Inspectors Report

Date: 12th September 2002

To: Board of Directors

From: Dr. Tom McLoughlin

Re: Report on notification for consent and draft consent conditions under Part III of S.I. No. 345 of 1994 of a deliberate release into the environment (clinical trial-Part B) to conduct a clinical trial in patients suffering from angina pectoris using a Genetically Modified Micro-organism-Ref: B/IE/02/134.

BACKGROUND

Schering Health Care Ltd. of The Brow, Burgess Hill, West Sussex, Great Britain, notified the EPA on 12th June 2002 of a proposal to conduct a clinical trial in patients suffering from angina pectoris, using a Genetically Modified Organism, under Part III of S.I. No. 345 of 1994 (deliberate release into the environment for purposes other than for placing on the market)[1].

If the proposal is approved by the EPA, the proposed clinical trial would also be regulated by the Irish Medicines Board under the Control of Clinical Trials Act 1987 and the Control of Clinical Trials and Drugs Amendment Act 1990.

TIME FRAME FOR AGENCY'S DECISION

The Agency received the notification on 12th June 2002 and is required to respond in writing to the notifier within **90 days** (9th September 2002) of receipt of the notification by indicating either:

(a) that it consents to the deliberate release, with or without conditions; or
(b) that consent is refused.

However, the clock was stopped on 11th July 2002 and again on the 24th July 2002 as the EPA sought further information and clarification from the notifier. The EPA received the final portion of the requested information on 25 th July 2002. A decision by the Agency is now required by **23rd September 2002.**

[1] The Agency decided in October 2001, that it would regulate Schering's proposed notification as a deliberate release into the environment as opposed to a contained use (which is the case in the UK)

Request from the notifier that certain information be kept confidential

The notification included a request that confidentiality be maintained, under Article 9 of the Regulations, in relation to the following items.

1. The nucleotide sequence of the FGF-4 transgene insert (Seventh Schedule, page 9-11 and Ninth Schedule, page 7-9),
2. The details relating to the responsible scientists (names, qualifications and experience)

The EPA considered and granted the notifier's request on the above items.

CONSIDERATIONS FOR THE BOARD

1. Role of the EPA in reviewing this notification

The EPA considers that the interpretation of human health should be in the context of the 'general population'. It also consider that this definition does not exclude the patients who receive the GMM insofar as they are part of the general population. If they are participating in the trial, however, the consequences for them of their participation in the programme and consequent voluntary exposure to the GMM would not be relevant to the Agency consideration. The Agency will, therefore, be considering the patient receiving the treatment only insofar as they are part of the general population and the wider environment and, therefore, will not be considering the risks that the treatment might pose for the patient as an individual volunteering to participate in the trial. Its consideration will be for the potential risk of the GMM moving from the patient to the general population and the wider environment and the consequences of such movement. The Agency does not have responsibility for care of patients, staff and visitors in hospitals. The Agency responsibility (which is for licensing) relates to the wider environment and the general population. It is a matter for those conducting the trials, medical staff and Health and Safety personnel, to conduct their trials in a proper manner and provide for matters such as isolation of patients and care of patients (including patients not directly involved in the trials), safety of staff and safe access by visitors to hospitals. This means that in deciding the licensing issue the Agency will be considering the potential risks to patients, staff and visitors to the hospital only insofar as they are part of the general population and the wider environment.

The EPA's responsibility under the Genetically Modified Organisms Regulations, 1994 (article 33(4)), is to make a proper assessment of the notification, and to give consent to the release only if satisfied that it will not result in adverse effects on human health or the environment.

In arriving at its decision, the Agency will be considering the following aspects:

- the patient receiving the treatment insofar as they are part of the general population and the wider environment;

- the potential risk of the GMM moving from the patient to the general population and the consequences of such a risk; and,

- potential environmental concerns.

The Agency will **not** be considering the risks that the treatment might pose for the patient as an individual volunteering to participate in the trial. This matter falls within the remit of the Irish Medicine's Board.

2. Description of the Genetically Modified Organism for use in the proposed clinical trial

Ad5FGF-4 is a new gene therapy treatment. It consists of two parts – an active therapeutic gene and a carrier. The active gene is called *FGF-4 gene* and in the patient it induces the production of a protein known as Fibroblast Growth Factor 4, or FGF-4 protein. FGF-4 protein has been found to make blood vessels grow. When a patient is injected with the Ad5FGF-4 gene therapy treatment, the gene is carried to the heart by the carrier, which is a modified (changed) adenovirus. Adenoviruses (Hazard Group 2 biological agent[2]) are usually associated with the common cold but in this gene therapy treatment the virus has been modified so that it cannot multiply and cause symptoms.

2.1 The use of viruses in combating human diseases

In recent times it has become apparent that some characteristics of viruses [3], which normally contribute to disease (e.g., the common cold), may be manipulated to treat disease rather than cause it. Thus viruses are being developed as vectors for vaccine construction, as gene therapy and as cancer therapy agents. The main viruses that have been exploited as vectors in this work so far are DNA viruses such as adeno and adeno-associated viruses, and RNA viruses that synthesise a DNA copy of their genome such as retroviruses. In this proposed clinical trial, in respect of which this notification was submitted, a disabled adenoviral vector is used to 'piggy back' a gene into the heart to treat angina pectoris (chest discomfort

[2] In accordance with Council Directive 90/679/EEC on the protection of workers from risks related to exposure to biological agents at work - group 2 biological agent is defined as:
means one that can cause human disease and might be a hazard to workers; it is unlikely to spread to the community; there is usually effective prophylaxis or treatment available.

Other Groups are defined as:
group 1- biological agent means one that is unlikely to cause human disease
group 3 - biological agent means one that can cause severe human disease and present a serious hazard to workers; it may present a risk of spreading to the community, but there is usually effective prophylaxis or treatment available.
group 4 - biological agent means one that causes severe human disease and is a serious hazard to workers; it may present a high risk of spreading to the community; there is usually no effective prophylaxis or treatment available.

[3] A virus is a microorganism that contains genetic information but cannot reproduce itself. To replicate, it must invade another cell and use part of that cell 's reproductive machinery

or pain, usually caused by narrowing of the blood vessels to the heart). This is a very common heart condition which is usually treated with drugs or by coronary artery bypass surgery.

The strategy is to use a manipulated adenovirus which expresses a human gene as if it were a viral gene. The gene concerned stimulates the development or formation of new blood vessels (angiogenesis) to replace coronary arteries that are damaged, after being administered directly to the heart.

3. Purpose of the proposed deliberate releases

The purpose of the clinical trial is to assess the efficacy (how effective it is) and safety of Ad5FGF-4 in patients with angina pectoris (chest discomfort or pain, usually caused by narrowing of the blood vessels to the heart). The patients to be treated will be those who are not the most suitable for surgical procedures and who, despite other medication, are still experiencing angina.

The notifier is also planning to carry out shedding studies during the course of this proposed release where they plan to look for the presence of the GMM in urine, faeces and sputum.

The Irish sites in this application form part of an international, multicentre clinical trial, in which Ad5FGF-4 is administered by intracoronary injection to patients with stable angina. Induction of angiogenesis (formation of new blood vessels) or arteriogenesis (formation of arteries from existing arterioles) in the myocardium by intracoronary administration of the angiogenic fibroblast growth factor gene (FGF-4), which is the insert, represents a potential new therapeutic approach to relieve myocardial ischaemia (muscle pain).

In addition to the proposed trial in Ireland, the notifier is planning to carry out clinical trials with this GMM in the following EU Member States: Netherlands, Finland, Belgium, Sweden and UK. All proposed trials are being regulated as contained use, with the exception of the Netherlands where it is being regulated as a deliberate release. A similar vector, GMM (Ad5.1FGF-4) , has also been notified under ‘Contained Use’ in UK, Germany, Finland, Sweden and under ‘Deliberate Release’ in France.

4. Proposed locations of the deliberate releases

(a) University College Hospital, Galway
(b) St James’s Hospital, James’s Street, Dublin
(c) Mater Misericordiae Hospital, Eccles Street, Dublin
(d) Beaumont Hospital, Beaumont Road, Dublin

It is envisaged that each site will be treating up to 45 patients.

5. Date or dates of the proposed clinical trial

The notification is to cover the treatment of clinical trial patients at the named hospital locations from September 2002 to February 2006. The investigators (doctors) at each clinical trial location will treat up to 45 patients during this time. The exact number will depend on the number of patients who meet the specified medical criteria and volunteer to undergo the treatment. Patients will receive one injection only and will then be hospitalised overnight.

6. Method(s) to be used for the release

The product itself will be controlled under Level 2 containment conditions (in accordance with containment measures under the Contained Use Regulations - S.I. No. 73 of 2001 (Genetically Modified Organisms (Contained Use) Regulations, 2001) at the study sites. The GMM product will be administered to the patient as an intracoronary injection.

7. Quantities of genetically modified organisms to be released

The product is supplied in vials containing 2.5 ml of solution. There are 2 strengths: 1.435×10^8 virus particles / ml and 1.435×10^9 virus particles / ml. There are two vials per patient (one is a back-up vial). It is envisaged that each centre will treat up to a maximum of 45 patients, one-third (approximately) of whom will receive non-active (placebo) medication, one third low dose and one third the high dose. For each patient, two 2.5 ml vials will be supplied, the second vial being a back-up / reserve. Supplies for each patient will only be sent to the site once the suitable patient has been identified.

8. Worker protection measures taken during the release

Level 2 containment measures (under the Contained Use Regulations, SI No.73 of 2001) will be used and other Safety Precautions as outlined in the notification, including:

⇒ the placing of a "Biohazard" sign in the working areas;

⇒ to prevent the dispersal of aerosols generated during working procedures in the working area, procedures are to be performed within a Class 2 Biological safety cabinet;

⇒ material for disinfecting hands is to be available near each sink;

⇒ all hospital staff involved in these studies are to be trained appropriately. Operational guidelines are to be prepared and made available to staff involved in the preparation and treatment rooms and care of patients at all times;

⇒ The research facility is to provide protective clothing which will include goggles, face mask, gloves and gowns which are to be worn by the patient and all personnel involved in experimental work. Protective clothing is not to be worn outside the designated working area;

⇒ Others as outlined in the notification.

9. Information about previous releases with this GMO

None submitted by the notifier. However, adenoviral vectors have been used in humans for several years in gene transfer trials and for DNA vaccines.

The conclusions of trial results (Grines et al. 2002) in patients with Stable Angina Pectoris in studies carried out in the USA showed evidence of favourable anti-ischemic effects with Ad5FGF-4 (same GMM as in this notification) compared to placebo.

10. Risk assessment by the notifier

The following information is provided by the notifier:

Assessment of overall risk of harm to humans, with respect to a) the adenoviral vector itself and b) the FGF-4 gene product, was defined by the combinations of degree of *likelihood* and *consequence* of a potential hazard. The approach is set out in the matrix below. For example, if the likelihood of a hazard occurring (e.g. contact by a person with the virus) was considered to be low and, in the event of such contact, the consequences were also considered to be low, the overall risk to humans is considered to be low. However, were the likelihood of the hazard occurring considered to be low and the consequences of such contact considered to be severe, the overall risk would be considered to be medium.

Overall risk of harm to humans

Consequence	**Likelihood of hazard occurring**			
	High	Moderate	**Low**	Negligible
Severe	High	High	Medium	Effectively zero
Medium	High	Medium	Medium/low	Effectively zero
Low	Medium/low	Low	**Low**	Effectively zero
Negligible	Effectively zero	Effectively zero	Effectively zero	Effectively zero

Using this approach, the overall risk of harm to humans associated with the adenoviral vector (i.e. the virus) was considered by the notifier to be low (i. e. the likelihood of humans coming into contact with the virus was considered to be low

and the consequences of such contact, were it to occur, was also considered to be to be low).

For the hazard related to the expression of FGF-4 protein the risk was also considered by the notifier to be low (i.e. the likelihood of contact with the protein was considered to be low and the consequence of such contact was also considered to be low.

The notifier has stated that the risk refers to persons who come in contact with the GMM, for example, the person in the next bed in the hospital. It does **not** refer to patients who are being **injected** with the GMM product. The safety of patients is not part of an environmental risk assessment. The notifier stated that patient safety has been dealt with in their application to the Irish Medicines Board (IMB).

Assessment of overall risk of harm to the environment

According to information submitted by the notifier, the overall risk for the environment was considered to be effectively zero, since the dilution of any virus that might be shed in waste water and the inability to replicate is assumed to make any infection of environmental organisms highly unlikely. The monitoring proposed for the trial is designed to establish the degree of shedding and survival, if any, of the virus, following its release into patients. This will add significantly to the level of information available about the survival and dissemination potential of the adenovirus.

11. Duration and frequency of monitoring

According to the notifier, venous blood, urine, stool and throat swab samples will be taken from the first 50 patients in this trial at approximately 8, 24, 48 and 72 hrs after injection, to determine if there is any viral shedding. The patient will come back into the hospital for samples to be taken at 48 hours and 72 hours.

Venous blood samples will be taken from patients during the in-hospital period and at the week 2 and week 4 visits to determine the FGF-4 levels in the serum. In addition, all patients will be monitored for clinically significant adverse events for 5 years after their injection**.**

The restriction of monitoring to the first 50 patients was queried by Professor Gregory Atkins, retained by the EPA to provide an expert opinion on the notification[1]. However, following consideration of additional information supplied by the notifier, Professor Atkins expressed satisfaction with the proposed monitoring arrangements.

12. Implications for Ireland/View of the GMO Advisory Committee

[1] Professor Atkins report is attached to this report.

Members of the GMO Advisory Committee were asked to review and comment on the notification. Members of the Committee (with the exception of one member) were of the opinion that this trial would be beneficial. It was generally agreed that it would benefit both Ireland and medicine and would add to the information currently available.

13. Benefits and concerns identified by Professor Gregory Atkins, expert reviewer retained by the EPA

Professor Gregory Atkins, Trinity College, Dublin, was retained by the EPA to provide an expert opinion on the notification. Professor Atkins is a virologist. His report to the EPA is attached. Benefits and concerns associated with using the GMM identified by him are summarised below.

Potential beneifts

- Gene therapy represents an exciting and plausible approach to develop new treatment methods, and will become an important component of the pharmaceutical industry in the future. However it should be pointed out that an adverse immune reaction to an adenovirus vector has been the probable cause of death of one patient being treated with such a vector at the University of Pennsylvania. On the other hand, about 4000 patients have now been treated with vectors such as the present one, with few adverse effects, and many such trials are ongoing.

  Successful development of therapies such as this would not only directly benefit human health, but would also be of great economic benefit to the health services, since it would reduce the cost of treatment.

Concerns

- The possibility of adverse immune reactions to the vector.
- The possibility of inappropriate angiogenesis, which may aggravate the development of pre-existing tumours (angiogenesis, or new blood vessel formation, is an essential step in the development of large malignant cancers).
- The possibility of cancer induction or exacerbation by expression of the transgene, i.e. the gene cloned into the vector to produce the therapeutic effect.

14. National Policy regarding the release of GMOs into the environment

National policy is a positive but precautionary approach to GM issues, which acknowledges the potential benefits of modern biotechnology, while maintaining a fundamental commitment to human safety and environmental sustainability. This policy emanates from the Chairing Panel report on the National consultation debate regarding GMOs and the environment and the Minister for the Environment and Local Government policy statement published in 1999. It also emanates from the report of the Inter-Departmental Group on Modern Biotechnology published in 2000.

15. **Representations made under article 31(4)**

None were received by the Agency within the 21 day statutory period or outside this period. A member of the GMO Advisory Committee did, however, raise some concerns about the proposed trial (these are documented in section 20 of this report).

16. **Request for further information on the notifications**

The Agency requested further information on this notification on 11th July, 2002 and again on 24th July 2002. This was received on 24th and 25th July, respectively, and evaluated by the Agency. This information was also forwarded to Professor Atkins for review and comment.

17. **Site Inspections of proposed deliberate release sites prior to the proposed release**

The EPA carried out site inspections of the proposed release sites on 6-11th September 2002 to verify that the proposed releases (if consent is granted) will be carried out in accordance with the information supplied by the notifier and to verify that relevant information provided by the notifier in relation to the proposed sites is correct.

18. **Review of the notification by the EPA**

The assessment of the notification involved:

(a) External review-circulation to various organisations/bodies as outlined below
(b) Internal review

18 (a) External review

Dept. of Agriculture Food and Rural Development (DAFRD

The EPA requested DAFRD views on the following aspects:

- environment and human health aspects

DAFRD - Plant/Crop Division (in an e-mail dated 12/07/02) stated that:

It is clear that there are no implications arising in relation to agriculture or in relation to food production and safety.

Adenoviruses are ubiquitous. Human serotypes do not normally infect other animal species. Replication takes approximately 20 hours and can only occur in permissive recombinant cells containing the E1 gene. Survival of the wild type adenovirus has been demonstrated for weeks on a variety of surfaces, survival being temperature and humidity dependant.

The modified organism Ad 5FGF-4 is genetically stable. Detection techniques for the identification of the inserted gene sequence and vector have not been validated for environmental samples - such validation might be made a condition of any consent granted.

While release from treated patients is considered extremely low as a consequence of dilution, the presence of the gene vector in faeces and sputum from patients has not been determined and was not quantifiable in the case of patients' urine. Such information should be made available before the product is considered in due course for licensing.

DAFRD - Animal Health Veterinary Medicines Division

In an e-mail dated 3rd September 2002 they stated:
No observations to make on this issue.

Dept. of Health & Children

In a fax dated 25th July 2002 the Department of Health and Children stated:

that it had consulted with the IMB and understood that Dr. Frank Hallinan had already submitted comments to the EPA as a member of the GMO AC.

They stated: *The Board (i.e. the Irish Medicine's Board) only has competence in relation to the safety of this product in the course of the proposed clinical trial. Other matters should be adjudicated by the EPA. The IMB will only issue a definite assessment of a clinical trial involving a GMO after the EPA has agreed that the product meets its requirements. Thus the Board is not in a position to give*

a definite response at this time but would recommend that the EPA arrive at a decision without reference to the specifics of a clinical trial, but with the clear understanding that the IMB will be responsible for ensuring that any such trial will only be allowed where the IMB consider that it does not pose an unacceptable risk to the health of the participants or the staff involved.

Health and Safety Authority (HSA)

No concern raised:

They stated:

There is a duty on the employer to notify the Health and Safety Authority in relation to first time use of a group 2 biological agent. If this has not previously been done there is a requirement for notification for the work proposed 30 days prior to commencement to include relevant information as specified in Regulation 5(f) of SI 146 1994.

The EPA informed the notifier by email regarding possible obligations under Health and Safety legislation pertaining to this GMM and informed the notifier that the Health and Safety Authority is the Competent Authority in Ireland to implement this legislation. This e-mail was forwarded to the Health and Safety Authority for information purposes.

Department of the Environment and Local Government (DELG)

The information was sent to the DELG for information purposes. No comments or observations were received.

GMO Advisory Committee

Members of the GMO Advisory Committee were asked to review and comment on the notification. The notification was discussed at a Committee meeting on 26th June 2002. The Committee was requested to consider human health (in the context of the general population). All of Committee members were in favour of the trial proceeding with the exception of one member[2]. The AC suggested that the Agency seek further clarification on a number of issues. The EPA agreed.

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2 This Committee member sent two (2) e-mails to the Agency in August 2002 with information re the use of GMM in Clinical Trials from a Dr MaeWan Ho, author of Genetic Engineering: Dream or Nightmare, and a review of the Schering notification by a Dr Antoniou, Kings Hospital, London, recommended to the Committee Member by Friends of the Earth.
The Committee Member raised a number of concerns (which were also raised at the AC meeting) as follows:

A Committee member (who could not attend the AC meeting) responded via e-mail on 21st June 2002 and said:

From the information supplied and based on the results of earlier similar adenovirus clinical trials the GMM is unlikely to cause adverse effects on human health other than to the patient to whom the GMM is administered. As with all new medical treatments there is a risk of side effects to the patients receiving the treatment. Consideration of this class of risk is not, I understand, within the remit of the Advisory Committee. The risk concerned is that from the 'controlled release' aspects of the GMM.

The GMM is unlikely to cause adverse effects in the environment as it is a replicant deficient GMM.

The proposed controls on the use of the GMM and the methods for spills or other non-standard events are adequate.

The monitoring arrangements for virus shedding by the patient are comprehensive. As the virus is non-replicating environmental monitoring as might normally be proposed for a GMM controlled release would be superfluous.

The Agency wrote to the members of the Committee on 1st August 2002, clarifying the regulatory role of the EPA in relation to 'human health' aspects of this notification, following its consideration of the matter.

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1. *I refer to the last paragraph of the summary on page 3 of the 'statement on the environmental risk assessment', where it says that the risks are effectively low, 'even considering the lack of knowledge about the survival and dissemination potential of the adenovirus under environmental conditions'.*
   A risk assessment is surely only as good as the knowledge that it is based on.
2. *I raised the issue of the testing, carried out 'up to 84 days'. I still think that it is a very short time.*
3. *Notwithstanding the fact that I raised this at the meeting, I still also wonder why they did not look at the possibility of ectopic blood vessel formation in the brain.*
4. *On page 6 of the same article, under the heading 'gene transfer', it also refers to the possibility of biological effects in contact persons, and states that with the small amounts 'it will most likely not be sufficient to result in biological effects'.*
   It is worrying to me that again, we have risk assessments based on insufficient information.
5. *Finally, also on page 6, under the heading 'survival, dissemination', it says that 'no information is available on how long the adenovirus persists in the human body' and later on 'no data are available yet on excretion pathways such as faeces or skin/mucosa secretions.*

The Committee Member also stated that:

I acknowledge that I do not fully understand genetic engineering techniques, but based on my understanding of the above, I would have serious concerns about this application.

Expert Opinion of Professor Gregory Atkins, Consultant Virologist

- The EPA sought the expert opinion of Professor Gregory Atkins, consultant virologist. He received both the confidential and non-confidential information. A copy of his report is attached.

Professor Atkins raised questions in his report about the monitoring proposed to be carried out during the course of the trial. However, following consideration of additional information supplied by the notifier, Professor Atkins expressed satisfaction with the proposed monitoring arrangements.

Professor Atkins concluded:

'*This clinical trial is part of an ongoing series being carried out with this vector and others. It represents the development of important new treatment methods for human disease. The risk to the environment from this trial is low and the potential benefit to human health high. Therefore permission should be granted, with the above provisos*'. (the provisos relating to monitoring – see above).

Views of other EU Member States contacted by the EPA

The EPA conferred with the competent authorities (CA) of the Netherlands, Finland, Belgium, Sweden and the United Kingdom for their views on the same GMM notification that they received from Schering and with the CA 's of Germany and France on a similiar GMM. The EPA also contacted the Spanish CA.

Replies were received from Finland, the Netherlands, Belgium, Sweden and Germany. The following paragraphs summarise the key points made by each of these countries.

Finland:

- Same GMM notification as Ireland's.
- They are regulating it as a contained use.
- Their interpretation of human health aspects is similar to that of Ireland's.
- The risk assessment documentation is adequate and informative.
- The monitoring plan was considered to be adequate.
- Consent was granted. They requested further information in relation to waste management and waste disposal of GMM in the hospital and in relation to record keeping.

Netherlands:

- Same GMM notification as Ireland's.
- They are regulating it as a deliberate release, as is the case in Ireland.
- Their interpretation of human health aspects is similiar to that of Ireland's.
- A draft consent was granted and will be made available to the public. In the draft consent it is stated that patients have to stay in the hospital until is proven

that two subsequent blood samples are free from Ad5-FGF4 vector particles. The two samples should be taken within an interval of at least 24 hours.[2]

Belgium:

- Same GMM notification as Ireland's.
- They are regulating it as a contained use.
- Same interpretation as the Irish authorities: principal concern is the safety for the general population (public health).
- already 11 authorisations have been given for clinical trial projects in Belguim with a genetically modified adenovirus; all were given in accordance with Directive 90/219 (i.e. contained use); one of those projects was also given authorisation under Directive 90/220/EC (i.e. deliberate release).

Sweden:

- Similar application to that received in Ireland.
- They are regulating it as a contained use.
- Thorough and extensive application. One of the best risk assessments they have seen.
- Interpretation of human health aspects is similar to Irelands.
- Consent has been granted to the notifier (March 29, 2001). Biosafety level 2 conditions apply.
- Infectivity of blood, urine, stool and throat swab samples, as well as leg tissue if available, will be performed during the 12 week study.
- Infectivity evaluation to be conducted at baseline, 1 hour, 6 hours and 25 hours to check whether 24 hour containment is necessary or whether the duration can be decreased or even eliminated in future studies.
- Monitoring plan submitted was accepted.

Germany:

They were informed that they will be receiving a notification of a GMM for medicinal purposes.

EU Commission:

The EPA requested clarification re the Commission's interpretation of human health aspects of such trials (Part B trials) in accordance with Directive 90/220/EEC.

[2] Length of stay by patients in hospitals following administration of the GMM was discussed by the GMO Advisory Committee. The conclusion was that the proposals submitted by the notifier were adequate, given the low risk of transmission of the GMM from the patient to other persons.

The Commission responded on 24th July 2002 and made the following points:

- *Directive 90/220/EEC foresees for deliberate releases of GMO(s) (part B) in Article 5 (2) that the notification shall include a technical dossier, in particular covering a statement evaluating the impacts and risks posed by the GMO(s) to human health or the environment from the uses envisaged. The competent authority evaluates the risks posed by the release and decides whether and under specific conditions the release may proceed by giving a written consent to the applicant.*

- *Potential risks to human health are addressed to the relevant human groups. Referring to Annex II of Directive 90/220/EEC, for example:*

  ⇒ *The information on the release shall include worker protection measures taken during the release and,*
  ⇒ *The information on the environment shall include the physical or biological proximity to humans and other significant biota.*

No part of the human population is excluded from the evaluation of the impacts and risks per se. Risks for different humans may be different for the same GMO.

- *Beyond Annex II of Directive 90/220/EEC there is no further guidance for the competent authorities in the Member States. The roles of the individual competent authorities have to be defined by the Member States themselves.*

- *Directive 90/220/EEC will be replaced by Directive 2001/18/EC which has to be implemented by 17 October 2002. Article 5 of Directive 2001/18/EC lays down that the deliberate release (part B) of medical substances and compounds for human use consisting of, or containing, a GMO or combination of GMOs can be authorised by other Community legislation if it provides several conditions, for example, a specific environmental risk assessment in accordance with Annex II of this Directive.*

18 (b) Internal review:

The EPA has reviewed the notification and the additional information.

19. **Recommendation**

The EM&P division is satisfied that on the basis of the review carried out and in particular, the comments of Professor Atkins and the GMO Advisory Committee, that the risks posed to the environment and human health (general population) by the deliberate release of this GMM are low.

That consent be given for these trials subject to the conditions set out in the attached “Draft Consent Conditions”

Signed:_____ Date:_____