of the Addictions Clinical Academic Group and a Consultant Psychiatrist for South London and Maudsley NHS Trust
Professor Sarah Galvani	Professor of Social Research and Substance Use, Manchester Metropolitan University
Lawrence Gibbons MBE	Head of Drug Threat (Intelligence Directorate, Commodities), National Crime Agency
Professor Graeme Henderson	Professor of Pharmacology, University of Bristol
Dr Hilary Hamnett	Senior Lecturer in Forensic Science, University of Lincoln
Dr Carole Hunter	Lead Pharmacist at the Alcohol and Drug Recovery Services, NHS Greater Glasgow and Clyde
Professor Roger Knaggs	Associate Professor in Clinical Pharmacy Practice, University of Nottingham
Professor Tim Millar	Professor of Substance Use and Addiction Research Strategy Lead, University of Manchester
Mr Rob Phipps	Former Head of Health Development Policy Branch, Department of Health, Social Services and Public Safety, Northern Ireland
Harry Shapiro	Director, DrugWise
Dr Richard Stevenson	Emergency Medicine Consultant, Glasgow Royal Infirmary
Dr Paul Stokes	Reader in Mood Disorders and Psychopharmacology, King's College London
Dr Ann Sullivan	Consultant Physician in HIV and Sexual Health and National Co-Lead for HIV Surveillance, PHE
Professor Matthew Sutton	Chair in Health Economics, University of Manchester
Professor David Taylor	Professor of Psychopharmacology, King's College, London and Director of Pharmacy and Pathology, South London and Maudsley NHS Foundation Trust

ACMD membership, at time of publication	
Professor Simon Thomas	Consultant Physician and Clinical Pharmacologist, Newcastle Hospitals NHS Foundation Trust and Professor of Clinical Pharmacology and Therapeutics, Newcastle University
Dr Derek Tracy	Consultant Psychiatrist and Clinical Director, Oxleas NHS Foundation Trust
Ms Rosalie Weetman	Public Health Lead (Alcohol, Drugs and Tobacco), Derbyshire County Council
Dr David Wood	Consultant Physician and Clinical Toxicologist, Guys and St Thomas' NHS Trust

Annex K Membership of the ACMD's Barriers to Research Working Group

The table below gives the membership of the Barriers to Research Working Group. This report has been produced by the Working Group, with support from the Advisory Council on the Misuse of Drugs (ACMD) Secretariat.

Barriers to Research Working Group membership		
Professor Judith Aldridge	ACMD member	Professor of Criminology at the University of Manchester
Professor Graeme Henderson	ACMD member	Professor of Pharmacology at the University of Bristol
Professor Roger Knaggs	ACMD member, Working Group Chair	Associate Professor in Clinical Pharmacy Practice, University of Nottingham
Dr Paul Stokes	ACMD member	Reader in Mood Disorders and Psychopharmacology at King's College London
Dr Ann Sullivan	ACMD member	Consultant in HIV Medicine, Chelsea and Westminster Hospital Foundation Trust and National Co-Lead for HIV Surveillance, Public Health England
Professor Simon Thomas	ACMD member	Consultant Physician and Clinical Pharmacologist at Newcastle Hospitals NHS Foundation Trust and Professor of Clinical Pharmacology and Therapeutics at Newcastle University
Ric Treble MBE	Co-opted member	Formerly Chief Forensic Scientist at LGC Forensics
Dr Mike White	Co-opted member	Forensic Chemist

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