Expert Peer Review No.1 for Pentedrone

1. Comments based on the review report

   a. Evidence on dependence and abuse potential
   Pentedrone binds to the dopamine (DAT) and to the noradrenergic transporters (NAT) and inhibits dopamine and noradrenergic uptake, but poorly binds to the serotonergic transporter (SERT) and does not meaningfully inhibit serotonergic uptake. It induces climbing behavior, increases locomotor activity and produces conditioned place preference in mice, and maintains intravenous self-administration in rats. These in vitro and in vivo effects are consistent with a profile similar to an abused stimulant such as methamphetamine. Importantly, it generalizes to cocaine and to methamphetamine in rat discrimination tests, suggesting it can produce their subjective effects and have an abuse liability similar to these drugs. It appears that systematically controlled abuse potential tests have not been conducted with human subjects, nor have such tests been conducted directly pertinent to its dependence potential in laboratory animals or human subjects.
   Suggestive of abuse, are seizure and bioanalytical data. Pentedrone has been detected in commercial products, confiscated in law enforcement seizures, and detected in biofluids in several countries in Europe and in North America.

   b. Risks to individual and society because of misuse
   Pentedrone can induce convulsions and cause lethality in laboratory animals. It demonstrates cytotoxicity in primary rat hepatocytes. It has been associated with driving under the influence arrests and in other cases of obvious intoxication, although in most instances multiple drugs have been involved. It may have helped precipitate a psychotic episode in at least one user. Pentedrone has been implicated in at least eight fatalities; in all decedents, other drugs were detected as well.

   c. Magnitude of the problem in countries (misuse, illicit production, smuggling etc.)
   Pentedrone has been detected in commercial products in several European countries, in Canada and in the United States. Hundreds of kilograms of pentedrone have been seized
in the EU alone. The Review does not report seizure or misuse in continents other than Europe or North America, although this may be attributable to factors other than to a lack of abuse.

d. Need of the substance for medical (including veterinary) practice
There are no approved therapeutic or medical indications for pentedrone, nor is it listed in the WHO Model List of Essential Medicines.

e. Need of the substance for other purposes (e.g. industrial)
There appear no important industrial uses of pentedrone.

f. Measures taken by countries to curb misuse
At the time of the preparation of the Review, and before questionnaires from countries regarding pentedrone's control had been received, several countries had already brought pentedrone under control, or it was being regulated under more generic controls such as those that govern cathinones generally. These countries span the globe from Europe including the UK, Austria, France, Germany and Sweden, as examples, to the US and Canada in North America, to Brazil in South America, to Australia and China.

g. Impact if this substance is scheduled
Considering that pentedrone has no approved therapeutic or industrial use, its control would unlikely have great impact. Its association with any previous drug developmental effort seems remote and unimpressive. There was nothing in the Critical Review that suggests that it would potentially have special therapeutic properties that could be cultivated. Overall, the impact if pentedrone were scheduled appears minimal.

2. Are there absent data that would be determinative for scheduling?
Although there appears to be a lack of controlled abuse potential and dependence studies using human subjects, and a lack of such dependence studies in laboratory animals, collected data from other sources compensates for these absences such that the overall body of data is sufficient for this reviewer to make a scheduling recommendation.

3. Other comments or opinions
Similarities of pentedrone to that of MDMA are made in the Critical Review document. It is important to also highlight the pharmacological differences between the two that could promote different patterns of abuse. A principal biochemical mechanism often identified
as important in mediating MDMA’s abuse-related effects is its ability to release the bioamines. Pentedrone does not cause the release of bioamines.

4. Expert reviewer’s view on scheduling with rationale

Although pentedrone’s pharmacology bears some similarity to cocaine, which is in Schedule I of the Single Convention on Narcotic Drugs, 1961, in keeping with the observation that regulated cathinones are under control of the Convention on Psychotropic Substances of 1971, and in keeping with the Guidance on the WHO Review of Psychoactive Substances for International Control that indicates, "...by virtue of an understanding of the Parties to the Conventions that the 1961 Convention did not apply to these substances even though the effects of amphetamines, barbiturates and tranquillizers were recognized to be similar to cocaine and morphine in some respects", pentedrone's potential regulation should be considered in reference to the criteria of the Convention on Psychotropic Substances of 1971. In this respect, because there is evidence of pentedrone’s abuse in several countries spanning at least two continents, because the likelihood of further abuse is great, because it has been associated with intoxications and fatalities, because the degree of the risk of seriousness to public health is high, and its likely therapeutic usefulness is low, it is recommended that pentedrone be placed in Schedule I of the Convention on Psychotropic Substances of 1971.