Oripavine (final decision)

a. Introduction
Oripavine, \(O^2\)-demethylthebaine, is a phenanthrene alkaloid contained in various species of the genus *Papaver*, including *P. bracteatum* Lindl. and *P. orientale* L.. It is not produced by traditionally cultivated varieties of opium poppy (*P. somniferum* L.) and is therefore not found in opium. However, in the last decade, a variety (a strain) of *P. somniferum* was created by plant breeders with a high content of oripavine and is now cultivated commercially on a considerable scale.

Oripavine was pre-reviewed by the 33rd ECDD in 2002. The reason for pre-review in 2002 was that oripavine is a substance that is convertible into thebaine, and because thebaine in its turn is convertible into morphine. Thebaine and morphine are both in Schedule I of the 1961 Convention, morphine because of its liability for abuse, and thebaine because it can be converted into substances that are morphine derivatives and are included in Schedule I of the 1961 Convention because of their liability for abuse. The Committee concluded from this that the conversion of oripavine into morphine derivatives was indirect and therefore it hesitated whether Article 3, para. 3 point iii of the 1961 Convention was applicable in this case. The Committee also remarked that the relation of this situation to the 1988 Convention is not clear, as the latter regulates substances frequently used in the production of narcotic drugs or psychotropic substances.

Due to these uncertainties, the 33rd ECDD did not finalize this review, but included in its report the following proposal: "The Committee urged WHO to develop additional scheduling guidelines in consultation with appropriate bodies of the United Nations for clarifying issues related to the conversion of precursors into scheduled substances."

However, supplementary Guidelines for the WHO review of dependence producing psychoactive substances for international control have not been established by WHO Executive Board, as will be discussed in a separate point on the agenda. As the consequence the 34th ECDD has to decide on a final recommendation concerning oripavine without having an additional guidance.

b. New information acquired by the Secretariat since 2002

In its document E/INCB/2002/2 (Statistical report for 2001) the International Narcotic Control Board (INCB) indicated that until the second half of 1990-ties commercial cultivation of opium poppy with the aim of producing poppy straw and poppy straw concentrate was carried out using varieties which contained morphine as the predominant alkaloid. Since then, new varieties appeared in the commercial cultivation, containing thebaine as the predominant alkaloid. To distinguish materials obtained from those varieties, INCB introduced designations poppy straw (M) and poppy straw (T).
INCB also indicated that poppy straw (T) contains a significant content of the oripavine alkaloid in addition to the thebaine alkaloid (see, for example, the technical report on narcotic drugs for 2004, document E/INCB/2004/2, Part IV, paragraph 41). Concentrate of poppy straw containing oripavine as the main alkaloid, designated by INCB as concentrate of poppy straw (O), has been manufactured commercially since 1999; in 2004 its manufacture reached 22 tons expressed at 100 per cent of oripavine alkaloid. Concentrate of poppy straw (O) has been used in Australia and the United States primarily for the manufacture of thebaine, a starting material to manufacture other opiates which are included in Schedule I of the 1961 Convention because of their abuse potential, such as hydromorphone, oxycodone and oxymorphone. Australia has been reporting also the use of oripavine itself for the manufacture of thebaine.

In 2005, INCB informed WHO that Australia reported for 2003 and 2004 the use of oripavine not only for the manufacture of thebaine, but also for a direct manufacture of oxymorphone, and in 2004, in addition, for a direct manufacture of hydromorphone, which are narcotic drugs included in Schedule I of the 1961 Convention because of their abuse potential.

c. General considerations concerning scheduling of oripavine as a convertible substance

In order to decide on the scheduling of oripavine, the usual assessment procedure described in "Guidelines for the WHO review of dependence producing psychoactive substances for international control guidelines", approved by decision EB105(3), is not appropriate. The procedure focuses on the dependence-producing properties of a substance, which is not the question. It is clear, and has already been established by the Committee, that "it is an easy industrial process to convert oripavine into thebaine through methylation" and there is also no doubt that thebaine is convertible into morphine derivatives included in Schedule I of the 1961 Convention. This means that there is agreement on the fact that oripavine can be converted in steps into substances controlled by the 1961 Convention.

From this, the issue of oripavine scheduling focuses on the question whether a two steps conversion is sufficient to put oripavine into the same schedule as substances which are end products of its conversion.

In addition the question of the relationship with the 1988 Convention that arises if oripavine is treated as an intermediate should also be elucidated.

This turns over the decision from a pharmaceutical, pharmacological and medical question into a legal question, which is not the primary focus of expertise the Committee but for this purpose the Committee can be advised by legal texts and the assistance of the WHO Office of Legal Council.
**d. Scheduling as a convertible substance under the 1961 Convention**

Article 3 in paragraph 3, subparagraph iii of the 1961 Convention reads as follows:

"If the World Health Organization finds that the substance is liable to similar abuse and productive of similar ill effects as the drugs in Schedule I or Schedule II or is convertible into a drug, it shall communicate that finding to the Commission which may, in accordance with the recommendation of the World Health Organization, decide that the substance shall be added to Schedule I or Schedule II."

The 33rd ECDD hesitated whether "convertible" in the sense of the Convention applies to a multi-step conversion of oripavine into morphine derivatives. To explore whether this is the case or not, in the first place the Commentary on the 1961 Convention should be studied. This Commentary contains a very long comment on subparagraph iii, consisting of 18 paragraphs (page 85-90). Some of these paragraphs elaborate on the question what "conversion" is, of which the paragraphs 4, 5 and 9-13 are relevant for the present question. These paragraphs are summarized in annex 1.

Paragraph 12 of the Commentary declares WHA resolution 7.7. (1954) applicable (see Annex 2 for full text). Although the resolution was adopted as an implementation measure for the Convention of 13 July 1931 for limiting the manufacture and regulating the distribution of narcotic Drugs (the 1931 Convention), as amended by the Protocol signed on 11 December 1946, the 1931 Convention was incorporated into the 1961 Single Convention on Narcotic Drugs (the 1961 Convention). The WHA7.7 resolution gives thus a guidance to the Committee to solve the question.

According to the WHA7.7 resolution, to determine whether a substance will be considered as "convertible" it should: (i) be easily converted and (II) the yield obtained should constitute a risk for public health. Paragraph 13 of the commentary put stress on practicability and profitability for the clandestine manufacturer, through ease and yield of the conversion process. This is, although related, different from the WHA resolution. Neither the resolution nor the commentary says that there is such criterion as "direct or indirect conversion". However, as a supplementary criterion, the resolution says that in case of doubt the substance should be considered as "convertible".

Thus, there is a discrepancy between the criteria given by the WHA resolution and by the Commentary itself in paragraph 13.

The criteria set by WHA are:

(i) easily converted
(ii) the yield should constitute a risk for public health

The criteria given by the UN Secretariat in the Commentary are:

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(i) the ease of conversion should be such that it is practicable and profitable for clandestine manufacturers
(ii) the yield should be such that it is practicable and profitable for clandestine manufacturers

It should be remarked that in these criteria the word "yield" is used in two different meanings. In the phrase "the yield should constitute a risk for public health" the word *yield* refers to qualitative properties of the yielded substance, which determine whether it is a risk for public health or not. This means that it refers to the identity of the substance produced. However, if the word *yield* is related to practicability and profitability it refers to the ratio between input and output, i.e. the percentage of product, given the amount of starting material, or, in other words, the effort that is needed to obtain a certain amount of substance.

Although these criteria are not far from each other, for the decision making it is important which of these criteria prevail. To know this, the status of their sources is important. WHA resolution 7.7 has the status of a resolution endorsed by the international community. It was recognized by the UN Secretary-General (in par. 12 of the Commentary), as applicable to the 1961 Convention. Nevertheless, the Secretary-General gave, probably unintentionally, new criteria in paragraph 13, and, although meant as a paraphrase of these, they are different from the WHA criteria. The criteria given by the Secretary-General are not endorsed by the international community, but have the status of a supplementary text to the 1961 Convention.

Clearly, the WHA criteria have more authority then the Secretary-Generals' criteria, and even the Secretary-General has recognized the WHA criteria. From this it should be concluded that the criteria given by WHA resolution 7.7. are the criteria that have to be applied.

It can also be concluded that there is no additional criterion regarding the directness of the conversion.

This position is further strengthened by the fact that the list of substances included into Schedule I of the 1961 Convention contains three pethidine intermediates designated as A, B and C and one moramide intermediate. Among them, two substances: pethidine intermediates A and C are convertible into pethidine in a one-step chemical process. However, the conversion of pethidine intermediate B to pethidine and of moramide intermediate into racemoramide can require, depending on the chemical procedure used, a two-step procedure.

Considering that the Committee already decided that it is an easy industrial process to convert oripavine into thebaine, the question remains whether it is also easy to convert thebaine into morphine. That this is the fact can be concluded from the fact that thebaine is included in Schedule I for its convertibility and not for its liability for abuse. From this it can be concluded that the conversion of oripavine into morphine is to be considered as easy.

Even if one takes in consideration that ease of the combined easy processes of converting oripavine into thebaine plus converting thebaine into substances listed in
Schedule I of the 1961 Convention (oxycodone, hydrocodone and oxymorphone), is less easy then the separate processes are, it should be born in mind that the WHA resolutions guides that in case of doubt the substance should be considered as "convertible".

Regarding the yield, there is no doubt, because oxycodone, hydrocodone, hydromorphone and oxymorphone are substances on Schedule I, and as such they constitute a risk for public health.

Regarding to the chemistry of synthesis starting from oripavine, the Laboratory and Scientific Section of UNODC contributed with an overview (annex)

Moreover, once INCB reported the direct conversion into oxymorphone and hydromorphone, the directness of the conversion into thebaine does not need to be any point of discussion any more, if the latter conversions are easily to carry out.

The conclusion from this should be that the criteria from WHA resolution 7.7. apply for scheduling oripavine, and that oripavine complies with these criteria. Hence, oripavine can be scheduled in Schedule I

e. Scheduling under the United Nations Convention against Illicit Traffic in Narcotic Drugs And Psychotropic Substances 1988

This Convention gives another opportunity for its parties to bring oripavine under international control if the substance is frequently used in the illicit manufacture of a narcotic drug or a psychotropic substance. Also the volume and extent of the illicit manufacture of the narcotic drug or psychotropic substance should create serious public health or social problems. If this is the case the substance can be taken under assessment of the International Narcotics Control Board and then with a two-thirds majority of the members Commission on Narcotic Drugs (CND) be scheduled on Table I or Table II of this Convention.

So far this has not happened and also no relevant assessment was communicated by the INCB to the CND.

It is not in the mandate of the Committee and WHO to advise on the composition of the tables of this Convention. This also means that the Committee has no mandate to weigh between Scheduling of oripavine on the 1961 Convention or listing it in one of the Tables of the 1988 Convention.

The Committee and WHO can only advise to schedule oripavine on one of the Schedules of the 1961 Convention, or not. If the Committee would advise to schedule the substance, this can be adopted by the CND according to art. 3 para. 3 subpara. (iii) quoted above. The Commission has also the right not to adopt the Committees' and WHO's advise. Instead, it could either do nothing (i.e. oripavine would remain an uncontrolled substance), or the CND could decide to place oripavine on one of the Tables of the 1988 Convention, following the procedures of that Convention.
However, it should be considered that oripavine is manufactured from poppy straw and is converted into thebaine, hydromorphone and oxymorphone and from thebaine into oxycodone, and hydrocodone. All these substances are controlled by the 1961 Convention and also the collection of data of their manufacturing and licit and illicit trade are performed by one and the same department in INCB. Bringing oripavine under a different convention would break up the logic of the control mechanisms of international drug control and make these mechanisms less effective. Thus, it is preferred to schedule oripavine under the 1961 Convention and not under any other convention.

f. Proposed conclusion
Proposed text: Oripavine is a substance that is easily converted into thebaine and other substances controlled by the 1961 Convention. Hence the Committee recommends that oripavine be scheduled, like the substances mentioned, in Schedule I of the 1961 Convention. Although the substance could also be brought under the international drug control by applying other treaties, the Committee recommends not to break the logic of international drug control mechanisms. It reminds that also the other substances that are specific for this production chain of morphine derivatives are scheduled under the 1961 Convention.
Annex 1:
Summary of relevant paragraphs from the Commentary on the 1961 Convention (art. 3 paragraph 3, subparagraph (iii)

paragraph 4
The technical Committee of the Plenipotentiary Conference that prepared the Convention stated that the substances which it listed for Schedule I were those:
"..(b) convertible into substances having addiction-producing or addiction-sustaining properties with an ease of yield such as to constitute a risk of abuse greater then codeine" or…
"..(d) convertible into substances having a liability to abuse comparable to that of cannabis, cannabis resin or cocaine."

paragraph 5
This paragraph reads:
"To sum up, it results that the substances in these two Schedules, i.e. the drugs under the narcotics régime, have morphine-like (..) effect, or are convertible in 'drugs' having such effects."

paragraph 9
This paragraph refers to the fact that already the 1931 Convention had a clause on convertibility (article 11), saying that convertible substances had to be products "obtained from any of the phenanthrene alkaloids of opium or from the eugonine alkaloids of the coca leaf".

paragraph 10
The Single Convention does not restrict the substances which may be brought under control to a specific chemical group. It cannot have been the intention of the authors of the Convention to place under international narcotics control anything which may be theoretically be "convertible" into narcotic drugs. The purpose of the provisions regarding convertible substances is to make it as difficult as practicable for illicit traffickers to obtain material which they could in practice i.e. with relative ease, transform into controlled dangerous drugs.

paragraph 11
This paragraph says that the delegates to the conference where was agreed on the 1961 Convention must have had in mind the meaning of the term "convertible", and must have been aware of a resolution adopted by the World Health Assembly in 1954, in which the Assembly declared that "a substance will be considered by the World Health Organization as 'convertible' where the ease of conversion and the yield obtained constitute a risk to public health and that in cases where there is uncertainty whether a substance will fall under this definition, the substance will be considered as 'convertible' rather than as 'not convertible'. "

paragraph 12
This paragraph declares that the Plenipotentiary Conference that decided on the 1961 Convention de facto declared applicability of the WHA resolution applicable to the decision making process for the 1961 Convention.
Paragraph 13 concludes that the criterion for "convertibility" is that it is practicable and profitable for a clandestine manufacturer - by the ease of the process and the yield - to transform the substance into question into controlled drugs.
Annex 2

**WHA7.7**

1931 Convention on Narcotic Drugs: Interpretation of "Convertible Substances"

The Seventh World Health Assembly,
Having considered resolution **EB13.R10**,
DECIDES that, so far as the functions conferred upon the World Health Organization by the 1931 Convention for Limiting the Manufacture and Regulating the Distribution of Narcotic Drugs are concerned, a substance will be considered by the World Health Organization as "convertible" where the ease of conversion and the yield obtained constitute a risk to public health, and that in cases where there is uncertainty as to whether a substance will fall under this definition, the substance will be considered as "convertible" rather than as "not convertible".

*Handb. Res., 2nd ed., 1.5.1* Adopted at the sixth plenary meeting, 14 May 1954 (section 4 of the first report of the Committee on Programme and Budget)