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To: All NHS Research Ethics Committees in the UK
All type i recognised ethics committees outside the NHS

Dear Chair

First time in man (FTIM) and other clinical trials subject to assessment by the Expert Advisory Group and Commission on Human Medicine

1. My letter of 28 April 2006 provided REC Chairs with interim guidance on the precautionary approach being taken by the Medicines and Healthcare products Regulatory Agency (MHRA) in relation to certain types of Phase 1 trial. This letter updates that guidance in the light of new procedures introduced by the MHRA following the submission of the final report of the Expert Scientific Group chaired by Professor Gordon Duff in November 2006. It supersedes the earlier guidance.

2. The guidance in this letter has been discussed and agreed by the Collaboration Group established under the Memorandum of Understanding between NRES, MHRA and the Gene Therapy Advisory Committee (GTAC). It has also been discussed with, and approved by, Professor Sir Bob Hepple (Chair) and the Board of the Appointing Authority for Phase 1 Ethics Committees (AAPEC). In joining with others to issue this guidance, NRES is acting on behalf of the United Kingdom Ethics Committee Authority (UKECA).

3. The guidance has also been discussed with, and reflects comments from, the following bodies:

- Association of the British Pharmaceutical Industry (ABPI)
- Bio-Industry Association (BIA)
- Clinical Contract Research Association (CCRA)
- Association of Human Pharmacology in the Pharmaceutical Industry (AHPPI).

MHRA process

Introduction

4. For certain types of clinical trial the MHRA will seek advice from an Expert Advisory Group (EAG) and the Commission on Human Medicine (CHM) before giving approval. Sponsors will be requested to make contact with the Agency before making the application for Clinical Trial Authorisation (CTA) for such trials and to make available a data package allowing that advice to be obtained. The normal CTA application process will then follow.

Scope

5. The arrangements will apply to the following types of trial:

- First time in man (FTIM) trials with new compounds acting (directly or indirectly) via the immune system with a novel target or a novel mechanism of action or having a secondary potential effect on the immune system via a mechanism of action which currently is not well characterised.

- FTIM trials with novel compounds acting via a possible or likely species specific mechanism or where animal data are unlikely to be predictive of activity in humans.

- Any clinical trial involving an integrin agonist, i.e. a compound which blocks or interacts with an integrin receptor or a cell adhesion molecule (CAM).

6. REC should note that the procedures for seeking advice from EAG/CHM are not restricted to FTIM trials. Trials with integrin agonists have recently been included within the scope of EAG/CHM. Other types of trial could be included in future where there are specific safety concerns warranting expert scrutiny.

7. The European Medicines Agency (EMEA) is currently developing a guideline on first time in human clinical trials. This is expected to be adopted shortly by the EMEA's Committee for Medicinal Products for Human Use (CHMP). The scope of the EAG/CHM arrangements will be reviewed by MHRA in the light of the EMEA guideline.

Expert Advisory Group on Clinical Trials

8. The Expert Advisory Group on Clinical Trials (referred to in this letter as "the EAG") is one of a number of such groups convened under the auspices of CHM, which has among its statutory duties to advise the Secretary of State on matters affecting the safety of medicines. The membership of the EAG includes distinguished international experts in the relevant fields of enquiry, including immunology, toxicology and clinical trials. The Secretary of State has appointed Professor Robert Lechler to chair the Group. Professor Lechler was a member of the Expert Scientific Group, chaired by Professor Gordon Duff, which reviewed the adverse events in the TGN1412 trial.

Procedures

9. The procedures for seeking advice from EAG/CHM and applying for CTA have been published at: http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=986

In summary, they are as follows:

- The sponsor decides whether their application falls within the above categories. Pre-submission advice may be sought from MHRA by providing a summary of the nature of the compound, its target/mechanism of action and the relevance of the animal model.

- The sponsor selects the date of the EAG/CHM meetings at which they wish the proposed trial to be discussed. MHRA has published a schedule of meetings. The CHM meeting is held the day after the EAG meeting.

- A data package containing all relevant documents is submitted to the MHRA Clinical Trials Unit (CTU) no later than 26 days before the EAG meeting.

- Following initial assessment by CTU, feedback on the content and completeness of the data package may be provided to the sponsor.

- The sponsor then submits the formal CTA application and the fee, to arrive during the week of the relevant EAG/CHM meetings.

- Following the CHM meeting, the CTU may enter into correspondence with the sponsor to request further information, clarification or changes to the proposed trial.

- A formal notice will normally be sent to the sponsor by letter within 7-14 days of the CHM meeting. This letter will either:

  (i) *Give grounds for non-acceptance*. This means the sponsor does not have CTA and would be required to submit an amended application, having provided further information and/or made changes to the proposed trial. Procedures for assessment of the amended application would be agreed with EAG/CHM in each case. The application could be assessed by the CTU alone, possibly consulting the EAG remotely. In some cases, the application might need to be re-reviewed at further meetings of EAG/CHM; or

  (ii) *Confirm authorisation*. This means the trial can start once it has also received a favourable opinion from the ethics committee. Notices confirming CTA could include remarks. They would not at this point require significant changes to be made to the trial as a condition of the CTA.

- The MHRA is committed to issuing notices in response to all applications for CTA within a maximum of 30 days from the date of submission.

Required areas of discussion by CHM

10. The MHRA has published a list of the areas for discussion by CHM as part of its assessment. These are listed in the Appendix to this letter.

Implications for ethics committee review

Responsibilities

11. The MHRA has primary responsibility for the safety of medicinal trials. The MHRA Clinical Trials Unit assesses the safety of all proposed CTIMPs, drawing on expertise in pharmaceutical quality and testing, toxicology and clinical medicine. The ethics committee may rely on the MHRA to assess the safety of medicinal trials. It is not required to undertake its own safety assessment or seek expert advice on safety issues from expert referees.

12. However, the expert assessment of safety by the MHRA will inform other aspects of the trial that are properly within the scope of ethical review and for which the main REC is responsible. In particular, the participant information sheet should fully and clearly describe the potential risks and any measures in place to minimise them (e.g. stopping rules, emergency procedures). There may also be implications for insurance and indemnity provision; and for the suitability of trial sites and investigators.

13. The sponsor is responsible for ensuring that the main REC is kept informed about the progress of the CTA application and any changes made to the trial as a result of the expert advice from EAG/CHM. The REC should be fully informed about this either as part of the initial application or through further information provided in the course of the ethical review. It is an offence under the Clinical Trials Regulations for a person to provide false or misleading information in applying for an ethics committee opinion, a clinical trial authorisation or a manufacturing authorisation.

14. Where appropriate, the REC may seek clarification of the status of the CTA application from the Clinical Trials Unit under the terms of the Memorandum of Understanding (MoU) between MHRA and ethics committees. The REC may also draw to the attention of CTU, and seek its advice on, significant concerns about the safety of the trial that have not been resolved by information provided by the applicant. Emails should be sent to clintrialhelpline@mhra.gsi.gov.uk marked "URGENT: REC correspondence for Head of CTU". A response will be sent within two working days. This procedure should only be used to raise specific safety issues. For general scientific advice, the REC should either seek further information from the sponsor or consult its own referees.

Procedures

15. The EU Directive and the Medicines for Human Use (Clinical Trials) Regulations 2004 allow for submission of applications to the competent authority and the ethics committee to be either in parallel or in sequence. This is a matter for the sponsor's discretion.

16. In general, parallel processing of clinical trial applications works well and minimises delay to trial start-up because it is comparatively rare for significant changes to be made as a result of the application to one reviewing body, which are within the ambit of, and require further review by, the other reviewing body. For example:

- The main REC may request changes to recruitment and consent procedures, volunteer information sheets or data protection arrangements, or seek further assurances relating to insurance and indemnity. SSA RECs and NHS R&D offices may seek further information about sites and investigators before confirming their suitability to the main REC. These matters would not need to be re-reviewed by the MHRA.

- Similarly, MHRA may issue grounds for non-acceptance relating to the adequacy of pre-clinical or toxicological data, or to the manufacturing, importation or labelling of the medicinal product, or the sponsor's arrangements for pharmacovigilance. These issues would need to be addressed in an amended application for CTA, but would rarely require review by the ethics committee.

17. However, in the case of trials involving higher risk compounds, it is possible that the additional advice from EAG/CHM will lead to changes in protocols, with potential implications for ethical review. It is essential that ethics committees are promptly notified of any additional information which is relevant to the ethics application. The primary responsibility for this lies with the sponsor (see paragraph 13).

Applications – identifying trials within the scope of EAG/CHM

18. A question on the sieve page of the REC application form asks the applicant to indicate whether the proposed trial is subject to expert advice from EAG/CHM. If so, the applicant is asked to include a covering letter for the ethics committee. This should explain the status of the application to CTA and, where applicable, any changes made to the proposed trial in the light of the expert advice. Any relevant correspondence with the MHRA should be enclosed with the application.

19. If the applicant indicates that the trial is not subject to expert advice and the REC has reason to question this, it may seek advice from the Clinical Trials Unit under the arrangements set out in the MoU.

Parallel processing

20. Sponsors may opt to apply either sequentially or in parallel and this decision by the sponsor may be influenced by a number of considerations. A sequential process may be preferable where, despite pre-submission advice from MHRA, factors such as the novelty of the compound including its mode of action and target, the relevance of animal models and the completeness of the data package available may result in protocol changes following EAG/CHM review. A sequential process would allow the ethics committee to receive the final version of the protocol and be fully informed about the outcome of the CTA application when undertaking its review. However, in other cases the sponsor may be confident that the protocol is unlikely to change and may wish to apply in parallel.

21. Where the sponsor applies in parallel, or applies to the ethics committee first, our advice to ethics committees is as follows:

(i) The Chief Investigator or sponsor should indicate the current status of the MHRA application when submitting the ethics application and keep the committee informed on its progress.

(ii) If the initial application is valid, the committee must proceed with the review under its normal SOPs.

(iii) Where the committee decides to issue a provisional opinion, the request for further information from the applicant may include a report on the outcome of the MHRA application, which may well be available to the sponsor at this stage. The clock stops until all the information requested has been received. (*Note: The responsibility to respond to the request lies with the Chief Investigator as the applicant for ethical review, but the sponsor has the overall responsibility for ensuring the committee is appropriately informed and may make arrangements with the CI to reply to the committee directly*.)

(iv) If CTA has by now been confirmed, the CI or sponsor should forward a copy of the MHRA letter to the committee together with any relevant correspondence.

(v) If grounds for non-acceptance have been raised, the CI or sponsor should forward a copy of the MHRA letter to the committee. The applicant may withdraw the ethics application and re-submit having made the changes required by the MHRA. Alternatively, if he/she continues with the ethics application, the sponsor should include with the further information requested by the committee a summary of how the issues raised by MHRA have been addressed.

(vi) If the outcome of the MHRA application is not yet available, the clock remains stopped until it is. Once the committee has received a complete response to the request for further information, including the outcome of the MHRA application, the clock re-starts. The committee should conclude its review and issue the final opinion as soon as possible. Further clarification on specific areas of concern may be sought from the MHRA at this stage if necessary.

22. Any ethics committee requiring further advice about the application of this guidance is welcome to contact David Neal (Head of Policy, NRES) at david.neal@nationalres.org.uk.

"Making Regulatory Decisions about Medicines and Medical Devices"

23. We are also taking this opportunity to draw attention to a document recently published by the MHRA, which summarises its role and describes how regulatory decisions are made about medicines and medical devices. A copy is attached and the document is also available at:

http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2030698&ssTargetNodeId=387

24. The MHRA has invited comments on this document. Ethics committees are welcome to comment directly by writing to john.watkins@mhra.gsi.gov.uk.

Yours sincerely

Dr Janet Wisely
Director
National Research Ethics Service (NRES)

Enclosures: "Making Regulatory Decisions about Medicines and Medical Devices"

Copy to:
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Commission on Human Medicine - required areas for discussion

A. First in man trials with higher risk compounds

1. A discussion of the function of the target in man.

2. A discussion of the ability of the subject to maintain a normal physiological response to challenge in the presence of the investigational product.

3. A discussion for the transition from preclinical to human testing, particularly with regard to highly species specific molecules.

4. A discussion of the potential for on-target and off-target effects and how this will be handled in the clinic.

5. A discussion of the doses used in the relevant animal species (particularly with regard to the use in the animal model of the starting dose to be administered to man).

6. A rationale for the starting dose in man (including, for example receptor occupancy).

7. A rationale for the study population (particularly for the use of human volunteers).

8. A rationale for the administration schedule for the initial and subsequent cohorts. This should include the time interval between doses administered to individual subjects.

9. A rationale for the dose escalation particularly with regard to potential adverse effect.

10. A rationale for the proposed trial site, including the facilities available.

B. Trials involving integrin agonists

1. A statement should be provided about whether the compound blocks or interacts with an integrin receptor or a cell adhesion molecule (CAM).

2. For integrin agonists, the specificity of the compound for a particular integrin should be discussed.

3. For CAM antagonists, the site of blockade or interaction should be identified.

4. A view should be given as to how the risk of the development of progressive multifocal leukoencephalopathy (PML) relates to the condition considered in the proposed trial.

5. A view should be provided as to whether previous immuno-suppressive therapy plays a crucial role in the development of PML. A comment should be made on specific immunotherapy regimes.

6. A discussion of the measures taken in the trial design to address the potential risks of the development of PML should be presented, in particular in relation to:

   - Monitoring for PML (e.g. magnetic resonance imaging (MRI) scanning, JC virus (JCV) screening)
   - Immunosuppression (concurrent or previous)
   - Information provided to study subjects (e.g. patient alert cards)
   - Based on the nature of the compound and the population under investigation, it is accepted that additional measures, as outlined above, might not be appropriate. However, a clear rationale should be provided.

7. A concise description and safety analysis of all relevant non-clinical and clinical data pertaining to the product under consideration should be provided.

8. A full appraisal should be presented of current risks against benefits for the trial population.