Expert Peer Review No.1 for Ethylphenidate

1. Comments based on the review report
   
a. Evidence on dependence and abuse potential
      
      Dependence potential:
      The Critical Review Report states there are no animal or human studies regarding dependence potential. However, a user case study has been published and user reports include suggestions of re-dosing.

      Abuse potential:
      The Critical Review Report states there are no animal (especially discrimination studies) or human studies regarding abuse potential. Nevertheless, the Critical Review Report demonstrates there is evidence of abuse of ethylphenidate by users seemingly for its amphetamine-like stimulant effects. Ethylphenidate is related to methylphenidate which is used as a medicinal product and controlled as a Schedule II substance under the 1971 Convention on Psychotropic Substances.

b. Risks to individual and society because of misuse
   The Critical Review Report details studies that have shown ethylphenidate to be pharmacologically similar to methylphenidate but with more dopaminergic activity, including greater dopamine uptake inhibition activity than cocaine. Review of data on analytically confirmed cases involving ethylphenidate showed that there are adverse health risks to the individual from use of the drug. Over twenty fatalities have involved ethylphenidate but due to the circumstances and often presence of other drugs coupled with the lack of available data, its direct contribution is unclear outside of some distinct cases presented. This included one case where ethylphenidate was the sole agent involved. Within the fatalities and non-fatal intoxications, amphetamine-like effects were reported, including adverse cardiovascular effects which present a serious risk to the individual. Furthermore, injection of ethylphenidate has been associated with soft tissue infections.
c. **Magnitude of the problem in countries (misuse, illicit production, smuggling etc)**
   The Critical Review Report highlights its detection (through drug seizures or biological fluid detection) in various European Union Member States. Ethylphenidate is reported to have been identified in confiscated material and is sold over the Internet. Seized items include ethylphenidate in powder and tablet form.

d. **Need of the substance for medical (including veterinary) practice**
   Ethylphenidate has no medical or veterinary use.

e. **Need of the substance for other purposes (e.g. industrial)**
   Ethylphenidate has no industrial or other use.

f. **Measures taken by countries to curb misuse**
   At the time the Critical Review Report, ethylphenidate was controlled (through national legislation) in the UK, Germany, Denmark, Poland, China, Austria and Sweden. It is also covered by analogue legislation in a number of countries due to its similarity to methylphenidate.

g. **Impact if this substance is scheduled**
   No specific information but there are no known approved therapeutic applications for ethylphenidate and it is not listed on the WHO Model List of Essential Medicines.

2. **Are there absent data that would be determinative for scheduling?**
   Animal discrimination and dependence studies may be beneficial but there is evidence of actual abuse in humans with associated reports of dependence in some cases.

3. **Other comments or opinions**
   The detectability of ethylphenidate within analytical toxicology is rightly mentioned within the Critical Review Report as it is unlikely to be detected as part of typical drug screening techniques used for biological fluid. Detection or confirmation of its presence requires reference material (especially if it is to be included in a targeted drug screening protocol) and with what could be seen to be a drug of lower prevalence than typical stimulants, analytical laboratories may not actively seek such reference materials. Consequently, the prevalence of ethylphenidate could be higher if more laboratories included the drug in routine drug testing methodologies.
4. Expert reviewer’s view on scheduling with rationale

The structural and pharmacological similarity of ethylphenidate to methylphenidate (a Schedule II substance controlled under the 1971 Convention on Psychotropic Substances) along with ethylphenidate’s documented abuse with associated toxicity and substantial public health risk would support its inclusion as a Schedule II substance under the 1971 Convention. Of concern is the dopaminergic update inhibition activity greater than that of cocaine.