ADVISORY COMMITTEE ON RELEASES TO THE ENVIRONMENT

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

Applicant: Emergent Product Development UK Ltd

Application: Application for Part B consent from Emergent Product Development UK Ltd to release live attenuated genetically modified *Salmonella enteri* (serovar typhi) for use in Phase II placebo-controlled clinical trials.

Ref: 10/R40/01

Date: 15 February 2011

Advice of the Advisory Committee on Releases to the Environment to the Secretary of State under section 124 of the Environmental Protection Act 1990

ACRE is satisfied that sufficient information of the requisite quality has been submitted by the applicant to demonstrate that the release of this GMO under the conditions of the trial will not have any adverse effect on human health and the environment. ACRE therefore sees no reason for the release not to proceed.

Background

At its meeting in February 2011, ACRE considered the application from Emergent Product Development UK Ltd for a clinical trial involving the release of this GM live attenuated oral vaccine against *S.typhi*. Members assessed the environmental risks[1] (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.

The GM vaccine

S.typhi (Ty2 aroC ssaV) ZH9 is a vaccine that has been developed by Emergent Product Development UK Ltd using a strain of *Salmonella typhi* that has been attenuated through mutations in two genes: (i) the *aroC* gene, which encodes chorismate synthase, an enzyme involved in the biosynthesis of aromatic compounds; (ii) the *ssaV* gene, which encodes a structural component of *Salmonella*

[1] ACRE's role is to give statutory advice to Ministers in the UK and devolved administrations on the risks to human health and the environment from the release and marketing of genetically modified organisms (GMOs). This does not include consideration of risks to volunteers in clinical trials.

pathogenicity island 2, required for survival and spread in the host genome. The mutations render the GMO unable to infect and colonise human hosts.

The clinical trial
This is a Phase II placebo-controlled clinical trial to investigate immune responses (including the potential protective effect) to the GMO *S.typhi* (Ty2 aroC ssaV) ZH9. Up to 180 healthy volunteers will be randomly assigned to one of three treatment groups to receive the GMO, placebo, or licensed typhoid fever vaccine. The applicant intends to administer a single dose of the GMO orally to a maximum of 60 volunteers. The highest dose of the GMO given to volunteers will be $1.7x10^{10}$ CFU. The vaccine will be administered at a single clinical study site in Oxford. Four weeks after treatment the volunteers will be challenged with the wild type *S. typhi* (Quailes strain). All volunteers will receive the antibiotic ciprofloxacin two weeks after being challenged with the wild type strain. Individuals that develop clinical typhoid fever will be treated with the antibiotic as soon as they are diagnosed. Three weeks after completing the antibiotic treatment, participants will be tested weekly until two successive stool samples test negative for *S. typhi*.

Inoculated volunteers will be leaving the health care facilities to join the wider community soon after administration of the vaccine. Volunteers will be asked to remain in England until 21 days after they have been dosed. The applicant has proposed exclusion criteria to minimise transmission of the GMO, particularly 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

In coming to its conclusion ACRE has considered the molecular characterisation of the GMO, its stability, potential routes of environmental exposure and proposed risk management measures and monitoring.

ACRE considered that the GMO was well-characterised. Risk of it reverting to wild type *S. typhi* or recombining with other bacteria in the environment to produce a novel pathogen is negligible. This is due to the characteristics of the organism – it is not prone to recombination and has 2 sizeable attenuating deletions (600 base pairs and 1909 base pairs). This is supported by evidence of stability in the application – serial passaging. The committee concluded that, given the history of previous releases of the GMO and that both deletions are sizeable, the GMO is well characterised and that the attenuating mutations are stable.

ACRE discussed the implications of the release of the GMO into the environment through shedding in stools. Once ingested, the GMO will not colonise or replicate in the host; it will pass through the GI tract and be shed in faeces. Blood and urine cultures from previous studies have returned negative results for the GMO and subsequently have not been considered by the applicant as potential routes for environmental exposure. ACRE concluded that the existing mechanisms in place in England, notably the separation of sewage and potable water supplies, are sufficient to ensure that the GMO (and the wild type *Salmonella typhi*) would be controlled effectively. This is supported by the fact that typhoid is not spread by infected travellers returning to the UK. However, not all water goes through typical sewerage system. Therefore, the applicant has provided data on persistence under other conditions. ACRE concluded that there were sufficient data from previous clinical

trials to conclude that the GMO, once outside human hosts[2] was not capable of replication and has a limited survival time and therefore would not persist for long periods in the environment.

ACRE considered the clinical study set up more broadly – to ensure that environmental exposure is minimised. The applicant has proposed strict exclusion criteria for the trial to minimise the risk of transmission of the GMO to potentially vulnerable groups 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. ACRE considered the exclusion criteria proposed by the applicant with the recommendation that this included care workers helping the elderly.

ACRE considered the monitoring that is intended for this release. The applicant does not propose to monitor the shedding profile of the GMO because of the data generated in previous studies. ACRE considered the data provided by the applicant and noted that the maximum dose of $1.7x10^{10}$ CFU had only been used in one previous trial and this was in the United States. ACRE concluded that given the historical record for management of typhoid in the natural environment in the UK and the administration of the antibiotic ciprofloxacin, persistent shedding will not be an issue and that the monitoring was proportionate given the low risks posed to human health and the environment from this release. However the applicant should consider whether the current trial plan will provide sufficient information to satisfy regulatory authorities on environmental issues at the full Marketing Authorisation application stage.

ACRE considered that the applicant had submitted a good quality dossier, which provided sufficient evidence for an assessment of potential risks. ACRE concluded that this assessment demonstrated that the risks posed to human health and the environment, by the proposed releases in this trial, are negligible.

Items arising from Public Representations

One representation was received on this application from members of the public. The representation expressed personal opinions on the use of GMOs and did not include reference to further scientific or technical information for consideration by the committee.

[2] *S.Typhi* is host restricted and only infects human. It does not infect and is not harboured by animals and plants.