PART B: INFORMATION ABOUT THE RELEASE APPLICATION TO BE INCLUDED ON THE PUBLIC REGISTER

B1. The name and address of the applicant.

Emergent Europe Ltd,
540-545 Eskdale Road,
Winnersh Triangle,
Wokingham,
Berkshire RG41 5TU.

B2. The full or general description of the genetically modified organisms in relation to which the application is being made.

The GMO to be released is a candidate oral immunotherapy (M04NM11) intended for use as a treatment for patients chronically infected with the Hepatitis B virus. The immunotherapy comprises an attenuated bacterial strain (the recipient strain) expressing a Hepatitis B virus antigen (Hep B antigen). The Hep B antigen can elicit an immune response against the Hepatitis B virus that may help to clear the virus from the patient. The attenuation and safety of the organism has been demonstrated in a previous clinical study involving healthy adult volunteers.

The organism is derived from the recipient strain by introduction of a promoter-gene fusion which allows expression of the Hep B antigen. Attenuation of the recipient strain has been achieved through the introduction of two deletion mutations into the chromosome. The first attenuating deletion is in a gene involved in metabolism. The safety of this attenuating strategy has been established in several clinical studies, this mutation being the basis of attenuation for several oral typhoid immunotherapies now in Phase II studies in the US. The second attenuating deletion is in a gene involved in survival and growth in the host. This mutation prevents replication of the immunotherapy strain in humans. A mutation in this gene provides an additional level of safety over that of the first mutation alone. The recipient strain was originally derived from a virulent bacterial strain (the parent strain). This strain has been used as a background strain for constructing candidate typhoid vaccines evaluated in volunteers previously. The currently U.S. and European licensed live oral typhoid vaccine is derived from this strain.

B3. The location(s) at which the genetically modified organisms will be released.

Clinical study site 1 is Royal London Hospital, Clinical Science Research Building, London E1 2AT.
Clinical study site 2 is King's College London School of Medicine, London SE5 9PJ.
B4. The general purpose or details of the purpose for which the genetically modified organisms will be released.

The organism will be evaluated as a candidate oral immunotherapy in a clinical study in patients who are chronic carriers of hepatitis B. The key objective of the study will be to evaluate the safety and immunogenicity of up to six oral doses of the immunotherapy.

B5. The foreseen dates of the release.

The clinical study will begin in May 2006. Recruitment of subjects is expected to take up to 15 months, with the last dose administered to the last subject approximately 6 months later (February 2008). The immunotherapy will be given orally to subjects who are likely to shed the organism in faeces at low levels for no longer than 7 days. Shedding constitutes the release, thus the release will end within 7 days of the last dose being given to the last subject (February 2008).

B6. The methods and plans for monitoring the genetically modified organisms and for emergency response.

The organism has been constructed so as not to cause harm and not to persist in the environment. The GMO can be uniquely identified by genetic analysis.

Safety monitoring of the volunteers is a vital aspect of monitoring for the organism. The immunotherapy will be given orally to volunteers who are likely to shed the organism in faeces for up to 7 days. Throughout the study subjects will have regular safety assessments. If a subject develops clinical symptoms that suggest an infection, he/she will be appropriately assessed by the Clinical Investigator and treated with antibiotics to clear the infection. As the clinical infection could lead to the organism being shed in faeces, samples of faeces will be cultured, before and after antibiotic therapy, to monitor for the presence of the organism.

Transmission of the organism within the environment is readily controlled by sewage treatment processes, disinfection of hard surfaces by standard disinfectants and chlorination of drinking water.
B7. The evaluation of the environmental impact of the genetically modified organisms, in particular any pathogenic and/or ecologically disruptive effects.

The GMO is a severely attenuated strain of a human-specific pathogen (the parent strain) expressing a Hep B antigen and is intended for use as an immunotherapy for Hepatitis B infection. The immunotherapy will be given orally to volunteers who are likely to shed the organism in stools at low levels for no longer than 7 days. This will constitute the release of the organism resulting in the potential release into the sewage system. Normal basic hygiene precautions, namely the use of toilets and hand washing, are considered sufficient to prevent person to person transmission.

The advantage of using the chosen parent strain as the vector is that there are no animal reservoirs and it does not persist in the environment. The GMO therefore will not persist in the environment as it does not have a selective or survival advantage.

The potential for genetic exchange with any other organisms in the environment is extremely low, given that the GMO does not contain any plasmids (or antibiotic resistance markers), will not persist in the subjects and does not persist in the environment. The health of the volunteers will be carefully monitored as their safety is paramount in this study.

The GMO has previously been tested in healthy human volunteers and has been shown to be safe, well tolerated and not persistently shed. It is not likely that the organism will become more persistent or invasive when administered to the subjects in the proposed study.

For the purpose of the release the GMO will be given to a maximum of 30 subjects at two sites. The subjects will be patients who are chronic carriers of Hepatitis B. The GMO will be shed in stools for up to 7 days after administration and therefore the subjects will not be permitted to travel outside England for 14 days following each dosing day.

The information presented in this application demonstrates the safety of the GMO, in terms of its inability to cause harm and to persist in the environment. Clearly it is the key objective of the clinical trial to assess the safety of the GMO in the subjects. The risk assessment shows a low hazard associated with administering the organism to these human volunteers, the risk to other humans is considered to be negligible and the risk to the environment is considered to be effectively zero.