



ADVISORY COMMITTEE ON RELEASES TO THE ENVIRONMENT

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

Applicant: Acambis Research Ltd

Application: To release genetically modified live attenuated enterotoxigenic *Escherichia coli* as part of a human clinical trial to test the effectiveness of a vaccine against travellers' diarrhoea.

Ref: ¹03/R35/3

Date: 18th August 2003

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 all appropriate measures have been taken to avoid adverse effects on human health and the environment from the proposed release and sees no reason for the release not to proceed on the following condition.

The holder of the consent shall notify the following information at the times shown:

The effects of the release as authorised by the consent, for the assessment of any risks there are of damage to human health and the environment from the genetically modified organisms concerned. This should be in the form of reports submitted:

- by one month after the date of administration of the last dose of the GMO in the clinical trial; to evaluate shedding of the GM bacteria during the clinical trial by assessment of the quantity and period over which shedding of the GMO from volunteers occurred. This to be provided with a report on the general health of the volunteers.

Background

ACRE considered this application at their meeting of the 5 June 2003 and in subsequent correspondence. The committee also received expert advice from the Director of the Laboratory of Enteric Pathogens at the Central Public Health

¹Application reference 03/R35/3 dated 16 May 2003 taking into account all information and amendments as in the applicant's letter dated 11 June 2003 and 15 August 2003.

Laboratory and a clinical and public health bacteriology expert from the West Midlands Public Health laboratory.

The GM strain

Acambis Research Ltd have developed a genetically modified enterotoxigenic *E. coli* (ETEC) strain as a candidate vaccine for use against travellers' diarrhoea.

Wild-type virulent ETEC bacteria adhere to and colonise the intestine where they secrete enterotoxins which are responsible for causing diarrhoea. The GM derivative being evaluated in the proposed clinical trial has been genetically engineered so that it has lost its' ability to produce toxins. In addition, the *aroC* gene which is required in the biosynthesis of aromatic amino acids, and the *ompC* and *ompR* genes which encode outer membrane proteins, have been deleted from the genome to create an attenuated ETEC vaccine strain. The resulting strain, known as ACAM2007, is the parent strain for which deliberate release consent was granted in July 2002 (Ref: 02/R35/1).

The GM ETEC strain for which consent is applied for in this application contains an additional colonisation factor (CS1) which has been obtained from a different ETEC strain and is inserted into the deleted *ompC* locus. CS1 is expressed in addition to two naturally expressed colonisation factors and is intended to induce an immune response to this protective antigen.

The clinical trial

To test the efficacy of the vaccine, the GM *E.coli* strain will be administered orally to healthy volunteers at the Clinical Research Centre at Barts & The Royal London School of Medicine & Dentistry. Volunteers will be able to leave the building soon after vaccination to go about their normal daily activities. Acambis predict that participants may excrete viable GM bacteria in their stools up to 38 days post-vaccination. The volunteers are likely to live predominantly in the area centred around the hospital site. Travel will be restricted due to the requirement to attend the hospital every 2-3 days and the volunteers are not permitted to leave England until they are no longer excreting GM bacteria. In the event that recipients of the vaccine experience significant diarrhoea or have to leave England in an emergency they will be treated with an antibiotic which has been shown to be effective in preventing any further excretion of the GM bacteria within 24 hours of giving the first dose.

Comment

Naturally occurring virulent enterotoxigenic *Escherichia coli* (ETEC) is a common cause of dehydrating diarrhoea worldwide. A significant proportion of travellers returning to the UK from overseas excrete ETEC in their stools. Such individuals constitute a source of continuous release of natural virulent ETEC into our sewage system.

A thorough risk assessment of the attenuated parent ETEC vaccine strain has already been made by ACRE during consideration of a previous deliberate release application 02/R35/1. The difference between the GMO in the earlier application and the one being considered here is the additional operon encoding a colonisation factor. ACRE considered whether the insertion of this operon would affect the risk assessment of the GMO. The committee is content that the CS1 insert is not expected to have any impact on survival or dissemination of the GMO in the environment. The Committee expressed interest in future development of this GM vaccine and commented that should further colonisation factors be added to the GMO that the committee would request greater consideration of the implications of

their presence with particular reference to persistence in the gut and the effect on shedding.

ACRE were satisfied that the detection methods specified in the application were sufficient to identify the GM ETEC strain within a diverse population of enteric bacteria. These methods are adequate for the purpose of monitoring for the occurrence and extent of shedding during the trial. However the Committee requested more detailed information on how the monitoring of volunteers would be achieved and was subsequently satisfied with the proposed plan.

In assessing this application ACRE considered the risk to trial volunteers, people in the wider community and the environment. ACRE concluded that based on the risk assessment provided by the applicant that the risk from this particular GMO to human health and the environment is low. This is based, in part, on the fact that the organism does not survive in the environment and is effectively destroyed in the sewage system along with a significant amount of other enteropathogens which are released in exactly the same manner in the UK on a daily basis.

Items arising from public representations

No representations were received from the public in relation to this application.