



ADVISORY COMMITTEE ON RELEASES TO THE ENVIRONMENT

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

Applicant: Microscience Ltd

Application: To release genetically modified *Salmonella typhi* for the purpose of a human clinical trial to test the effectiveness of a vaccine against Hepatitis B.

Ref: 02/R37/02¹

Date: 4th July 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 GMOs concerned. This should be in the form of a report 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

The GM strain

Microscience Ltd have developed this GM vaccine using a strain of *Salmonella typhi* in which a gene involved in metabolism and another gene for growth and survival have been mutated so that they are no longer functional. These mutations reduce the pathogenicity of the organism and its ability to survive, multiply and cause

¹Application reference 02/R37/02 dated 20th December 2002 taking into account all information and amendments as in the applicant's letters dated 3rd January 2003, 21st January 2003, 6th February 2003, 17th March 2003, 20th March 2003, 15th April 2003 and 19th June 2003.

disease. The attenuated strain has been further modified by insertion of a gene encoding a synthetic version of an antigen from Hepatitis B virus. The GMO will be used as a vaccine to deliver the Hepatitis B virus antigen to cells where an immune response would be stimulated.

The clinical trial

To test the efficacy of the vaccine, the proposal is to give the vaccine orally to healthy volunteers at BIBRA International Ltd, Carshalton, Surrey. The consenting volunteers will be able to leave the facility soon after the vaccination to go about their normal daily activities. Microscience expect that some of the participants may excrete viable GM bacteria in their stools for up to 7 days following vaccination and this will consequently pass into the sewage system. Travel will be restricted due to the requirement to attend the hospital daily and the volunteers are not permitted to leave England until they are no longer excreting GM bacteria. This will be determined by sampling of blood, urine and stool samples until they are clear of the GMO on two consecutive days. In the event that a subject is considered to have a clinically-significant infection with the GMO they will be treated with antibiotics.

Comment

In coming to its conclusion ACRE considered not only the risk to the environment and to people in the wider community, but also considered the safety of volunteers in the trial. In arriving at its advice Members considered the application against the requirements of the legislation and in particular:

- What is the likelihood of and consequences for reversion of the GM vaccine strains to the wild-type state?
- Is the host range of the strains altered? Could they infect livestock?
- Will these strains persist in the environment as self-sustaining colonies?
- Will they harm the environment?
- Can the strains be detected and identified in the environment – particularly sewage where most will be shed which is replete with similar bacteria?
- Are the volunteers who ingest the vaccine safe? Will those in the wider community be safe?

A thorough assessment of the attenuated *S. typhi* strain has already been made by ACRE during the Committee's consideration of a previous deliberate release application, 02/R37/01 and ACRE's detailed consideration is explained in the advice on that application. The essential difference between the GMO considered in that application and the one considered here is the inserted gene encoding a synthetic version of an antigen from the Hepatitis B virus. In particular ACRE considered whether the insertion of this gene would affect the risk assessment of the GMO in any way.

In assessing this application ACRE raised a number of questions which were referred back to the applicants. In particular, as with the previous application, ACRE noted with concern that the applicant had made an assumption that treatment of waste water in England always involved the use of chlorinated water. The applicants were asked to revise their application from the perspective that waste may enter unchlorinated water or the wider environment. ACRE also considered the possibility that the GMO may not always be disseminated into the sewers but into the wider environment.

In considering potential persistence in the environment ACRE requested further information on survival of the GMO in sewage and were subsequently content that this particular GMO will not have a competitive advantage in sewage over naturally occurring organisms. The committee also took into account the potential for a vaccinated individual to become a persistent shedder of the GMO. The committee was satisfied that, following release of the GMO in stools of vaccinated volunteers, the GMO is unlikely to proliferate.

ACRE considered the potential for reversion of the GMO by acquisition of wild type sequences from other bacteria and was content that, since the sequence of the antigen gene inserted is viral rather than bacterial in origin, it is unlikely to contribute to recombination with genes from enteric bacteria.

S. typhi is very host specific. There are no known animals, plants or insects that it can colonise or use as a vector for transmission. The genetic modifications in the vaccine strain have been designed to reduce growth and survival of the GMO and not to change the host range. Attenuation of the GMO makes it weaker than the wild type strain and puts it at a competitive disadvantage. It is therefore not likely to be more competitive in terms of host range and pathogenicity. ACRE requested further information on potential host range of the GMO and was satisfied that the likelihood of a change in host range for the GM bacterium were low.

ACRE were satisfied that the detection methods specified in the application were sufficient to identify the GM *S typhi* within a diverse population of enteric bacteria. These methods are adequate for the purpose of monitoring the occurrence and extent of shedding during the trial. The Committee requested that monitoring reports be provided following vaccination of volunteers for evaluation of the level of shedding of the GMO.

Items arising from Public Representations

ACRE considered the representation received from a member of the public regarding potential transmission of the GMO to vulnerable members of the community. ACRE was content that this issue had been considered thoroughly during the Committee's assessment of the dossier. ACRE was satisfied that no new issues had been raised from the public with respect to this application.