



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.¹

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: 06/R40/1²

Date: 8 March 2007

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 has considered the new information provided by Emergent Biosolutions concerning proposed changes to the notification for the release of genetically modified *Salmonella typhi*, for the purpose of a human clinical trial. On the basis of the information supplied, the Committee is satisfied that the notified changes to the procedures and dates of the release do not affect the environmental risk assessment for this release or the advice previously issued by this Committee.

Comment

ACRE considered the application to release this GMO as part of a clinical trial and issued advice (attached at Annex I) on 12th April 2006.

Further Information

The company provided information on a proposed change to the location of scheduled blood draws specified in the original protocol. The company proposes to change the location of such visits from the clinical study room used for the administration of the GMO to the phlebotomy service within the main Royal London Hospital. All staff administering the GMOs will still require registration by the local Advisory Committee on Genetic Manipulation. However, staff taking scheduled blood samples may not be registered by the Committee but will have occupational health clearance to work with hepatitis B infected patients.

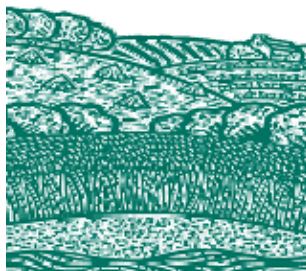
¹ The consent for this release was issued to Emergent Europe Ltd., the company subsequently changed it's name to Emergent Product Development UK Ltd..

² The consent for this release was issued to Emergent Europe Ltd. on 26 April 2006. The consent was subsequently varied on 20 June and 15 August 2006.

The company also provided further information on the timing of the release. Emergent Biosolutions proposes to extend the release period until September 2008, following a delayed start to this trial in December 2006.

The Committee is satisfied that the change in the location of the blood sampling and the staff involved with blood samples taken during the course of the study do not affect the environmental risk assessment associated with this release. The Committee considers that live GMOs are very unlikely to be present in the blood of patients following dosing with the attenuated *S. typhi* strain. Even if a patient did develop bacteraemia all staff trained to work with patients suffering from Hepatitis B operate under strict safety standards and are therefore very unlikely to be exposed to *S. typhi*. The precautions taken by staff will ensure that contaminated medical waste is disposed of in a manner that minimises the risk of exposure to others. ACRE is also satisfied that the change in the timing of the release does not affect the environmental risk assessment.

Annex I



ADVISORY COMMITTEE ON RELEASES TO THE ENVIRONMENT

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Applicant: Emergent Europe 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: 06/R40/1³

Date: 12 April 2006

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 seven months after the date of administration of the last dose of the GMO in the clinical trial; on the general health of the volunteers during the period of the study and to include information on whether the GMO was shed by volunteers in stool samples taken 6 months after the final dosing.

Background

The GM strain

Emergent Europe Ltd have developed this GM immunotherapy 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

³Application reference 06/R40/01 dated 20th February 2006 as amended by information from the applicant on 1st and 3rd March 2006.

and cause 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 an immunotherapy to deliver the Hepatitis B virus antigen to cells where an immune response would be stimulated.

ACRE previously considered the release of this GMO in a Phase I trial ref 02/R37/02 on healthy volunteers and issued advice on 4th July 2003.

The clinical trial

To test the efficacy of the immunotherapy, the proposal is to administer the immunotherapy orally to patients suffering from Hepatitis B infection. The patients will be able to leave the facility soon after dosing to go about their normal daily activities. Emergent Europe expect that 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. Volunteers will be asked to remain in England until 14 days after they have been dosed and it is anticipated that they will no longer be excreting GM bacteria at this stage. Participants will be examined for signs of systemic infection in the period following dosing and a stool sample will be taken at a final health check 6 months after the final dose is given. 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 the risk posed by this release to the environment and to people in the wider community. In arriving at its advice members considered the application including the results of the post market monitoring report from the previous release against the requirements of the legislation.

In assessing this application ACRE focussed its assessment on the differences between the protocol for the proposed release and that used in the release previously granted consent (ref. 02/R37/02). In particular:

- Whether the results of the post-trial monitoring from the previous release indicated that any element of the Committee's former assessment should be altered.
- The impact of increased dose on the shedding profile of the GMO.
- The impact of reducing the number of occasions on which shedding in stools was assessed.

The committee considered the post-trial monitoring report from the previous release of this GMO and concluded that the results supported ACRE's risk assessment of the previous release of this GMO given as advice on 4th July 2003.

The Committee considered whether the increased dose of the GMO that the notifier intends to administer to patients during this release was likely to alter the duration of shedding of this GMO. The notifier provided evidence that a range of doses up to 10⁹ of a related organism did not increase the duration shedding to more than 7 days following vaccination. The Committee concluded that there was no reason to expect that this organism would be shed for longer than the time stated in the notifier's risk assessment.

ACRE welcomed the additional information that had been provided in this application on the persistence of the GMO in sewage and accepted the conclusion of the notifier

that this organism is unlikely to persist in sewage. The applicant states in the application that any organisms remaining in sewage would be killed by UV treatment, the Committee note that UV treatment of sewage in the UK is not typical but concluded that this does not change the assessment that this GMO will not have a competitive advantage in sewage over naturally occurring organisms and is no more likely to persist than the wild type *Salmonella typhi*. The Committee was satisfied that, following release of the GMO in stools of vaccinated volunteers, the GMO is unlikely to proliferate.

The Committee considered whether the proposed monitoring of patients' health during this release was sufficient to ensure that a treated individual would not become a persistent shedder of the GMO. The Committee concluded that the attenuation of this strain was well documented and therefore that systemic infection would not result as a consequence of dosing patients with this GMO. The Committee noted that shedding beyond the 7 day period had resulted from the release of a related GMO but that no clinical infection was indicated.

The Committee concluded that their previous advice on this GMO was still applicable and that attenuation of this GMO was sufficient to ensure that administration to the patients in this trial would not result in systemic infection or increased persistence of this GMO in the environment. The Committee also considered that the provision of hygiene training to patients involved in the trial, together with the exclusion criteria to be used and the monitoring of patient health, was sufficient to ensure that this release would not pose a risk to human health or the environment. The Committee recommended that this dossier should be accepted as provided.

Items arising from Public Representations

No public representations were received on this application from members of the public.