Advisory Committee on Releases to the Environment

Advice on an application for deliberate release of a GMO for research and development purposes

Applicant: The Oxford Vaccine Group

Application: Investigating the role of typhoid toxin in the pathogenesis of enteric fever: A double-blinded, randomised, outpatient human challenge study.

Ref: 16/R48/01

Date: 10th February 2017

Advice of the Advisory Committee on Releases to the Environment under section 124 of the Environmental Protection Act 1990 to the Secretary of State for Environment, Food and Rural Affairs and Ministers of the Welsh Assembly Government.

ACRE is satisfied that the information provided by the applicant in accordance with the current regulations on the Deliberate Release of GMOs, demonstrates that the 'release' of this GMO under the conditions of the trial will not have an adverse effect on human health or the environment. ACRE therefore sees no reason for the release not to proceed.

Background

In July 2016 ACRE considered an application from the Oxford Vaccine Group for a clinical trial involving the release of this GMO in accordance with Directive 2001/18/EC. Members assessed the environmental risks (including risks to humans who have not been administered this GM vaccine) associated with the release of this GMO under the conditions of the trial set out in the application. No public representations were received on this trial.

The GMO

Salmonella Typhi is an obligate pathogen of humans – no other host is capable of developing infections or becoming colonised. To produce the vaccine for this clinical trial, S. Typhi (Quailes strain) was genetically modified such that the three genes responsible for producing typhoid toxins were

deleted from its genome. The main objective of the clinical trial is to compare the proportion of participants developing typhoid infection following administration of the wild type S. Typhi Quailes strain, with participants challenged with the genetically modified typhoid toxin-deficient strain (SB6000). The data gathered will provide important information regarding the role of typhoid toxin in the pathogenesis of enteric fever and could lead to a vaccine against a significant global health problem especially prevalent in low income nations.

The clinical trial

The study is expected to involve around 40 adult participants, half of which will receive the GM salmonella strain. Administration will be via the oral route and there is an expectation that faecal shedding of the GMO will occur in some participants at low levels until the completion of a 2 week course of antibiotics. Monitoring will take place for the duration of the clinical study. After receiving the relevant dose, participants will leave the health care facility but will be monitored daily for the first 14 days. The procedure for visits will depend on whether the participant develops infection or not.

If enteric fever is diagnosed, blood and stool sampling will be performed at 6, 12, 24, 48, 72 and 96 hours post diagnosis. Following completion of antibiotic treatment and confirmed clearance of the GMO in stool samples, participants will be monitored by way of long term follow-up visits at one, three, six and 12 months. The applicant has proposed volunteer exclusion criteria as a risk management measure to prevent transmission of the GMO to vulnerable groups. To minimise accidental transmission of the GMO to surfaces or to other individuals, the volunteers will be instructed to maintain strict personal hygiene during the study and proper hand washing techniques will be taught.

Comment

Following its initial consideration of the dossier, ACRE concluded that the environmental risk assessment was generally very thorough, and included a good description of the key areas where environmental exposure was most likely to occur as well as the measures that will be employed in order to minimise this risk. However, there were a few areas where ACRE required additional information in order to complete a full assessment of the risks to human health and the environment. These included a full sequence comparison with the wild type bacterium, data on environmental persistence and clarification of the monitoring regime. Following a detailed consideration of the additional information supplied by the applicant, ACRE were satisfied that sufficient evidence had been provided to demonstrate that the risk to

human health and the environment, by the proposed releases in this trial is negligible.

A potential route of environmental exposure is from the sewage system since shedding from stools is expected to occur in a proportion of participants. However, the existing mechanisms in place, notably the separation of sewage from potable water supplies, are sufficient to prevent onward transmission of the GMO (and the wild type Salmonella Typhi). This is supported by the fact that typhoid is not spread by infected travellers returning to the UK. It is possible that some of the shed organisms could enter environmental niches other than the sewage system, e.g. soil and water bodies, if a breach of the sewage system were to occur or if faecal samples containing the GMO were disposed of via facilities that do not involve a mains sewage system. However, the applicant provided robust data on the persistence of the parental GMO strain under other environmental scenarios, which demonstrated that that both strains survive only transiently in the environment and that the wild type and SB6000 strains are phenotypically similar with respect to persistence.

A further potential route of environmental exposure is at the point of administration. The applicant had treated this issue thoroughly. All waste materials will correctly be treated as ‘clinical waste’. In addition, the applicant has proposed volunteer exclusion criteria as a risk management measure to prevent transmission of the GMO to vulnerable groups. These are identified as follows; female participants who are pregnant or lactating, clinical or social workers with direct contact with young children or highly susceptible patients, commercial food handlers and; household contact with a young child and/or with someone who is immunocompromised. To minimise accidental transmission of the GMO to surfaces or to other individuals, the volunteers will be instructed to maintain strict personal hygiene during the study and proper hand washing techniques will be taught.

In conclusion ACRE is satisfied that the information provided by the applicant in accordance with the current regulations on the Deliberate Release of GMOs, demonstrates that the ‘release’ of this GMO under the conditions of the trial will not have an adverse effect on human health or the environment. ACRE therefore sees no reason for the release not to proceed.