1. Comments based on the review report

a. Evidence on dependence and abuse potential

*Dependence potential:* The critical review report described that there is no information available in animal and human studies.

*Abuse potential:* The critical review report described that the pharmacological potency of XLR-11 was several-fold greater than Δ9-THC. XLR-11 substituted for Δ9-THC in a Δ9-THC discrimination procedure in mice and rats, and then the substitutive effects were attenuated by a CB1 antagonist rimonabant. They suggested that XLR-11 share a pharmacological profile of *in vitro* and *in vivo* effects with Δ9-THC and would be predicted to produce Δ9-THC-like subjective effects in humans. However, there is no information available in human studies.

b. Risks to individual and society because of misuse

The critical review report described that the non-fatals cases with XLR-11 feature an association with acute kidney injuries. Commonly reported adverse reactions associated with a range of synthetic cannabinoids frequently include agitation, cardiovascular events including tachycardia and hypertension, hallucination, nausea/hyperemesis, seizures and hypokalemia. Chest pain myoclonia and psychiatric complications were also reported.

The high potency associated with many synthetic cannabinoids carries the risk of accidental overdose and potentially severe adverse events but information specific to XLR-11 is limited.

c. Magnitude of the problem in countries (misuse, illicit production, smuggling etc)

The critical review report described that the majority of available synthetic cannabinoid products including those identified to contain XLR-11 are sold in the form of herbal mixtures, and designed for smoking purposes. It is common for retailers
to purchase bulk quantities of the synthetic substance and to add a synthetic material to a variety of vegetable matter as a plant base. Products sold as herbal smoking mixtures frequently change in drug composition and quantity, often without indications on product labels.

XLR-11 (first reported in 2012) was encountered in seizures or as a used substance in 22 European countries. XLR-11 was reported 97 times to the UNODC by 39 countries since 2012. In South Korea, XLR-11 has been reported to represent the most frequently seized synthetic cannabinoid in 2013 with a total number of synthetic cannabinoid seizures reaching more than 40. Until 2014, XLR-11 was identified in 75 seized materials in 24 cases submitted to the National Forensic Service by the police or public prosecutor’s office. Furthermore, the US NFLIS 2015 midyear report documented that XLR-11 was featured in 3,769 out of 17,053 reports on synthetic cannabinoids. The total number of reports for the top 25 was 659,842 (cannabis/THC = 204,030 reports).

d. **Need of the substance for medical (including veterinary) practice**
XLR-11 has no medical or veterinary use.

e. **Need of the substance for other purposes (e.g. industrial)**
XLR-11 has no industrial or other use.

f. **Measures taken by countries to curb misuse**
XLR-11 is controlled in the following countries: Belgium, the Czech Republic, Denmark, Estonia, Finland, Hungary, Lithuania, Portugal, Romania, Turkey, the United Kingdom, China, Japan and the United States.

g. **Impact if this substance is scheduled**
There is no specific information but there are no known approved therapeutic and industrial applications for XLR-11 and it is not listed on the WHO Model List of Essential Medicines. Therefore, it is thought that there is no big influence even if this substance is controlled.

2. **Are there absent data that would be determinative for scheduling?**
Data regarding abuse and dependence potential are not enough for scheduling.
3. Other comments or opinions

The critical review report showed that XLR-11 acts as a full agonist for CB1 and CB2, and XLR-11 shows a higher potency than Δ⁹-THC in its ability to mediate Δ⁹-THC-like effects. It is known that XLR-11 possesses an abuse liability. Furthermore, severe adverse effects have been associated with a range of synthetic cannabinoids but the total numbers of cases that have been specifically linked to XLR-11 are more limited. Adverse effects associated with XLR-11 included acute kidney injury, low body temperature, rigid muscle tone, back or abdominal pain, elevated peak systolic blood pressure, slurred speech, lack of convergence, and body and eyelid tremors. Therefore, it is thought that it is preferable for XLR-11 to be scheduling.

4. Expert reviewer’s view on scheduling with rationale

Although XLR-11 possesses an abuse liability, data regarding abuse and dependence potential are not enough. The pharmacological effects of XLR-11 are stronger than those of Δ⁹-THC. Furthermore, adverse effects associated with XLR-11 included acute kidney injury, low body temperature, rigid muscle tone, back or abdominal pain, elevated peak systolic blood pressure, slurred speech, lack of convergence, and body and eyelid tremors. Δ⁹-THC is controlled as a Schedule I substance under the 1971 Convention.

Examinations concerning the dependence and abuse ability of XLR-11 are not sufficient, but when we think about the possibilities of its expanded abuse and the harmful effects which could be felt by this substance, XLR-11 could be placed under international control in Schedule II of the 1971 Convention.