PART 1 (COUNCIL DECISION 2002/813/EC)

SUMMARY NOTIFICATION INFORMATION FORMAT FOR THE RELEASE OF GENETICALLY MODIFIED ORGANISMS OTHER THAN HIGHER PLANTS IN ACCORDANCE WITH ARTICLE 11 OF DIRECTIVE 2001/18/EC

In order to tick one or several possibilities, please use crosses (meaning x or X) into the space provided as (.)

A. General information

1. Details of notification

Member State of notification GE

(a) Notification number B/DE/08/PEI574

(b) Date of acknowledgement of notification 02/01/2008

Title of the project Phase I Open Label, Randomized, Controlled, Dose-Escalation Study to Evaluate Safety and Immunogenicity of VPM1002 in Comparison with BCG in Healthy Male Volunteers Stratified for History of BCG-Vaccination

(c)

Proposed period of release From 21/08/2008 until 23/11/2009

(d)

2. Notifier

Name of institution or company: Vakzine Projekt Management GmbH

3. GMO characterisation

(a) Indicate whether the GMO is a:

viroid	(.)
RNA virus	(.)
DNA virus	(.)
bacterium	(x)
fungus	(.)
animal	
- mammals	(.)
- insect	(.)
- fish	(.)
- other animal	(.)

specify phylum, class …

(b) Identity of the GMO (genus and species)
rBCGΔureC::Hly+::Hyg+ (VPM1002) (Mycobacterium bovis Bacille Calmette-Guérin (BCG) strain)

(c) Genetic stability – according to Annex IIIa, II, A(10)
There is genetic variety in the mycobacteria family. There are no other mycobacterial typical factors known except the general mutational factors like multi passages and radioactivity and/or chemicals. During the scientific development, several passages of the strain VPM1002 were performed and genetic instability was never observed. To the contrary, it was proven that all strains, starting with parental seed up to the IMP-1, have a 100% homology in the inserted sequence

4. Is the same GMO release planned elsewhere in the Community (in conformity with Article 6(1)), by the same notifier?
Yes (.) No (x)
If yes, insert the country code(s) …

5. Has the same GMO been notified for release elsewhere in the Community by the same notifier?
Yes (.) No (x)
If yes:
- Member State of notification …
- Notification number B/../../…

Please use the following country codes:
Austria AT; Belgium BE; Germany DE; Denmark DK; Spain ES; Finland FI; France FR; United Kingdom GB; Greece GR; Ireland IE; Iceland IS; Italy IT; Luxembourg LU; Netherlands NL; Norway NO; Portugal PT; Sweden SE

6. Has the same GMO been notified for release or placing on the market outside the Community by the same or other notifier?
Yes (.) No (x)
If yes:
- Member State of notification …
- Notification number B/../../…

7. Summary of the potential environmental impact of the release of the GMOs.

The following conclusions base on the knowledge about the original organism BCG in combination with VPM1002-specific preclinical data. The likelihood that VPM1002 becomes persistent and invasive in natural habitats under the conditions of this clinical trial is negligible. Only persistence in the vaccinated volunteers is anticipated as part of the intended strategy of vaccination (live vaccine).
There is no selective advantage of VPM1002 in the environment.
A transmission of chromosomally integrated genes can be ruled out for BCG organisms.
The probability of immediate and/or delayed environmental impact of the direct or indirect interactions between VPM1002 with non-target organisms is negligible.
The elucidation of immediate and/or delayed effects on human health resulting from interactions of the GMO and the vaccinated volunteers is the primary objective of the intended clinical study.
There will be no impact on animal health and consequences for the feed/food chain because only humans will be vaccinated.
The techniques for management of the GMO are either common laboratory practice (e.g. Page 3 of 16

PCR) or medical practice (e.g. vaccination procedure identical to that of well established BCG).

B. Information relating to the recipient or parental organism from which the GMO is derived

1. Recipient or parental organism characterisation:

(a) Indicate whether the recipient or parental organism is a:

(select one only)

viroid	(.)
RNA virus	(.)
DNA virus	(.)
bacterium	(x)
fungus	(.)
animal	
- mammals	(.)
- insect	(.)
- fish	(.)
- other animal	(.)
(specify phylum, class)	…

other, specify …

2. Name

(i)	order and/or higher taxon (for animals)	…
(ii)	genus	Mycobacterium
(iii)	species	bovis
(iv)	subspecies	…
(v)	strain	BCG subtype Prague
(vi)	pathovar (biotype, ecotype, race, etc.)	…
(vii)	common name	M. bovis Bacille Calmette-Guerin

3. Geographical distribution of the organism

(a) Indigenous to, or otherwise established in, the country where the notification is made:
Yes (x) No (.) Not known (.)

(b) Indigenous to, or otherwise established in, other EC countries:
(i) Yes (.)

If yes, indicate the type of ecosystem in which it is found:

Atlantic	x
Mediteranean	x
Boreal	x

	Alpine	x
	Continental	x.
	Macaronesian	x

(ii) No (.)
(iii) Not known (.)

(c) Is it frequently used in the country where the notification is made?
Yes (.) No (x)

(d) Is it frequently kept in the country where the notification is made?
Yes (x) No (.)

4. Natural habitat of the organism
None

(a) If the organism is a microorganism

water	(.)
soil, free-living	(.)
soil in association with plant-root systems	(.)
in association with plant leaf/stem systems	(.)
other, specify …	

(b) If the organism is an animal: natural habitat or usual agroecosystem:
…

5. (a) Detection techniques
PCR fingerprint and sequencing,

(b) Identification techniques
PCR fingerprint and sequencing,

6. Is the recipient organism classified under existing Community rules relating to the protection of human health and/or the environment?
Yes (x) No (.)
If yes, specify
PCR fingerprint and sequencing,

7. Is the recipient organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?
Yes (.) No (x) Not known (.)
The recipient organism is a medicinal product and has been used millions of times. The undesirable effects are described in the summary of product characteristics of a marketed BCG vaccine:
The expected reaction to successful vaccination with BCG Vaccine includes induration at the injection site followed by a local lesion that may ulcerate some weeks later and heal over some months leaving a small, flat scar. It also may include enlargement of a regional lymph node to < 1 cm. Undesirable effects of the vaccine include the following:

Uncommon (>1/1000,<1/100)
Systemic: Headache, fever.
Local: Enlargement of regional lymph node >1 cm. Ulceration with a discharging ulcer at the site of injection
Rare (<1/1000)
Systemic: Disseminated BCG complications as osteitis or osteomyelitis. Allergic reactions, including anaphylactic reactions.
Local: Suppurative lymphadenitis, abscess formation.
An excessive response to the BCG Vaccine SSI may result in a discharging ulcer.
If yes:

(a) to which of the following organisms:

humans	(.)
animals	(.)
plants	(.)
other	(.)

(b) give the relevant information specified under Annex III A, point II. (A)(11)(d) of Directive 2001/18/EC
…

8. Information concerning reproduction

(a) Generation time in natural ecosystems:
No natural ecosystem. See. 3. There is no significant replication of M. bovis BCG outside its hosts (vaccinated mammalians) or special culture media

(b) Generation time in the ecosystem where the release will take place:
Not known. The generation time of VPM1002 under optimal culture conditions is 8 hours.

(c) Way of reproduction: Sexual .. Asexual x

(c) Factors affecting reproduction:
host defense

9. Survivability

(a) ability to form structures enhancing survival or dormancy:

(i)	endospores	(.)
(ii)	cysts	(.)
(iii)	sclerotia	(.)
(iv)	asexual spores (fungi)	(.)
(v)	sexual spores (funghi)	(.)
(vi)	eggs	(.)
(vii)	pupae	(.)
(viii)	larvae	(.)
(ix)	other, specify …	

(b) relevant factors affecting survivability:
host defense

10. (a) Ways of dissemination
Multiplication or dissemination of M. bovis BCG in the environment has never been detected

(b) Factors affecting dissemination
Multiplication or dissemination of M. bovis BCG in the environment has never been detected

11. Previous genetic modifications of the recipient or parental organism already notified for release in the country where the notification is made (give notification numbers)
none

C. **Information relating to the genetic modification**

1. Type of the genetic modification

(i)	insertion of genetic material	(x)
(ii)	deletion of genetic material	(x)
(iii)	base substitution	(.)
(iv)	cell fusion	(.)
(v)	others, specify …	

2. Intended outcome of the genetic modification
The intended outcome after insertion of the listeriolysin gene and the deletion of parts of the urease C gene was the efficacious and well-tolerated immune induction against *M. tuberculosis.*

3. (a) Has a vector been used in the process of modification?
Yes (x) No (.)

If no, go straight to question 5.

(b) If yes, is the vector wholly or partially present in the modified organism?
Yes (x) No (.)

If no, go straight to question 5.

4. If the answer to 3(b) is yes, supply the following information

(a) Type of vector

plasmid	(x)
bacteriophage	(.)
virus	(.)
cosmid	(.)
transposable element	(.)
other, specify …	

(b) Identity of the vector
pVEP2003, the plasmid used to generate the VPM1002 is an E. coli shuttle vector, based on the pJSC284 plasmid

(c) Host range of the vector
Escherichia coli

(d) Presence in the vector of sequences giving a selectable or identifiable phenotype

Yes (x) No (.)

antibiotic resistance (x)
other, specify …

Indication of which antibiotic resistance gene is inserted
Hygromycin

(e) Constituent fragments of the vector
The plasmid carries an E. coli origin of replication but no Mycobacterial origin of replication, which makes this plasmid to a suicide plasmid which cannot replicate in mycobacteria.

(f) Method for introducing the vector into the recipient organism

(i)	transformation	(.)
(ii)	electroporation	(x)
(iii)	macroinjection	(.)
(iv)	microinjection	(.)
(v)	infection	(.)
(vi)	other, specify …	

5. If the answer to question B.3(a) and (b) is no, what was the method used in the process of modification?

(i)	transformation	(.)
(ii)	microinjection	(.)
(iii)	microencapsulation	(.)
(iv)	macroinjection	(.)
(v)	other, specify …	

6. Composition of the insert

(a) Composition of the insert
The vector contains a Listeriolysin (hly) expressing cassette under the regulation of the mycobacterial promoter sequence from the heat shock protein 65 (hsp65) fused to the leading sequences of the Antigen85B (Ag85B) to allow the secretion of the hly. A hygromycin resistance cassette is as well included in the vector for selection reasons. For homologous recombination reasons approx. 800bp UreC flanking regions were cloned up- and downstream the hly-hyg cassette. Homologous recombination of these regions in the genome of BCG would lead to the replacement of the UreC coding Page 8 of 16 region with the hygromycin + hly. The hygromycin cassette is flanked by 2 γδ resolvase recognition sites which can be used to excise the hygromycin out of the VPM1002 vaccine candidate upon extrachromosomal expression of the resolvase. The plasmid carries an E. coli origin of replication but no Mycobacterial origin of replication, which makes this plasmid to a suicide plasmid which cannot replicate in mycobacteria. Upon homologous recombination of the plasmid only the sequences between UreC-P1-P2 and

UreC P3-P4 would be integrated in the genome. The plasmid carries no transposable elements

(b) Source of each constituent part of the insert
hly Listeria monocytogenes…

(c) Intended function of each constituent part of the insert in the GMO
hly: disruption of the UreC gene to enhance acidification of phagosome, escape of VPM1002 from phagosome into cytoplasm

(d) Location of the insert in the host organism

- on a free plasmid (.)
- integrated in the chromosome (x)
- other, specify …

(e) Does the insert contain parts whose product or function are not known?
Yes (.) No (x)
If yes, specify …

D. Information on the organism(s) from which the insert is derived

1. Indicate whether it is a:

viroid (.)
RNA virus (.)
DNA virus (.)
bacterium (x)
fungus (.)
animal
- mammals (.)
- insect (.)
- fish (.)
- other animal (.)
(specify phylum, class) …

other, specify …

2. Complete name

(i)	order and/or higher taxon (for animals)	…
(ii)	family name for plants	…
(iii)	genus	Listeria
(iv)	species	monocytogens
(v)	subspecies	…
(vi)	strain	…
(vii)	cultivar/breeding line	…
(viii)	pathovar	…
(ix)	common name	L. monocytogenes

3. Is the organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?
Yes (x) No (.) Not known (.)
If yes, specify the following:

(b) to which of the following organisms:

humans (x)
animals (x)
plants (.)
other ..

(b) are the donated sequences involved in any way to the pathogenic or harmful properties of the organism
Yes (x) No (.) Not known (.)

If yes, give the relevant information under Annex III A, point II(A)(11)(d):
Due to the fact that only one truncated gene of L. monocytogenes is used, details on the parameters mentioned in this paragraph were omitted.

4. Is the donor organism classified under existing Community rules relating to the protection of human health and the environment, such as Directive 90/679/EEC on the protection of workers from risks to exposure to biological agents at work?
Yes (x) No (.)
If yes, specify *L. monocytogenes* is classified as risk group 2 according to §3 "Biostoffverordnung".

5. Do the donor and recipient organism exchange genetic material naturally?
Yes (.) No (x) Not known (.)

E. Information relating to the genetically modified organism

1. Genetic traits and phenotypic characteristics of the recipient or parental organism which have been changed as a result of the genetic modification

(a) is the GMO different from the recipient as far as survivability is concerned?
Yes (.) No (x) Not known (.)
Specify No shedding of the GMO has been observed in the performed study

(b) is the GMO in any way different from the recipient as far as mode and/or rate of reproduction is concerned?
Yes (.) No (x) Unknown (.)
Specify No faster replication time has been observed in vitro. No shedding of the GMO has been observed in the performed study

(c) is the GMO in any way different from the recipient as far as dissemination is concerned?
Yes (.) No (x) Not known (.)

Specify No shedding of the GMO (nor of the parent organism BCG) has been observed in the performed study.

(d) is the GMO in any way different from the recipient as far as pathogenicity is concerned?

Yes (.) No (x) Not known (.)

Specify The rate of adverse events was lower for the GMO than for the parent organism in the performed study.

2. Genetic stability of the genetically modified organism

There is genetic variety in the mycobacteria family. There are no other mycobacterial typical factors known except the general mutational factors like multi passages and radioactivity and/or chemicals. During the scientific development, several passages of the strain VPM1002 were performed and genetic instability was never observed. To the contrary, it was proven that all strains, starting with parental seed up to the IMP, have a 100% homology in the inserted sequence.

Mycobacterial recombinant strains have repeatedly been shown to be genetically stable. Tthe whole genome of several mycobacteria was analysed and no evidence of any horizontal gene transfer was observed. This was confirmed also for a genetically modified BCG (with a genetical modification of plasmidic origin. In VPM1002 the genetic modification is of genomic and not of exosomal plasmidic origin. Hence, the genetic stability is even higher than that observed.

3. Is the GMO significantly pathogenic or harmful in any way (including its extracellular products), either living or dead?

Yes (.) No (x) Unknown (.)

(a) to which of the following organisms?

humans (.)
animals (.)
plants (.)
other …

(b) give the relevant information specified under Annex III A, point II(A)(11)(d) and II(C)(2)(i)

…

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment

PCR fingerprint and sequencing

(b) Techniques used to identify the GMO

PCR fingerprint and sequencing

F. Information relating to the release

1. Purpose of the release (including any significant potential environmental benefits that may be expected)

The goal of VPM is the development of a recombinant urease C-deficient listeriolysin expressing BCG vaccine strain (VPM1002) as a safe, well tolerated and efficacious vaccine against TB for residents in endemic areas and persons at risk in non-endemic areas. VPM1002 is to replace the currently used BCG vaccine. The new vaccine should be at least as potent as the current strain and should cause fewer side effects. The vaccine is formulated as live lyophilised bacteria to be resuspended before intradermal injection. This vaccine shall be applied to humans for the first time in the clinical trial VPM1002-GE-1.01TB. Primary objective of the clinical trial: to investigate the safety of single doses of VPM1002. Secondary objective: to investigate the immunogenicity of single doses of VPM1002 for vaccination against tuberculosis

2. Is the site of the release different from the natural habitat or from the ecosystem in which the recipient or parental organism is regularly used, kept or found?

   Yes (.) No (x)

   There are no natural habitats reservoirs of the parental organism. See B3.

   If yes, specify …

3. Information concerning the release and the surrounding area

   (a) Geographical location (administrative region and where appropriate grid reference):
   The vaccine VPM1002 will be applied to volunteers at FOCUS CDD, Neuss, Germany. Thereafter volunteers will be monitored on an outpatient basis

   (b) Size of the site (m^2): … m^2
   (i) actual release site (m^2): … m^2
   (ii) wider release site (m^2): … m^2
   The site for release of the GMO is the injection site at the vaccinated volunteer. Vaccination was done within the S1 area at FOCUS CDD, Neuss, Germany

   (c) Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs), which could be affected:
   VPM1002 or BCG was intra-dermally applied to the human volunteers randomized to either of the VPM1002/BCG-groups. They were monitored on an out-patient basis. They had usual contacts to other humans or biota.

   (d) Flora and fauna including crops, livestock and migratory species which may potentially interact with the GMO
   See F3.c)

4. Method and amount of release

   (a) Quantities of GMOs to be released:
   Number of Subjects : N=80 (4 x 20 volunteers), thereof 60 volunteers will receive the GMO.
   In detail, each subject will receive a single dose of VPM1002 or reference therapy BCG administered intradermally. The following dose levels will be administered:
   Dosage group Planned dose levels
   BCG 5 x 10e5 CFU (colony forming units) BCG (range 2 - 8 x 10e5)
   1 5 x 10e3 CFU VPM1002 (range 2 - 8 x 10e3)
   2 5 x 10e4 CFU VPM1002 (range 2 - 8 x 10e4)
   3 5 x 10e5 CFU VPM1002 (range 2 - 8 x 10e5) …

(b) Duration of the operation:
Vaccinated volunteers were followed-up on an outpatient basis for 180 days.

(c) Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of the release
Following the intra-dermal application of BCG or VPM1002 the injection site was monitored carefully by the investigator and it was covered by a suitable plaster before the subject was discharged from the clinic of FOCUS CDD GmbH. In the time-period following the vaccination, the subjects came to the FOCUS clinic at predefined intervals to monitor the injection site and to perform safety assessments. The subjects were instructed about the following behavioural procedures:

- after vaccination the injection site should stay covered by the suitable plaster or bandage; any contact should be avoided to prevent transmission of the vaccine to other parts of the body, to other persons or objects; it is helpful to wear clothing with sleeves that cover the arm down to the elbow.
- the injection site should not be touched, scraped or rubbed within the first days, especially if the site has opened, to prevent an infection of the injection site and spreading of mycobacteria into the environment.
- in case a direct contact to the site of vaccination or to the material that covered it, the subjects should wash their hands thoroughly using warm water and soap.
- it is not allowed to apply ointments or cremes to the opened vaccination site; the site should only be bandaged professionally and dry.
- showering of the opened skin region is only allowed after complete healing up.

In case the vaccination site opened and ulcerated the subjects were informed in detail about essential emergency and behavioural procedures. The subject was informed about the importance of keeping the opened injection site covered and preventing any contact to it. The subject was supplied with suitable plaster or bandage material in case the wound cover should be detached. He received suitable plastic bags to collect the detached bandage material for returning it to FOCUS for professional disposal. Depending on the development of the ulceration subsequent appointments for ambulant visits were arranged with the subject.
In addition the subjects were informed about general procedures how to behave following vaccination. These contained information on:

- the avoidance of exhausting physical exercises including sports;
- taking care of the injection site during every day activities like cooking or sharing objects or the bed with other persons;
- the strict instruction not to swim or bath while an opened injection site is not completely healed up;
- a general instruction how to act after having contact to the (opened) vaccination site.

5. Short description of average environmental conditions (weather, temperature, etc.)
The release was performed indoors at standard room conditions.

6. Relevant data regarding previous releases carried out with the same GMO, if any, specially related to the potential environmental and human health impacts from the release.
No prior release.

G. Interactions of the GMO with the environment and potential impact on the environment, if significantly different from the recipient or parent organism

1. Name of target organism (if applicable)

(i)	order and/or higher taxon (for animals)	…
(ii)	family name for plants	…
(iii)	genus	homo
(iv)	species	sapiens
(v)	subspecies	…
(vi)	strain	…
(vii)	cultivar/breeding line	…
(viii)	pathovar	…
(ix)	common name	man

2. Anticipated mechanism and result of interaction between the released GMOs and the target organism (if applicable)
VPM1002 shall induce immunogenicity in the vaccinated volunteers and may result in protection against tuberculosis.

3. Any other potentially significant interactions with other organisms in the environment
None

4. Is post-release selection such as increased competitiveness, increased invasiveness for the GMO likely to occur?
Yes (.) No (x) Not known (.)
Give details
Clinically, VPM1002 has been designed to replace the currently used BCG vaccine in medicine. The new vaccine should be at least as potent as the current strain and should cause fewer side effects. Regarding environmental aspects, no competition with the unmodified BCG or wild-type *M. bovis* is anticipated.

5. Types of ecosystems to which the GMO could be disseminated from the site of release and in which it could become established
The parent organism BCG has no natural habitats reservoirs. It is not anticipated that this is different for VPM1002. No dissemination has been observed in the clinical study.

6. Complete name of non-target organisms which (taking into account the nature of the receiving environment) may be unintentionally significantly harmed by the release of the GMO
None

(i)	order and/or higher taxon (for animals)	…
(ii)	family name for plants	…
(iii)	genus	…
(iv)	species	…
(v)	subspecies	…
(vi)	strain	…
(vii)	cultivar/breeding line	…
(viii)	pathovar	…
(ix)	common name	…

7. Likelihood of genetic exchange in vivo

   (a) from the GMO to other organisms in the release ecosystem:
   Not anticipated

   (b) from other organisms to the GMO:
   Not anticipated

   (c) likely consequences of gene transfer:
   None

8. Give references to relevant results (if available) from studies of the behaviour and characteristics of the GMO and its ecological impact carried out in stimulated natural environments (e.g. microcosms, etc.):
   Not available

9. Possible environmentally significant interactions with biogeochemical processes (if different from the recipient or parental organism)
   Not anticipated

H. Information relating to monitoring

1. Methods for monitoring the GMOs
   A set of surveillance tests has been implemented in the clinical study protocol to collect data on the potential risk of spreading the vaccine strain into the environment and the potential human-to-human transmission. Two strategies were followed to monitor for events of transmission: 1.) based on possible spreading after reported contact to and following known or potential transmission of vaccine to other persons or objects or 2.) an assessment of possible spreading from treated subjects by supervision of potential routes of transmission.
   1.) In case of a known contact to the vaccine and possible transmission to other persons or objects the subjects were asked to inform FOCUS about this event. The subjects were asked to report to FOCUS any signs or symptoms reported by a contact person that resemble symptoms of an adverse drug reaction against one of the vaccines. A supervision of the contact persons reporting these symptoms by suitable medical assessments was intended, provided the person in question agrees to this procedure. If the medical supervision

confirmed the reported symptoms a further analysis by suitable detection methods (PCR analysis) was intended.
2.) To gain data on possible routes of transmission of the vaccine into the environment samples were collected from 3 subjects from each cohort. The samples were be analysed for traces of vaccine using a validated PCR method detecting unique genomic DNA regions of VPM1002. Samples were collected prior to vaccination at baseline and on day 11 and after 6 months and will comprise of a blood, a urine, a stool and a saliva sample. The samples were analysed at FOCUS Immuology Laboratory Heidelberg. As a result, no hint on dissemination in the environment was detected.

2. Methods for monitoring ecosystem effects
See H1

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms
See H1

4. Size of the monitoring area (m^2)
Human blood, urine, stool and saliva samples of standard laboratory size.

5. Duration of the monitoring
180 days overall

6. Frequency of the monitoring
Day 1, Day 2, Day 3, Day 5, Day 11, Day 29, Day 57, Month 6 (Follow-up) post vaccination

I. Information on post-release and waste treatment

1. Post-release treatment of the site
The site for release of the GMO is the injection site at the vaccinated volunteer. Details on treatment are given F4.(c)

2. Post-release treatment of the GMOs
The GMO stays in the body of the vaccinated volunteer until it is eliminated by the host defense.

3. (a) Type and amount of waste generated
Vials and syringes used for preparation and application of the vaccine, wounddressing.

3. (b) Treatment of waste
The waste described above was collected in autoclave waste bags positioned in plastic waste containers with a volume of approx. 500mL. The waste container was placed in an autoclave (Zirbus Laborautoklav 1x2x3) located in the S1-area of FOCUS CDD GmbH and GMOs were inactivated by steam autoclaving. The inactivation process was monitored using a biological indicator (*Geobacillus stearothermophilus* spores) included in each autoclave run. After inactivation the waste was collected in hard plastic disposal boxes and was shipped for professional disposal. The procedures are laid down in the standard operating procedures of FOCUS CDD.

J. Information on emergency response plans

1. Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread

PCR-methodology is available for detection of VPM1002 in samples. In the highly improbable case of a detected human-to-human transmission leading to an unsustainable adverse drug reaction a set of suitable rescue medication was available for treatment. It was not needed in the study

2. Methods for removal of the GMO(s) of the areas potentially affected
According to the list on approved disinfectants and disinfection procedures published by the Robert-Koch Institut, disinfectants and disinfection procedures are classified depending on their range of effectiveness against distinct infectious agents. The classification consists of classes A-D where class A is defined as disinfectants or disinfectant procedures that are suited for inactivation of vegetative bacteria including mycobacteria as well as fungi and their spores. All disinfectants mentioned in the RKI list that contain formaldehyde or other aldehydes or derivatives thereof (e.g. Incidin®, Lysoformin® or Melsitt®) are qualified for surface disinfection according to class A definition without exceptions.

3. Methods for disposal or sanitation of plants, animals, soils, etc. that could be exposed during or after the spread
Autoclave or disinfectants class A.

4. Plans for protecting human health and the environment in the event of an undesirable effect
In the highly improbable case of a detected human-to-human transmission leading to an unsustainable adverse drug reaction a set of suitable rescue medication was available for treatment.
The supervision measures and emergency procedures including safety procedures described for conduct of the study suffice to ensure the well-being of the participants as well as of contact persons.