Request for Proposals: Author contributions to WHO Expert Committee on Drug Dependence (ECDD) Pre-Reviews of Cannabis-Related Substances

Request for Proposals (RFP)

Bid Reference

HQ/HIS/EMP/2017/004

Unit Name
Essential Medicines and Health Products

The World Health Organization (WHO) is seeking offers for contributions to the authorship of Pre-Review reports on cannabis-related substances for the 40th Expert Committee on Drug Dependence (ECDD). Your institution and/or any individual is invited to submit a proposal for the work in response to this Request for Proposals (RFP).

WHO is a public international organization, consisting of 194 Member States, and a Specialized Agency of the United Nations with the mandate to act as the directing and coordinating authority on international health work. As such, WHO is dependent on the budgetary and extra-budgetary contributions it receives for the implementation of its activities. Bidders are, therefore, requested to propose the best and most cost-effective solution to meet WHO requirements, while ensuring a high level of service.

- WHO requires the successful bidder, the provider, to carry out the preparation of Pre-Reviews of cannabis-related substances according to the Guidance on the WHO Review of Psychoactive Substances for International Control document (http://www.who.int/medicines/areas/quality_safety/GLS_WHORev_PsychoactSubst_IntC_2010.pdf?ua=1).
- The standard Pre-Review template comprises 19 headings. However, for the purpose of these commissioned Pre-Review reports, the standard headings have been grouped by scientific topic to cover A) Chemistry B) Pharmacology C) Toxicology D) Epidemiology and E) Therapeutic Use. Further information on the specific contents of each scientific topic can be found in the Terms of Reference (Annexes A-E)
- Interested providers are invited to submit Pre-Review proposals for one or more of these scientific topics
- One Pre-Review proposal must be submitted for each of the above scientific topics that the interested provider wishes to apply for.
- For each scientific topic, the provider will produce **four separate** Pre-Review reports in total for the following cannabis-related substances.
    - Cannabis plant and cannabis resin
    - Extracts and tinctures of cannabis
    - Delta-9-tetrahydrocannabinol (THC)
    - Isomers of THC

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The provider shall be a not for profit, research, or academic institution operating in the field of drug dependence, with proven expertise in research and evidence synthesis.

GENERAL INSTRUCTIONS

- **Please send an Acknowledgement Form to ecddsecretariat@who.int no later than 12th November 2017 to indicate whether you wish to submit a proposal**
- **Proposals for the Pre-Reviews will be accepted until 19th November 2017**
- **Final Pre-Review Reports will be due by 15th March 2018**

Bidders should follow the instructions set forth below in the submission of their proposal to WHO.

The proposal and all correspondence and documents relating thereto shall be prepared and submitted in the English language.

The proposal should be concisely presented and structured to include the following information:

- **Identify the proposed area/s of work from the following scientific topics** (As defined in the Terms of Reference)**:**
    - Chemistry
    - Pharmacology
    - Toxicology/ Adverse Effects
    - Epidemiology
    - Therapeutic Use
- **Approach/Methodology** for searching the literature and synthesizing the evidence base. Specify a plan for how aggregate data across substances will be reported against substance-specific data.
- **Proposed time line** for completion of each Pre-Review report.
- **Financial proposal** as per the template attached in the Acceptance Form or any other form of financial proposal.

Information which the bidder considers confidential, if any, should be clearly marked as such.
The bidder shall submit the complete proposal to WHO in writing no later than _____ **19th November 2017 at 18:00 hours Geneva (CET) time** ("the closing date"), by email at the following address:

ecddsecretariat@who.int.

Each proposal shall be marked Ref: **HQ/HIS/EMP/2017/004** and be signed by a person or persons duly authorized to represent the bidder, to submit a proposal and to bind the bidder to the terms of this RFP.

WHO may, at its own discretion, extend the closing date for the submission of proposals by notifying all bidders thereof in writing.

Any proposal received by WHO after the closing date for submission of proposals may be rejected.

The offer outlined in the proposal must be valid for a minimum period of 90 calendar days after the closing date. A proposal valid for a shorter period may be rejected by WHO. In exceptional circumstances, WHO may solicit the bidder's consent to an extension of the period of validity. The request and the responses thereto shall be made in writing. Any bidder granting such an extension will not, however, be permitted to otherwise modify its proposal.

The bidder may withdraw its proposal any time after the proposal's submission and before the above mentioned closing date, provided that written notice of the withdrawal is received by WHO via email as provided above, before the closing date.

No proposal may be modified after its submission, unless WHO has issued an amendment to the RFP allowing such modifications.

No proposal may be withdrawn in the interval between the closing date and the expiration of the period of proposal validity specified by the bidder in the proposal (subject always to the minimum period of validity referred to above).

WHO may, at any time before the closing date, for any reason, whether on its own initiative or in response to a clarification requested by a (prospective) bidder, modify the RFP by written amendment. Amendments could, *inter alia*, include modification of the project scope or requirements, the project timeline expectations and/or extension of the closing date for submission.

All prospective bidders that have received the RFP will be notified in writing of all amendments to the RFP and will, where applicable, be invited to amend their proposal accordingly.

Before conducting the technical and financial evaluation of the proposals it has received, WHO will perform a preliminary examination of these proposals to determine whether they are complete, whether any computational errors have been made, whether the documents have been properly signed, and whether the proposals are generally in order. Proposals which are not in order as aforesaid may be rejected.

Please note that WHO is not bound to select any bidder and may reject all proposals. Furthermore, since a contract would be awarded in respect of the proposal which is considered most responsive to the needs of the project concerned, due consideration being given to WHO's general principles, including economy and efficiency, WHO does not bind itself in any way to select the bidder offering the lowest price.

WHO may, at its discretion, ask any bidder for clarification of any part of its proposal. The request for clarification and the response shall be in writing. No change in price or substance of the proposal shall be sought, offered or permitted during this exchange.

WHO reserves the right to:

a) Award the contract to a bidder of its choice, even if its bid is not the lowest;
b) Award separate contracts for parts of the work, components or items, to one or more bidders of its choice, even if their bids are not the lowest;
c) Accept or reject any proposal, and to annul the solicitation process and reject all proposals at any time prior to award of contract, without thereby incurring any liability to the affected bidder or bidders and without any obligation to inform the affected bidder or bidders of the grounds for WHO's action;
d) Award the contract on the basis of the Organization's particular objectives to a bidder whose proposal is considered to be the most responsive to the needs of the Organization and the activity concerned;
e) Not award any contract at all.

WHO has the right to eliminate bids for technical or other reasons throughout the evaluation/selection process. WHO shall not in any way be obliged to reveal, or discuss with any bidder, how a proposal was assessed, or to provide any other information relating to the evaluation/selection process or to state the reasons for elimination to any bidder.

NOTE: WHO is acting in good faith by issuing this RFP. However, this document does not oblige WHO to contract for the performance of any work, nor for the supply of any products or services.

At any time during the evaluation/selection process, WHO reserves the right to modify the scope of the work, services and/or goods called for under this RFP. WHO shall notify the change to only those bidders who have not been officially eliminated due to technical reasons at that point in time.

WHO reserves the right at the time of award of contract to extend, reduce or otherwise revise the scope of the work, services and/or goods called for under this RFP without any change in the base price or other terms and conditions offered by the selected bidder.

WHO also reserves the right to enter into negotiations with one or more bidders of its choice, including but not limited to negotiation of the terms of the proposal(s), the price quoted in such

proposal(s) and/or the deletion of certain parts of the work, components or items called for under this RFP.

Within 30 days of receipt of the contract, the successful bidder shall sign and date the contract provided to it by WHO, and return it to WHO according to the instructions provided at that time. If the bidder does not accept the contract terms without changes, then WHO has the right not to proceed with the selected bidder and instead contract with another bidder of its choice.

All bidders must adhere to the UN Supplier Code of Conduct, which is available at the following link: https://www.un.org/Depts/ptd/sites/www.un.org.Depts.ptd/files/files/attachment/page/2014/February%202014/conduct_english.pdf

WHO reserves the right to publish (e.g. on the procurement page of its internet site) or otherwise make public the contractor's name and address, information regarding the contract, including a description of the goods or services provided under the contract and the contract value.

Any and all of the contractor's (general and/or special) conditions of contract are hereby explicitly excluded from the contract, i.e., regardless of whether such conditions are included in the contractor's offer, or printed or referred to on the contractor's letterhead, invoices and/or other material, documentation or communications.

We look forward to receiving your response to this RFP.

Yours sincerely,
Dr Gilles Forte
Coordinator

Annex A
Terms of Reference: Chemistry

- **The purpose of the Pre-Review is to synthesize existing scientific evidence about the therapeutic use and potential for dependence and abuse of cannabis-related compounds**
- Any recommendations on the scheduling of the substances are to be made by the Expert Committee, and should not be included in the Pre-Review
- The WHO Pre-Review [1] template for substances under review by the Expert Committee on Drug Dependence comprises five scientific topics:
    - Chemistry
    - Pharmacology
    - Toxicology/ Adverse Effects
    - Epidemiology
    - Therapeutic Use

- The author will complete the Pre-Review report for the scientific topic of **chemistry** based on the template found on Annex Page 7

- The author will prepare **four separate** reports on the **chemistry** of the following cannabis related compounds:
    Report 1: Cannabis plant and cannabis resin
    Report 2: Extracts and tinctures of cannabis
    Report 3: Delta-9-tetrahydrocannabinol (THC)
    Report 4: Isomers of THC
- Where authors refer to a specific compound (e.g. type of cannabis plant, extract, or isomer), they are asked to clearly indicate this in the report
- The reports will be prepared in accordance with the specific inclusion and exclusion criteria to minimise overlap and repetition of information (Annex Pages 3-6).
- The reports should include information, where feasible, in all the required sections of the template in accordance with the *Guidance on the WHO review of psychoactive substances for international control* document. The guidance document is available online at the WHO Expert Committee on Drug Dependence website: http://www.who.int/medicines/access/controlled-substances/ecdd/en/
- The reports should be presented in a manner that will facilitate an evidence-based assessment by the Expert Committee.
- The reports should be written in an objective manner without bias or opinions.

[1] Pre-Review: An initial review to determine whether a critical review is warranted. If the Expert Committee finds the information may justify scheduling or a change in the scheduling of the substance they can recommend a Critical Review. A critical review is to consider whether the Expert Committee should advise the Director-General to recommend the scheduling of, or amending of the scheduling status of, a substance.

- The reports should summarise the literature in a manner that presents the relevant information, without necessarily producing an exhaustive report. The use of existing reviews is encouraged, provided adequate referencing is utilised.
- Preliminary drafts should be submitted to the WHO ECDD Secretariat for assessment of quality and suitability for the Expert Committee. The Secretariat may request editorial changes and follow up drafts, if deemed necessary.
- The final draft of the reports will be peer-reviewed by experts from WHO's Expert Advisory Panels. This will include an evaluation of the strength of evidence presented. If there are data limitations or omissions, they will be discussed with, and adapted as needed, by the author.
- Examples of previous Pre-Reviews are available on the WHO Expert Committee on Drug Dependence website. For example, two Pre-Reviews (phenazepam and etizolam) were prepared for the 37th ECDD in 2015.
- Authors should include a comprehensive list of references, and specify the methodology used in the report

Inclusion and Exclusion Criteria for Reports

Report 1: Cannabis plant and Cannabis Resin Pre-Review

Inclusion Criteria

Studies to be included in the report are those involving:

- Cannabis as defined by the International Drug Control Conventions as "the flowering tops of the cannabis plant from which the resin has not been extracted"[2]. The term "cannabis" generally refers to a dried preparation of the flowering tops or other parts of the cannabis plant.
- Cannabis resin which is defined as "the separated resin, whether crude or purified, obtained from the cannabis plant". It is normally in solid form and is sometimes known as hashish.

Exclusion Criteria

Studies to be excluded from the report:

- Tinctures and extracts of cannabis including preparations or mixtures of cannabis substances (e.g. nabiximols)
- Pure delta-9-tetrahydrocannabinol (THC) and its four stereochemical variants
    - (-)-trans-delta-9-tetrahydrocannabinol
    - (+)-trans-delta-9-tetrahydrocannabinol
    - (-)-cis-delta-9-tetrahydrocannabinol
    - (+)-cis-delta-9-tetrahydrocannabinol
- Pure cannabidiol (CBD)
- Isomers of tetrahydrocannabinol (THC)
    - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
    - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

[2]https://www.unodc.org/documents/commissions/CND/Int_Drug_Control_Conventions/Ebook/The_International_Drug_Control_Conventions_E.pdf

Report 2: Extracts and Tinctures of Cannabis

Inclusion criteria

Studies to be included in the report are those involving:

- Cannabis extracts: this term refers to a plant extract mixture from the leaves and flowers of Cannabis sativa
- Cannabis tinctures: this term refers to specific alcohol extractions of the flowering tops or other parts of Cannabis sativa.
- Cannabis oils e.g. Butane Hash Oil, Hemp Seed Oil
- Aqueous extracts e.g. marijuana tea
- Nabiximols (e.g. Sativex®)

Exclusion criteria

Studies to be excluded from the report:

- Cannabis plant (dried preparations of the flowering tops or other parts of the cannabis plant) and cannabis resin (separated resin obtained from the plant)
- Pure delta-9-tetrahydrocannabinol (THC) and its four stereochemical variants except when delta-9-THC is extracted from the cannabis plant.
    - (-)-trans-delta-9-tetrahydrocannabinol
    - (+)-trans-delta-9-tetrahydrocannabinol
    - (-)-cis-delta-9-tetrahydrocannabinol
    - (+)-cis-delta-9-tetrahydrocannabinol
- Pure cannabidiol (CBD) when not in a preparation with other cannabis related ingredients
- Isomers of tetrahydrocannabinol (THC)
    - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
    - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

Report 3: Delta-9-tetrahydrocannabinol

Inclusion criteria

Studies to be included in the report are those involving:

- Pure delta-9-tetrahydrocannabinol that is obtained either directly from the cannabis plant or synthesised.
- The stereochemical variants of delta-9-tetrahydrocannabinol:
    - (-)-trans-delta-9-tetrahydrocannabinol (also known as dronabinol)
    - (+)-trans-delta-9-tetrahydrocannabinol
    - (-)-cis-delta-9-tetrahydrocannabinol
    - (+)-cis-delta-9-tetrahydrocannabinol

Exclusion criteria

Studies to be excluded from the report:

- Cannabis plant (dried preparations of the flowering tops or other parts of the cannabis plant) and cannabis resin (separated resin obtained from the plant)
- Tinctures and extracts of cannabis including preparations or mixtures of cannabis substances (e.g. nabiximols), except those that are pure delta-9-THC
- Pure cannabidiol
- Isomers and stereochemical variants of tetrahydrocannabinol as listed in Schedule 1 of the 1971 Convention on Psychotropic Substances
    - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
    - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H- dibenzo[b,d]pyran -1- ol
    - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene- 3-pentyl-6Hdibenzo[b,d]pyran-1-ol

Report 4: Isomers of THC

Inclusion criteria

Studies to be included in the report are those involving:

- Isomers and stereochemical variants of tetrahydrocannabinol as listed in Schedule 1 of the 1971 Convention on Psychotropic Substances:
    - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
    - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

Exclusion criteria

Studies to be excluded from the report:

- Cannabis plant (dried preparations of the flowering tops or other parts of the cannabis plant) and cannabis resin (separated resin obtained from the plant)
- Tinctures and extracts of cannabis including preparations or mixtures of cannabis substances (e.g. nabiximols)
- Delta-9-tetrahydrocannabinol (THC) and its four stereochemical variants
    - (-)-trans-delta-9-tetrahydrocannabinol (also known as Dronabinol)
    - (+)-trans-delta-9-tetrahydrocannabinol
    - (-)-cis-delta-9-tetrahydrocannabinol
    - (+)-cis-delta-9-tetrahydrocannabinol
- Cannabidiol

Template for the review report

Chemistry

Pre-Review Report: Chemistry of (*insert substance name/s)*

I. Substance identification (1)[3]

International Nonproprietary Name (INN)

Chemical Abstract Service (CAS) Registry Number

Other Chemical Names

Trade Names

(Including brand names)

Street Names

Physical Appearance

(For example: color, taste and smell)

WHO Review History

(*For example: previous reviews by the ECDD or WHO committees*)

II. Chemistry (2)

Chemical Name

IUPAC Name:
CA Index Name:

Chemical Structure

Free base:
Molecular Formula:
Molecular Weight:

Stereoisomers

Methods and Ease of Illicit Manufacturing

(*Diagrams of pathways during synthesis can be included. Effect of environment and climate on plant growth can be included*)

[3] () indicates corresponding report section in Paragraph 23: Guidance on the WHO Review of psychoactive substances for international control
http://www.who.int/medicines/areas/quality_safety/GLS_WHORev_PsychoactSubst_IntC_2010.pdf?ua=1

Chemical Properties

Melting point
Boiling point
Solubility

Identification and Analysis

(*For example: chemical spot tests, immunoassays, mass spectrometry, chromatography*)

III. Ease of Convertibility Into Controlled Substances (3)

Annex B
Terms of Reference: Pharmacology

- **The purpose of the pre-review is to synthesize existing scientific evidence about the therapeutic use and potential for dependence and abuse of cannabis-related compounds**
- Any recommendations on the scheduling of the substances are to be made by the Expert Committee, and should not be included in the pre-review
- The WHO pre-review[1] template for substances under review by the Expert Committee on Drug Dependence comprises five scientific topics:
    - Chemistry
    - Pharmacology
    - Toxicology/ Adverse Effects
    - Epidemiology
    - Therapeutic Use
- The author will complete the Pre-Review report for the scientific topic of **pharmacology** based on the template found on Annex Page 7

- The author will prepare **four separate** Pre-Review reports on the **pharmacology** of the following cannabis related compounds:
    Report 1: Cannabis plant and cannabis resin
    Report 2: Extracts and tinctures of cannabis
    Report 3: Delta-9-tetrahydrocannabinol (THC)
    Report 4: Isomers of THC
- Where authors refer to a specific compound (e.g. type of cannabis plant, extract, or isomer), they are asked to clearly indicate this in the report
- The Pre-Review reports will be prepared in accordance with the specific inclusion and exclusion criteria to minimise overlap and repetition of information (Annex Pages 3-6).
- The Pre-Review reports should include information, where feasible, in all the required sections of the template in accordance with the *Guidance on the WHO review of psychoactive substances for international control* document. The guidance document is available online at the WHO Expert Committee on Drug Dependence website: http://www.who.int/medicines/access/controlled-substances/ecdd/en/
- The Pre-Review reports should be presented in a manner that will facilitate an evidence-based assessment by the Expert Committee.

[1] Pre-Review: An initial review to determine whether a critical review is warranted. If the Expert Committee finds the information may justify scheduling or a change in the scheduling of the substance they can recommend a Critical Review. A critical review is to consider whether the Expert Committee should advise the Director-General to recommend the scheduling of, or amending of the scheduling status of, a substance.

- The Pre-Review reports should be written in an objective manner without bias or opinions.
- The Pre-Review reports should summarise the literature in a manner that presents the relevant information, without necessarily producing an exhaustive report. The use of existing reviews is encouraged, provided adequate referencing is utilised.
- Preliminary drafts should be submitted to the WHO ECDD Secretariat for assessment of quality and suitability for the Expert Committee. The Secretariat may request editorial changes and follow up drafts, if deemed necessary.
- The final draft of the Pre-Review reports will be peer-reviewed by experts from WHO's Expert Advisory Panels. This will include an evaluation of the strength of evidence presented. If there are data limitations or omissions, they will be discussed with, and adapted as needed, by the author.
- Examples of previous pre-reviews are available on the WHO Expert Committee on Drug Dependence website. For example, two pre-reviews (phenazepam and etizolam) were prepared for the 37th ECDD in 2015.
- Authors should include a comprehensive list of references, and specify the methodology used in the report

Inclusion and Exclusion Criteria for Pre-Review reports

Report 1: Cannabis plant and Cannabis Resin Pre-Review

Inclusion Criteria

Studies to be included in the report are those involving:

- Cannabis as defined by the International Drug Control Conventions as "the flowering tops of the cannabis plant from which the resin has not been extracted"[2]. The term "cannabis" generally refers to a dried preparation of the flowering tops or other parts of the cannabis plant.
- Cannabis resin which isdefined as "the separated resin, whether crude or purified, obtained from the cannabis plant". It is normally in solid form and is sometimes known as hashish.

Exclusion Criteria

Studies to be excluded from the report:

- Tinctures and extracts of cannabis including preparations or mixtures of cannabis substances (e.g. nabiximols)
- Pure delta-9-tetrahydrocannabinol (THC) and its four stereochemical variants
    - (-)-trans-delta-9-tetrahydrocannabinol
    - (+)-trans-delta-9-tetrahydrocannabinol
    - (-)-cis-delta-9-tetrahydrocannabinol
    - (+)-cis-delta-9-tetrahydrocannabinol
- Pure cannabidiol (CBD)
- Isomers of tetrahydrocannabinol (THC)
    - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
    - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

[2]https://www.unodc.org/documents/commissions/CND/Int_Drug_Control_Conventions/Ebook/The_International_Drug_Control_Conventions_E.pdf

Report 2: Extracts and Tinctures of Cannabis

Inclusion criteria

Studies to be included in the report are those involving:

- Cannabis extracts: this term refers to a plant extract mixture from the leaves and flowers of Cannabis sativa
- Cannabis tinctures: this term refers to specific alcohol extractions of the flowering tops or other parts of Cannabis sativa.
- Cannabis oils e.g. Butane Hash Oil, Hemp Seed Oil
- Aqueous extracts e.g. marijuana tea
- Nabiximols (e.g. Sativex®)

Exclusion criteria

Studies to be excluded from the report:

- Cannabis plant (dried preparations of the flowering tops or other parts of the cannabis plant) and cannabis resin (separated resin obtained from the plant)
- Pure delta-9-tetrahydrocannabinol (THC) and its four stereochemical variants except when delta-9-THC is extracted from the cannabis plant.
    - (-)-trans-delta-9-tetrahydrocannabinol
    - (+)-trans-delta-9-tetrahydrocannabinol
    - (-)-cis-delta-9-tetrahydrocannabinol
    - (+)-cis-delta-9-tetrahydrocannabinol
- Pure cannabidiol (CBD) when not in a preparation with other cannabis related ingredients
- Isomers of tetrahydrocannabinol (THC)
    - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
    - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

Report 3: Delta-9-tetrahydrocannabinol

Inclusion criteria

Studies to be included in the report are those involving:

- Pure delta-9-tetrahydrocannabinol that is obtained either directly from the cannabis plant or synthesised.
- The stereochemical variants of delta-9-tetrahydrocannabinol:
    - (-)-trans-delta-9-tetrahydrocannabinol (also known as dronabinol)
    - (+)-trans-delta-9-tetrahydrocannabinol
    - (-)-cis-delta-9-tetrahydrocannabinol
    - (+)-cis-delta-9-tetrahydrocannabinol

Exclusion criteria

Studies to be excluded from the report:

- Cannabis plant (dried preparations of the flowering tops or other parts of the cannabis plant) and cannabis resin (separated resin obtained from the plant)
- Tinctures and extracts of cannabis including preparations or mixtures of cannabis substances (e.g. nabiximols), except those that are pure delta-9-THC
- Pure cannabidiol
- Isomers and stereochemical variants of tetrahydrocannabinol as listed in Schedule 1 of the 1971 Convention on Psychotropic Substances
    - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
    - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H- dibenzo[b,d]pyran -1- ol
    - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene- 3-pentyl-6Hdibenzo[b,d]pyran-1-ol

Report 4: Isomers of THC

Inclusion criteria

Studies to be included in the report are those involving:

- Isomers and stereochemical variants of tetrahydrocannabinol as listed in Schedule 1 of the 1971 Convention on Psychotropic Substances:
    - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
    - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

Exclusion criteria

Studies to be excluded from the report:

- Cannabis plant (dried preparations of the flowering tops or other parts of the cannabis plant) and cannabis resin (separated resin obtained from the plant)
- Tinctures and extracts of cannabis including preparations or mixtures of cannabis substances (e.g. nabiximols)
- Delta-9-tetrahydrocannabinol (THC) and its four stereochemical variants
    - (-)-trans-delta-9-tetrahydrocannabinol (also known as Dronabinol)
    - (+)-trans-delta-9-tetrahydrocannabinol
    - (-)-cis-delta-9-tetrahydrocannabinol
    - (+)-cis-delta-9-tetrahydrocannabinol
- Cannabidiol

Template for the each pre-review report

Pharmacology

Pre-Review Report: Pharmacology of (*insert substance name/s*)

I. General Pharmacology (4)[3]

Routes of administration and dosage

- Clinically approved routes of administration
- Routes used for substance misuse

Pharmacokinetics

- Absorption
- Distribution
- Metabolism and Elimination

Pharmacodynamics

II. Dependence Potential (7)

(Including physical dependence effects e.g. withdrawal and tolerance)

Animal Studies

Human Studies

III. Abuse Potential (8)

(For example: drug discrimination and self-administration results)

Animal Studies

Human Studies

IV. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance (19)

[3] () indicates corresponding report section in Paragraph 23: Guidance on the WHO Review of psychoactive substances for international control http://www.who.int/medicines/areas/quality_safety/GLS_WHORev_PsychoactSubst_IntC_2010.pdf?ua=1

Annex C
Terms of Reference: Toxicology

- **The purpose of the Pre-Review is to synthesize existing scientific evidence about the therapeutic use and potential for dependence and abuse of cannabis-related compounds**
- Any recommendations on the scheduling of the substances are to be made by the Expert Committee, and should not be included in the Pre-Review
- The author will complete the Pre-Review report for the scientific topic of **toxicology** based on the template found on Annex Page 7
- The WHO Pre-Review report template[1] for substances under review by the Expert Committee on Drug Dependence comprises five scientific topics:
    - Chemistry
    - Pharmacology
    - Toxicology/ Adverse Effects
    - Epidemiology
    - Therapeutic Use
- The author will prepare **four separate** Pre-Review reports on the **toxicology** of the following cannabis related compounds:

    Report 1: Cannabis plant and cannabis resin
    Report 2: Extracts and tinctures of cannabis
    Report 3: Delta-9-tetrahydrocannabinol (THC)
    Report 4: Isomers of THC
- Where authors refer to a specific compound (e.g. type of cannabis plant, extract, or isomer), they are asked to clearly indicate this in the report
- The Pre-Review reports will be prepared in accordance with the specific inclusion and exclusion criteria to minimise overlap and repetition of information (Annex Pages 3-6).
- The Pre-Review reports should include information, where feasible, in all the required sections of the template in accordance with the *Guidance on the WHO review of psychoactive substances for international control* document. The guidance document is available online at the WHO Expert Committee on Drug Dependence website: http://www.who.int/medicines/access/controlled-substances/ecdd/en/
- The Pre-Review reports should be presented in a manner that will facilitate an evidence-based assessment by the Expert Committee.
- The Pre-Review reports should be written in an objective manner without bias or opinions.

[1] Pre-Review: An initial review to determine whether a critical review is warranted. If the Expert Committee finds the information may justify scheduling or a change in the scheduling of the substance they can recommend a Critical Review. A critical review is to consider whether the Expert Committee should advise the Director-General to recommend the scheduling of, or amending of the scheduling status of, a substance.

- The Pre-Review reports should summarise the literature in a manner that presents the relevant information, without necessarily producing an exhaustive report. The use of existing reviews is encouraged, provided adequate referencing is utilised.
- Preliminary drafts should be submitted to the WHO ECDD Secretariat for assessment of quality and suitability for the Expert Committee. The Secretariat may request editorial changes and follow up drafts, if deemed necessary.
- The final draft of the Pre-Review reports will be peer-reviewed by experts from WHO's Expert Advisory Panels. This will include an evaluation of the strength of evidence presented. If there are data limitations or omissions, they will be discussed with, and adapted as needed, by the author.
- Examples of previous Pre-Reviews are available on the WHO Expert Committee on Drug Dependence website. For example, two Pre-Reviews (phenazepam and etizolam) were prepared for the 37th ECDD in 2015.
- Authors should include a comprehensive list of references, and specify the methodology used in the report

Inclusion and Exclusion Criteria for Pre-Review reports

Report 1: Cannabis plant and Cannabis Resin Pre-Review

Inclusion Criteria

Studies to be included in the report are those involving:

- Cannabis as defined by the International Drug Control Conventions as "the flowering tops of the cannabis plant from which the resin has not been extracted"[2]. The term "cannabis" generally refers to a dried preparation of the flowering tops or other parts of the cannabis plant.
- Cannabis resin which isdefined as "the separated resin, whether crude or purified, obtained from the cannabis plant". It is normally in solid form and is sometimes known as hashish.

Exclusion Criteria

Studies to be excluded from the report:

- Tinctures and extracts of cannabis including preparations or mixtures of cannabis substances (e.g. nabiximols)
- Pure delta-9-tetrahydrocannabinol (THC) and its four stereochemical variants
    - (-)-trans-delta-9-tetrahydrocannabinol
    - (+)-trans-delta-9-tetrahydrocannabinol
    - (-)-cis-delta-9-tetrahydrocannabinol
    - (+)-cis-delta-9-tetrahydrocannabinol
- Pure cannabidiol (CBD)
- Isomers of tetrahydrocannabinol (THC)
    - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
    - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

[2]https://www.unodc.org/documents/commissions/CND/Int_Drug_Control_Conventions/Ebook/The_International_Drug_Control_Conventions_E.pdf

Report 2: Extracts and Tinctures of Cannabis

Inclusion criteria

Studies to be included in the report are those involving:

- Cannabis extracts: this term refers to a plant extract mixture from the leaves and flowers of Cannabis sativa
- Cannabis tinctures: this term refers to specific alcohol extractions of the flowering tops or other parts of Cannabis sativa.
- Cannabis oils e.g. Butane Hash Oil, Hemp Seed Oil
- Aqueous extracts e.g. marijuana tea
- Nabiximols (e.g. Sativex®)

Exclusion criteria

Studies to be excluded from the report:

- Cannabis plant (dried preparations of the flowering tops or other parts of the cannabis plant) and cannabis resin (separated resin obtained from the plant)
- Pure delta-9-tetrahydrocannabinol (THC) and its four stereochemical variants except when delta-9-THC is extracted from the cannabis plant.
    - (-)-trans-delta-9-tetrahydrocannabinol
    - (+)-trans-delta-9-tetrahydrocannabinol
    - (-)-cis-delta-9-tetrahydrocannabinol
    - (+)-cis-delta-9-tetrahydrocannabinol
- Pure cannabidiol (CBD) when not in a preparation with other cannabis related ingredients
- Isomers of tetrahydrocannabinol (THC)
    - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
    - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

Report 3: Delta-9-tetrahydrocannabinol

Inclusion criteria

Studies to be included in the report are those involving:

- Pure delta-9-tetrahydrocannabinol that is obtained either directly from the cannabis plant or synthesised.
- The stereochemical variants of delta-9-tetrahydrocannabinol:
    - (-)-trans-delta-9-tetrahydrocannabinol (also known as dronabinol)
    - (+)-trans-delta-9-tetrahydrocannabinol
    - (-)-cis-delta-9-tetrahydrocannabinol
    - (+)-cis-delta-9-tetrahydrocannabinol

Exclusion criteria

Studies to be excluded from the report:

- Cannabis plant (dried preparations of the flowering tops or other parts of the cannabis plant) and cannabis resin (separated resin obtained from the plant)
- Tinctures and extracts of cannabis including preparations or mixtures of cannabis substances (e.g. nabiximols), except those that are pure delta-9-THC
- Pure cannabidiol
- Isomers and stereochemical variants of tetrahydrocannabinol as listed in Schedule 1 of the 1971 Convention on Psychotropic Substances
    - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
    - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H- dibenzo[b,d]pyran -1- ol
    - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene- 3-pentyl-6Hdibenzo[b,d]pyran-1-ol

Report 4: Isomers of THC

Inclusion criteria

Studies to be included in the report are those involving:

- Isomers and stereochemical variants of tetrahydrocannabinol as listed in Schedule 1 of the 1971 Convention on Psychotropic Substances:
    - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
    - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

Exclusion criteria

Studies to be excluded from the report:

- Cannabis plant (dried preparations of the flowering tops or other parts of the cannabis plant) and cannabis resin (separated resin obtained from the plant)
- Tinctures and extracts of cannabis including preparations or mixtures of cannabis substances (e.g. nabiximols)
- Delta-9-tetrahydrocannabinol (THC) and its four stereochemical variants
    - (-)-trans-delta-9-tetrahydrocannabinol (also known as Dronabinol)
    - (+)-trans-delta-9-tetrahydrocannabinol
    - (-)-cis-delta-9-tetrahydrocannabinol
    - (+)-cis-delta-9-tetrahydrocannabinol
- Cannabidiol

Template for the each Pre-Review report

Toxicology

Pre-Review Report: Toxicology and Adverse Effects of (*insert substance name/s*)

I. Toxicology (5)[3]

(*For example: cellular toxicology, animal studies, acute and chronic preclinical toxicology*)

II. Adverse Reactions in Humans (6)

(*For example*: *clinical trial outcomes, acute and chronic physical and psychological effects, case Pre-Review reports or series on intoxications*)

III. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance (19)

[3] () indicates corresponding report section in Paragraph 23: Guidance on the WHO Review of psychoactive substances for international control
http://www.who.int/medicines/areas/quality_safety/GLS_WHORev_PsychoactSubst_IntC_2010.pdf?ua=1

Annex D
Terms of Reference: Epidemiology

- **The purpose of the pre-review is to synthesize existing scientific evidence about the therapeutic use and potential for dependence and abuse of cannabis-related compounds**
- Any recommendations on the scheduling of the substances are to be made by the Expert Committee, and should not be included in the pre-review
- The WHO pre-review[1] template for substances under review by the Expert Committee on Drug Dependence comprises five scientific topics:
    - Chemistry
    - Pharmacology
    - Toxicology/ Adverse Effects
    - Epidemiology
    - Therapeutic Use
- The author will complete the Pre-Review report for the scientific topic of **epidemiology** based on the template found on Annex Page 7

- The author will prepare **four separate** Pre-Review reports on the **epidemiology** of the following cannabis related compounds:
    Report 1: Cannabis plant and cannabis resin
    Report 2: Extracts and tinctures of cannabis
    Report 3: Delta-9-tetrahydrocannabinol (THC)
    Report 4: Isomers of THC
- Where authors refer to a specific compound (e.g. type of cannabis plant, extract, or isomer), they are asked to clearly indicate this in the report
- The Pre-Review reports will be prepared in accordance with the specific inclusion and exclusion criteria to minimise overlap and repetition of information (Annex Pages 3-6).
- The Pre-Review reports should include information, where feasible, in all the required sections of the template in accordance with the *Guidance on the WHO review of psychoactive substances for international control* document. The guidance document is available online at the WHO Expert Committee on Drug Dependence website: http://www.who.int/medicines/access/controlled-substances/ecdd/en/
- The Pre-Review reports should be presented in a manner that will facilitate an evidence-based assessment by the Expert Committee.

[1] Pre-Review: An initial review to determine whether a critical review is warranted. If the Expert Committee finds the information may justify scheduling or a change in the scheduling of the substance they can recommend a Critical Review. A critical review is to consider whether the Expert Committee should advise the Director-General to recommend the scheduling of, or amending of the scheduling status of, a substance.

- The Pre-Review reports should be written in an objective manner without bias or opinions.
- The Pre-Review reports should summarise the literature in a manner that presents the relevant information, without necessarily producing an exhaustive report. The use of existing reviews is encouraged, provided adequate referencing is utilised.
- Preliminary drafts should be submitted to the WHO ECDD Secretariat for assessment of quality and suitability for the Expert Committee. The Secretariat may request editorial changes and follow up drafts, if deemed necessary.
- The final draft of the Pre-Review reports will be peer-reviewed by experts from WHO's Expert Advisory Panels. This will include an evaluation of the strength of evidence presented. If there are data limitations or omissions, they will be discussed with, and adapted as needed, by the author.
- Examples of previous pre-reviews are available on the WHO Expert Committee on Drug Dependence website. For example, two pre-reviews (phenazepam and etizolam) were prepared for the 37th ECDD in 2015.
- Authors should include a comprehensive list of references, and specify the methodology used in the report

Inclusion and Exclusion Criteria for Pre-Review reports

Report 1: Cannabis plant and Cannabis Resin Pre-Review

Inclusion Criteria

Studies to be included in the report are those involving:

- Cannabis as defined by the International Drug Control Conventions as "the flowering tops of the cannabis plant from which the resin has not been extracted"[2]. The term "cannabis" generally refers to a dried preparation of the flowering tops or other parts of the cannabis plant.
- Cannabis resin which is defined as "the separated resin, whether crude or purified, obtained from the cannabis plant". It is normally in solid form and is sometimes known as hashish.

Exclusion Criteria

Studies to be excluded from the report:

- Tinctures and extracts of cannabis including preparations or mixtures of cannabis substances (e.g. nabiximols)
- Pure delta-9-tetrahydrocannabinol (THC) and its four stereochemical variants
    - (-)-trans-delta-9-tetrahydrocannabinol
    - (+)-trans-delta-9-tetrahydrocannabinol
    - (-)-cis-delta-9-tetrahydrocannabinol
    - (+)-cis-delta-9-tetrahydrocannabinol
- Pure cannabidiol (CBD)
- Isomers of tetrahydrocannabinol (THC)
    - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
    - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

[2]https://www.unodc.org/documents/commissions/CND/Int_Drug_Control_Conventions/Ebook/The_International_Drug_Control_Conventions_E.pdf

Report 2: Extracts and Tinctures of Cannabis

Inclusion criteria

Studies to be included in the report are those involving:

- Cannabis extracts: this term refers to a plant extract mixture from the leaves and flowers of Cannabis sativa
- Cannabis tinctures: this term refers to specific alcohol extractions of the flowering tops or other parts of Cannabis sativa.
- Cannabis oils e.g. Butane Hash Oil, Hemp Seed Oil
- Aqueous extracts e.g. marijuana tea
- Nabiximols (e.g. Sativex®)

Exclusion criteria

Studies to be excluded from the report:

- Cannabis plant (dried preparations of the flowering tops or other parts of the cannabis plant) and cannabis resin (separated resin obtained from the plant)
- Pure delta-9-tetrahydrocannabinol (THC) and its four stereochemical variants except when delta-9-THC is extracted from the cannabis plant.
    - (-)-trans-delta-9-tetrahydrocannabinol
    - (+)-trans-delta-9-tetrahydrocannabinol
    - (-)-cis-delta-9-tetrahydrocannabinol
    - (+)-cis-delta-9-tetrahydrocannabinol
- Pure cannabidiol (CBD) when not in a preparation with other cannabis related ingredients
- Isomers of tetrahydrocannabinol (THC)
    - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
    - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

Report 3: Delta-9-tetrahydrocannabinol

Inclusion criteria

Studies to be included in the report are those involving:

- Pure delta-9-tetrahydrocannabinol that is obtained either directly from the cannabis plant or synthesised.
- The stereochemical variants of delta-9-tetrahydrocannabinol:
    - (-)-trans-delta-9-tetrahydrocannabinol (also known as dronabinol)
    - (+)-trans-delta-9-tetrahydrocannabinol
    - (-)-cis-delta-9-tetrahydrocannabinol
    - (+)-cis-delta-9-tetrahydrocannabinol

Exclusion criteria

Studies to be excluded from the report:

- Cannabis plant (dried preparations of the flowering tops or other parts of the cannabis plant) and cannabis resin (separated resin obtained from the plant)
- Tinctures and extracts of cannabis including preparations or mixtures of cannabis substances (e.g. nabiximols), except those that are pure delta-9-THC
- Pure cannabidiol
- Isomers and stereochemical variants of tetrahydrocannabinol as listed in Schedule 1 of the 1971 Convention on Psychotropic Substances
    - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
    - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H- dibenzo[b,d]pyran -1- ol
    - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene- 3-pentyl-6Hdibenzo[b,d]pyran-1-ol

Report 4: Isomers of THC

Inclusion criteria

Studies to be included in the report are those involving:

- Isomers and stereochemical variants of tetrahydrocannabinol as listed in Schedule 1 of the 1971 Convention on Psychotropic Substances:
  - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
  - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
  - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
  - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
  - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
  - (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

Exclusion criteria

Studies to be excluded from the report:

- Cannabis plant (dried preparations of the flowering tops or other parts of the cannabis plant) and cannabis resin (separated resin obtained from the plant)
- Tinctures and extracts of cannabis including preparations or mixtures of cannabis substances (e.g. nabiximols)
- Delta-9-tetrahydrocannabinol (THC) and its four stereochemical variants
  - (-)-trans-delta-9-tetrahydrocannabinol (also known as Dronabinol)
  - (+)-trans-delta-9-tetrahydrocannabinol
  - (-)-cis-delta-9-tetrahydrocannabinol
  - (+)-cis-delta-9-tetrahydrocannabinol
- Cannabidiol

Template for the each pre-review report

Epidemiology

Pre-Review Report: Epidemiology of (*insert substance name/s*)

I. Industrial Use (12)[3]

II. Non-Medical Use, Abuse and Dependence (13)

(*For example: epidemiology (e.g., prevalence) of nonmedical use, abuse and dependence, e.g. household survey results*)

III. **Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence (14)**

(For example: impaired driving, co-morbidities, vulnerable populations, consequences of injection drug use, harm to others etc.)

IV. Licit production, consumption, and international trade (15)

V. Illicit manufacture and traffic (16)

VI. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance (19)

[3] () indicates corresponding report section in Paragraph 23: Guidance on the WHO Review of psychoactive substances for international control
http://www.who.int/medicines/areas/quality_safety/GLS_WHORev_PsychoactSubst_IntC_2010.pdf?ua=1

Annex E
Terms of Reference: Therapeutic use

- **The purpose of the pre-review report is to synthesize existing scientific evidence about the therapeutic use and potential for dependence and abuse of cannabis-related compounds**
- Any recommendations on the scheduling of the substances are to be made by the Expert Committee, and should not be included in the pre-review
- The WHO pre-review report template[1] for substances under review by the Expert Committee on Drug Dependence comprises five scientific topics:
    - Chemistry
    - Pharmacology
    - Toxicology/ Adverse Effects
    - Epidemiology
    - Therapeutic Use
- The author will complete the Pre-Review report for the scientific topic of **therapeutic use** based on the template found on Annex Page 7
- The author will prepare **four separate** Pre-Review reports on the **therapeutic use** of the following cannabis related compounds:

    Report 1: Cannabis plant and cannabis resin
    Report 2: Extracts and tinctures of cannabis
    Report 3: Delta-9-tetrahydrocannabinol (THC)
    Report 4: Isomers of THC
- Where authors refer to a specific compound (e.g. type of cannabis plant, extract, or isomer), they are asked to clearly indicate this in the report
- The Pre-Review reports will be prepared in accordance with the specific inclusion and exclusion criteria to minimise overlap and repetition of information (Annex Pages 3-6).
- The Pre-Review reports should include information, where feasible, in all the required sections of the template in accordance with the *Guidance on the WHO review of psychoactive substances for international control* document. The guidance document is available online at the WHO Expert Committee on Drug Dependence website: http://www.who.int/medicines/access/controlled-substances/ecdd/en/
- The Pre-Review reports should be presented in a manner that will facilitate an evidence-based assessment by the Expert Committee.
- The Pre-Review reports should be written in an objective manner without bias or opinions.

[1] Pre-review: An initial review to determine whether a critical review is warranted. If the Expert Committee finds the information may justify scheduling or a change in the scheduling of the substance they can recommend a Critical Review. A critical review is to consider whether the Expert Committee should advise the Director-General to recommend the scheduling of, or amending of the scheduling status of, a substance.

- The Pre-Review reports should summarise the literature in a manner that presents the relevant information, without necessarily producing an exhaustive report. The use of existing reviews is encouraged, provided adequate referencing is utilised.
- Preliminary drafts should be submitted to the WHO ECDD Secretariat for assessment of quality and suitability for the Expert Committee. The Secretariat may request editorial changes and follow up drafts, if deemed necessary.
- The final draft of the Pre-Review reports will be peer-reviewed by experts from WHO's Expert Advisory Panels. This will include an evaluation of the strength of evidence presented. If there are data limitations or omissions, they will be discussed with, and adapted as needed, by the author.
- Examples of previous pre-reviews are available on the WHO Expert Committee on Drug Dependence website. For example, two pre-reviews (phenazepam and etizolam) were prepared for the 37th ECDD in 2015.
- Authors should include a comprehensive list of references, and specify the methodology used in the report

Inclusion and Exclusion Criteria for Pre-Review reports

Report 1: Cannabis plant and Cannabis Resin Pre-Review

Inclusion Criteria

Studies to be included in the report are those involving:

- Cannabis as defined by the International Drug Control Conventions as "the flowering tops of the cannabis plant from which the resin has not been extracted"[2]. The term "cannabis" generally refers to a dried preparation of the flowering tops or other parts of the cannabis plant.
- Cannabis resin which is defined as "the separated resin, whether crude or purified, obtained from the cannabis plant". It is normally in solid form and is sometimes known as hashish.

Exclusion Criteria

Studies to be excluded from the report:

- Tinctures and extracts of cannabis including preparations or mixtures of cannabis substances (e.g. nabiximols)
- Pure delta-9-tetrahydrocannabinol (THC) and its four stereochemical variants
    - (-)-trans-delta-9-tetrahydrocannabinol
    - (+)-trans-delta-9-tetrahydrocannabinol
    - (-)-cis-delta-9-tetrahydrocannabinol
    - (+)-cis-delta-9-tetrahydrocannabinol
- Pure cannabidiol (CBD)
- Isomers of tetrahydrocannabinol (THC)
    - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
    - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

[2]https://www.unodc.org/documents/commissions/CND/Int_Drug_Control_Conventions/Ebook/The_International_Drug_Control_Conventions_E.pdf

Report 2: Extracts and Tinctures of Cannabis

Inclusion criteria

Studies to be included in the report are those involving:

- Cannabis extracts: this term refers to a plant extract mixture from the leaves and flowers of Cannabis sativa
- Cannabis tinctures: this term refers to specific alcohol extractions of the flowering tops or other parts of Cannabis sativa.
- Cannabis oils e.g. Butane Hash Oil, Hemp Seed Oil
- Aqueous extracts e.g. marijuana tea
- Nabiximols (e.g. Sativex®)

Exclusion criteria

Studies to be excluded from the report:

- Cannabis plant (dried preparations of the flowering tops or other parts of the cannabis plant) and cannabis resin (separated resin obtained from the plant)
- Pure delta-9-tetrahydrocannabinol (THC) and its four stereochemical variants except when delta-9-THC is extracted from the cannabis plant.
    - (-)-trans-delta-9-tetrahydrocannabinol
    - (+)-trans-delta-9-tetrahydrocannabinol
    - (-)-cis-delta-9-tetrahydrocannabinol
    - (+)-cis-delta-9-tetrahydrocannabinol
- Pure cannabidiol (CBD) when not in a preparation with other cannabis related ingredients
- Isomers of tetrahydrocannabinol (THC)
    - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
    - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

Report 3: Delta-9-tetrahydrocannabinol

Inclusion criteria

Studies to be included in the report are those involving:

- Pure delta-9-tetrahydrocannabinol that is obtained either directly from the cannabis plant or synthesised.
- The stereochemical variants of delta-9-tetrahydrocannabinol:
    - (-)-trans-delta-9-tetrahydrocannabinol (also known as dronabinol)
    - (+)-trans-delta-9-tetrahydrocannabinol
    - (-)-cis-delta-9-tetrahydrocannabinol
    - (+)-cis-delta-9-tetrahydrocannabinol

Exclusion criteria

Studies to be excluded from the report:

- Cannabis plant (dried preparations of the flowering tops or other parts of the cannabis plant) and cannabis resin (separated resin obtained from the plant)
- Tinctures and extracts of cannabis including preparations or mixtures of cannabis substances (e.g. nabiximols), except those that are pure delta-9-THC
- Pure cannabidiol
- Isomers and stereochemical variants of tetrahydrocannabinol as listed in Schedule 1 of the 1971 Convention on Psychotropic Substances
    - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
    - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H- dibenzo[b,d]pyran -1- ol
    - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene- 3-pentyl-6Hdibenzo[b,d]pyran-1-ol

Report 4: Isomers of THC

Inclusion criteria

Studies to be included in the report are those involving:

- Isomers and stereochemical variants of tetrahydrocannabinol as listed in Schedule 1 of the 1971 Convention on Psychotropic Substances:
    - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
    - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
    - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
    - (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

Exclusion criteria

Studies to be excluded from the report:

- Cannabis plant (dried preparations of the flowering tops or other parts of the cannabis plant) and cannabis resin (separated resin obtained from the plant)
- Tinctures and extracts of cannabis including preparations or mixtures of cannabis substances (e.g. nabiximols)
- Delta-9-tetrahydrocannabinol (THC) and its four stereochemical variants
    - (-)-trans-delta-9-tetrahydrocannabinol (also known as Dronabinol)
    - (+)-trans-delta-9-tetrahydrocannabinol
    - (-)-cis-delta-9-tetrahydrocannabinol
    - (+)-cis-delta-9-tetrahydrocannabinol
- Cannabidiol

Template for the each pre-review report

Therapeutic Use

Pre-Review Report: Therapeutic Use of (*insert substance name/s*)

I. Marketing Authorizations (as a Medicinal Product) (11)[3]

(*For example: company names and countries which hold authority to produce substance as a medicinal product. Name of medicinal product can be included*)

II. Listing on the WHO Model List of Essential Medicines (10)

III. Therapeutic Applications (9)

Extent of Therapeutic Use

Epidemiology of Medical Use

Effectiveness of Therapeutic Uses

- Systematic reviews and meta-analysis
- RCTs
- Quasi-experimental studies
- Cohort studies
- Case control studies
- Cross-sectional surveys
- Case Pre-Review reports

IV. Adverse reactions in humans (6)

V. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance (19)

[3] () indicates corresponding report section in Paragraph 23: Guidance on the WHO Review of psychoactive substances for international control http://www.who.int/medicines/areas/quality_safety/GLS_WHORev_PsychoactSubst_IntC_2010.pdf?ua=1