Rethinking early clinical testing:
The translation from laboratory to clinic

16-17 April 2007
Cobham, Surrey, UK

Workshop Report

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CMR International

Institute for Regulatory Science

CMR INTERNATIONAL INSTITUTE FOR REGULATORY SCIENCE

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Workshop on Rethinking Early Clinical Testing:
The translation from laboratory to clinic

16-17 April 2007
The Woodlands Park Hotel
Cobham, Surrey, UK

Workshop Organisation

Workshop organised by: Professor Stuart Walker and Dr Neil McAuslane, CMR International, Institute for Regulatory Science

Report prepared by Margaret Cone, CMR International Institute for Regulatory Science

Background documents referenced in this report

1 Expert Scientific Group on Phase One Clinical Trials, Final Report, 3O November 2006, Published by The Stationery Office (TSO) and available from www.tsoshop.co.uk. (ESG chaired by Professor Gordon Duff

2 Early Stage Clinical Trial Taskforce – Joint ABPI/BIA Report, published July 2006, available via www.abpi.org.uk (Task Force chaired by Sir Colin Dollery and Dr David Chiswell

3 Guideline on Requirements for First-In-Man Clinical Trials for Potential High-Risk Medicinal Products, 22 March 2007, Doc. Ref.EMEA/CHMP/SWP/28367/2007 Corr. Available via www.emea.org

4 Guidance for Industry, Investigators, and Reviewers: Exploratory IND Studies, FDA (CDER), January 2006, available via www.fda/cder/guidance

5 Position Paper on Non-Clinical Safety studies to support clinical Trials with a single microdose, 23 June 2004, CPMP/SWP/2599/02/Rev1. Available via www.emea.org

CMR International INSTITUTE FOR REGULATORY SCIENCE

WORKSHOP ON RETHINKING EARLY CLINICAL TESTING: The translation from laboratory to clinic

Section 1: Overview

Background to the Workshop

In March 2006, just over a year before this CMR International Institute Workshop took place, the world of pharmaceutical research received an unpleasant 'wake-up call' when the *TGN 1412* incident hit the headlines. Six healthy volunteers ended up in intensive care following a first-in-man volunteer study on a novel anti-CD28 monoclonal antibody in the UK and brought into focus the whole question of safety and best practice when bringing new medicines out of the laboratory and into clinical development.

Although the Institute Workshop had this incident and the immediate outcome (the 'Duff report'[1], the Joint ABPI/BIA report[2], the EMEA consultation guidelines[3]) as a backdrop to much of its discussions, the scope of the programme was wider. It reviewed the changing paradigm for early clinical testing, the role of translational medicine and the strategies and science behind the introduction of new technologies at the discovery-development interface

Syndicate Discussions

Following the formal Workshop presentations, participants divided into three Syndicates and discussed:

- Safety at the research-development interface
- The regulatory implications of the changing paradigm for early clinical testing
- The role of translational medicine in improving success rates in development

The Syndicates made three recommendations for specific action by the CMR International Institute:

Disclosure of unpublished/failed results

There was strong support for the recommendation in the Expert Scientific Group (Duff report[1]) that *Regulatory authorities should consider ways to expedite the sharing of safety information on phase one clinical trials between regulators within the EU and worldwide.*

It was recommended that the Institute could support such an initiative by carrying out a study among pharmaceutical companies to determine their views and current practices in relation to transparency in sharing information on research projects that fail at an early stage for safety reasons.

Workshop on Translational Research

The concept of 'translational research' (also known as translational science/medicine and formerly as clinical pharmacology) is a fast developing scientific discipline. Its role at the research-development interface is becoming increasingly important and the concept of cyclic 'bench/clinic/bench' learning can be extended throughout a product's life-cycle.

It was recommended that the Institute should hold a future Workshop on the topic, with the objective of increasing awareness of the role, nature and value of the new discipline. Participation should include academia, ethicists and other stakeholders.

The respective roles of Ethics Committees and Regulatory Agencies

It was agreed that there is a lack of harmonised guidance on the relative responsibilities of Ethics Committees (Institutional Review Boards - IRBs) and regulatory agencies.

It was recommended that the Institute should carry out a study to compare existing guidance on the respective roles and remit of the two parties with a view to stimulating discussions on a revision of key guidelines and the adoption of internationally standardised practices.

Good Practices for early clinical studies

The Syndicates made a further four recommendations on specific issues related to the conduct of early clinical studies.

- **The implementation of new regulatory guidelines:** monitoring is needed to ensure consistent interpretation of guidance and that the scope of the guidelines with respect to 'higher risk' compounds is not allowed to 'creep' and impose unnecessarily burdensome requirements on an increasing range of new products.
- **Screening for cytokine release** should become part of the routine preclinical *in vitro* screening requirements for new agents
- **Risk Management** plans must be initiated at a much earlier stage and be revised throughout a product's lifecycle
- **Scientific Advice** should be sought from agencies more frequently at a pre-IND stage

Highlights from the Workshop

The opening Session, on the *Changing Face of the Discovery/Development Interface* was chaired by Professor Sir Colin Dollery, *Senior R&D Consultant to Glaxo SmithKline, UK*. He emphasised that the drug development process must become more *iterative* with new agents, even if they do not eventually make the grade as therapeutic entities, having an essential role in expanding the knowledge base of the pathophysiology of disease.

The theme of cycling findings between the laboratory bench and the clinic to maximise knowledge was continued in the presentation by Dr Bruce Littman, *Vice President, Global Translational Medicine, Pfizer Inc, USA* on the ways in which translational medicine and research are becoming critical to early development. He also discussed the role of Phase zero (Exploratory IND[4]) translational research studies as a means of increasing Phase 2 success and reducing attrition.

Changing regulatory environment

The immediate regulatory impact of the TGN1412 incident was discussed by Dr Ian Hudson *Head of Licensing Division, MHRA, UK*, who guided participants through the recommendations in the Duff report[1] and their implementation. One of the recommendations to which he referred was on the he collection of '*information from unpublished preclinical studies relevant to the safety of human exposure'* that was subsequently taken up by the Syndicates.

The balance between ensuring safety at the research-development interface without imposing such restrictive conditions that research is inhibited was taken up from a regulatory perspective by Dr Eric Abadie Vice Chair, *Committee for Medicinal Products for Human Use CHMP) , EMEA a*nd from an industry perspective by Dr Mary Ellen Cosenza, *Executive Director, Regulatory Affairs, Amgen Inc, USA*

Dr Abadie described the development of the EMEA draft guideline[3], which had been achieved within an extremely tight timeline, and discussed the definition of 'potential high risk' compounds.

Dr Cosenza believed that the TGN1412 incident would, in future years, be seen as bringing about 'sentinel' change in attitudes to FTIM studies but expressed concerns about 'scope creep' in the guideline definition of high-risk compounds requiring additional safeguards.

Preclinical strategies

Dr Frank Sistare, *Executive Director, Laboratory Sciences and Investigative Toxicology, Merck & Co, USA,* discussed opportunities for improved animal testing strategies and expanding the safety biomarker toolbox to advance more quickly from the laboratory to the clinic. He argued that opportunities for greater exploratory research freedom are needed in undertaking the studies for regulatory purposes.

Professor Colin Garner, *Chief Executive Officer, Xceleron, UK,* described the real and potential role of microdosing in exploratory INDs, particularly in relation to use of accelerator mass spectroscopy (AMS) that is capable of detecting substances at *zeptogram* levels (10^{-21} g). He reported on candidate drugs being taken into humans using the Phase 0 microdosing approach and referred to the FDA and EMEA guidance that enabled such studies[4,5].

Translational Research

The potential of translational research and the 'bottlenecks' encountered in practice were discussed by Dr Christos Papageorgiou, *Vice President, SCPPS, Global Preclinical Development, Science & Medical Affairs, Sanofi-Aventis, France.* He argued that discovery begins and ends with man and that it is necessary first to understand the pathophysiological pathways of the disease processes in humans and identify suitable therapeutic targets before animal studies can be meaningful.

The need for better knowledge about disease processes was taken up by Professor Bruno Flamion, *Chairman, EMEA Scientific Advice Working Party (SAWP),* who discussed the ways in which the EMEA is adapting to the new discipline of translational science. He outlined frequent serious objections from SAWP regarding early translational studies including lack of knowledge about mechanism of action and dose-response, the selection of biomarkers and unwise selections of target populations.

The adoption of a new 'Learn and Confirm' paradigm for the development of new medicines was discussed by Dr Evan Loh, *Vice President, Clinical Research and Development, Wyeth, USA.* He emphasised how a single 'learn' stage has replaced the formal Phases I, IIa and IIb, to proof of concept. Learning is iterative and based on translational approaches, frequent stop-go decision points, feedback loops and carefully selected endpoints.

Looking to the future

Three speakers looked at what the future may have in store in the transition from laboratory to clinic.

Dr Phil Barrington, *Senior Clinical Pharmacologist, Lilly Research Laboratories, UK,* suggested that it is time to expand the established PK/PD model for clinical development. Customers are demanding a better understanding of which patients should receive the new generation of medicines and he advocated models that combine knowledge of metabolic pathways with genotype and PK/PD data to identify the profiles of those who will benefit most or least from a drug.

Speaking from a preclinical toxicology viewpoint, Dr Herman Van Cauteren, *Senior Vice President/Global Head, Global Preclinical Development, Johnson & Johnson, Belgium,* discussed the increasing overlap in the interface between discovery and development. Among other innovations, this requires a different training approach to produce medics who understand animal pathophysiology and pathology and biologists/ veterinarians who understand these aspects in humans. This view was reflected in the outcome of the Syndicate discussions.

Finally, Prof Gunnar Alvan, *Director General, Medical Products Agency, Sweden* rounded off the Workshop with a regulators viewpoint. Although regulators have an important role in observing and advising on scientific innovation in the transitional and 'learn' phases, their ultimate responsibility comes at the end of the 'confirm' stage when data must establish the statistical and clinical significance of therapeutic effects and enable an assessment of benefit and risk to be made on safety grounds.

References 1-5 See inside cover for references to background information cited in this report

WORKSHOP ON RETHINKING EARLY CLINICAL TRIALS:
The translation from laboratory to clinic

Section 2: Outcome

Syndicate Discussions

Session 3 of the Workshop, during which the Syndicate discussions took place, was chaired by **Professor Robert Peterson**, *Clinical Professor of Paediatrics, University of British Columbia Faculty of Medicine, Canada*

The Workshop participants formed three Syndicate groups and discussed

- Safety at the research-development interface
- The Regulatory implications of the changing paradigm for early clinical testing
- The Role of translational medicine in improving success in development

The Chairpersons and Rapporteurs for the three groups were:

Syndicate 1	*Chair:*	**Professor Sir Alasdair Breckenridge**, *Chairman, MHRA, UK*
	Rapporteur:	**Dr Martha Brumfield,** *Senior Vice President, Worldwide Regulatory Affairs & Quality Assurance, Pfizer Inc, USA*
Syndicate 2	*Chair:*	**Dr Paul Huckle ,***Senior Vice President, US Regulatory Affairs, GlaxoSmithKline*
	Rapporteur:	**Dr Jan Willem van der Laan,** *Head, Safety of Medicines and Teratology, National Institute for Public Health and the Environment, The Netherlands*
Syndicate 3	*Chair:*	**Dr Simon Larkin,** *Vice President, Kyowa Hakko UK Ltd*
	Rapporteur:	**Dr Petra Dörr,** *Head of Staff and International Affairs, Swissmedic*

The Syndicate groups were asked to identify key issues and formulate recommendations, taking into account the presentations made in the earlier part of the Workshop (*Annex 1*)

GENERAL OBSERVATIONS

The TGN1412 experience, when four healthy volunteers ended up in intensive care following a volunteer study on a novel anti-CD28 monoclonal antibody, provided an important 'wake-up call' for *first tests in man* (FTIM) studies. It has had a marked impact in terms of ensuring more focused and 'robust' thinking before new medicines are first administered to humans. The new regulatory guidance contained in the recommendations from the Duff report[1] and the EMEA draft guidelines[2] are welcomed for focusing and clarifying the issues but do not, represent a major change in the current paradigm for early clinical testing.

Both industry and regulatory agencies will, naturally, be implementing additional safeguards to identify 'high risk' compounds in order to prevent similar safety crises occurring in the future but companies are concerned that there should not be an 'over-reaction' by regulators that makes the transition from the laboratory to the clinic an increasingly difficult hurdle to overcome and acts as a deterrent to innovative research.

1. SUMMARY OF THE SYNDICATE RECOMMENDATIONS

1.1 Disclosure of unpublished/failed results

There was strong support for the recommendation in the Expert Scientific Group (Duff report[1]) that *Regulatory authorities should consider ways to expedite the sharing of safety information on phase one clinical trials between regulators within the EU and worldwide.*

It was recommended that the CMR International Institute could support such an initiative by carrying out a study among pharmaceutical companies to determine their views and current practices in relation to transparency in sharing information on research projects that fail at an early stage for safety reasons.

1.2 Workshop on Translational Research

The concept of 'translational research' (also known as translational science/medicine and formerly as clinical pharmacology) is a fast-developing scientific discipline. Its role at the research-development interface is becoming increasingly important and the concept of cyclic 'bench/clinic/bench' learning can be extended throughout a product's life-cycle.

It was recommended that the Institute hold a future Workshop on the topic, with the objective of increasing awareness of the role nature and value of the new discipline. Wider participation than industry and regulatory agencies might be considered to include academia, ethicists and other stakeholders.

1.3 The respective roles of Ethics Committees and Regulatory Agencies

It was agreed that there is a lack of harmonised guidance on the relative responsibilities of Ethics Committees (Institutional Review Boards -IRBs) and the advisory committees within regulatory systems.

It was recommended that the Institute should carry out a study to compare existing guidance documents relating to the roles of ethics committees and the remit of regulatory agencies and their advisory committees. The objective would be to stimulate discussions on the revision of key guidelines with a view to the adoption of internationally standardised practices.

The results of such a project could be integrated into discussions at a future Workshop (e.g., as proposed above) when the design and conduct of clinical studies is under review.

1.4 Good Practices for early clinical studies

The Syndicates made the four following specific recommendations and reviewed other aspects, as set out in Section 2.

1.4.1 Implementation of new regulatory requirements

The implementation of new regulatory guidelines needs to be monitored to ensure that definitions of 'potential high-risk' substances are interpreted consistently and that the scope of the guidelines is not allowed to 'creep' and impose unnecessarily burdensome requirements on an increasing range of new products.

1.4.2 Routine screening for cytokine release

The assessment of cytokine release should become part of the routine preclinical in vitro screening requirements for new agents

1.4.3 Risk Management

Risk Management plans must be initiated at a much earlier stage and become a 'living document' from first-in-man studies and throughout a product's lifecycle.

1.4.4 Scientific Advice

Companies should seek early Scientific Advice from agencies more frequently, and regularly engage in dialogue at a pre-IND stage

2. POINTS FROM THE DISCUSSION

2.1 Disclosure of unpublished/failed results

Recommendation: *CMR International Institute could support initiatives to facilitate sharing unpublished information that has safety implications (see Box 1) by carrying out a study among pharmaceutical companies. The aim would be to determine their views and current practices in relation to transparency in sharing information on research projects that fail at an early stage for safety reasons.*

Information on products that fail in the pre-clinical or early clinical stages for safety reasons could provide an invaluable information resource if ways could be found to share such information and make it available among and between regulators and companies:

- The focus would be on products with a novel mode of action and/or target where a safety alert would be of value in protecting FTIM volunteers who may be exposed to similar compounds and in preventing wasted, duplicative research.
- The database would need to be 'blinded' to the extent that individual research projects cannot be identified but compounds can be linked and searched through structure and mode of action
- The survey should include questions on companies' willingness to share information on products terminated in Phase II or III for reasons other than safety, e.g., commercial issues.
- Relevant data from toxicology studies should be included for compounds that fail on safety grounds
- The database would primarily be a resource for regulators but the level of feedback to companies would also need to be agreed.
- An extension of the database to include control data and human placebo data from trials would also provide a valuable research tool to investigate whether safety signals are real or background.

Box 1

Expert Scientific Group on Phase One Clinical Trials (Chaired by Professor Gordon W Duff)[1]

Recommendation 4.

Regulatory authorities should consider ways to expedite the sharing of safety information on phase one clinical trials between regulators within the EU and worldwide. This should certainly include information on first-in-man experience with higher risk medicines. Trials with negative safety outcomes should be included. This database might be widened to include products that may not currently be perceived as high risk, or trials conducted later in development, that suggest a strong warning for first-in-man use of similar products. In the EU, this collection and sharing of information could be based on the model of the existing clinical trial database EudraCT (for first-in-man trials since 2004) and the EudraVigilance database for 'Suspected Unexpected Serious Adverse Reactions (SUSARs)'. Relevant information from first-in-man trials prior to 2004 could be submitted on a voluntary basis. This would ensure access to relevant safety information by national regulators.

- It was acknowledged that the database would need to build up over time in order to reach its full potential but that the inclusion of retrospective data was probably not feasible.
- The EMEA EudraVigilance and EudraCT (clinical trial) databases will be examined to determine whether they might be developed as a possible tool[a] but discussions on a joint resource should extend to the US FDA and PMDA, Japan
- On the subject of sharing information on the identity of research compounds, reference could be made to patent lawyers who routinely deal with the disclosure of the structure of novel compounds.

Although individuals from companies recognised the potential value of the envisaged database they could foresee significant difficulties in obtaining agreement to share information for both legal and resource reasons.

[a] Presentation to the Workshop on *Lessons from TGN1412: the Impact on Phase I Clinical Trials,* by Dr Ian Hudson Director, Licensing Division, MHRA, UK

It was, however, pointed out that there is public pressure and an expectation that regulatory agencies would have access to such in order to fulfil their role in protecting public health. Where safety issues are concerned, commercial confidentiality is unlikely to be accepted as a valid argument.

2.2 Workshop on Translational Research

Recommendation: *The CMR International Institute should hold a future Workshop on Translational Research, with the objective of increasing awareness of the role, nature and value of the new discipline. Wider participation than industry and regulatory agencies might be considered to include academia, ethicists and other stakeholders.*

Definition

Although the subject of 'translational research' (also 'translational medicine' and 'translational science') is currently much under discussion there does not appear to be a single, clear definition. Dr Bruce Littman, in his Workshop presentation[b] proposed a definition (see *Box 2*) and, for the purpose of the Syndicate discussions, the topic was characterised by the following elements:

- Building feedback loops into the development process for new medicines;
- Helping to improve the decision-making process in the early stages of clinical testing;
- Having an integrated, multi-disciplinary approach that includes physicians, pharmacologists, toxicologists and other research scientists

It was suggested that, as a starting point for the proposed Workshop, the Institute should prepare a working definition that would position the science in the context of the drug development process.

This might also clarify the relationship to the previous concept of 'discovery medicine' and to 'clinical pharmacology' from which the concept derives (*see note on page 10*).

Box 2

Translational Medicine is the integrated application of innovative pharmacology tools, biomarkers, clinical methods, clinical technologies and study designs to improve confidence in human drug targets and increase confidence in drug candidates, understand the therapeutic index in humans, enhance cost-effective decision-making in exploratory development and increase phase 2 success leading to a sustainable pipeline of new products.

Dr Bruce Littman

A new discipline

Translational science/medicine may need a new type 'physician scientist'. Ideally, such an individual would need to understand pharmacology, toxicology, medicinal chemistry, human physiology, and have experience of drug development and human experimentation. In practice, it would be a case of having a broad understanding of the subject and knowing where to find the right information and advice within a multi-disciplinary team.

Other points from the discussion

- To make best use of translational science companies need to have in place:
  - The right culture of 'learn and confirm' methodology and utilisation of feed-back loops;
  - The right people trained in the new discipline of 'physician-scientist';
  - The right procedures for decision-making
- Translational science cannot, of itself, change the attrition rate of new medicines but it can facilitate early decision-making and reduce failure in later stages of development, thus saving costs and resources:
  - If you have a poor target and a poor molecule, translational medicine will not help;
  - The efficiency and sensitivity of the early stages of development can, however, be improved.

[b] Translational medicine and research: Why are these becoming critical to early development? Dr Bruce Littman, Vice President, Global Translational Medicine, Pfizer Inc, USA

- Translational science can have a major impact on the design of FTIM and early clinical studies by:
  - Injecting more pharmacodynamics into the early stages of development;
  - Utilising the concept of 'bench to clinic to bench' as a departure from the classic 'one way street' development programmes
  - Providing the re-iterative approach required for investigation of agents with a precise mode of action

A role in conditional approvals

Although the concept of translational science was discussed primarily in relation to early clinical development the same concepts can be applied at the post marketing stage. Increasingly, products for serious and life-threatening conditions are being approved on a 'conditional' basis with commitments to carry out further post-authorisation studies. This can apply if approval was granted on the basis of a likely, but unproven, surrogate end point or where the nature of the disease means that only a small database of patient data was available.

In either case, follow-up studies can be carried out on an 'iterative' basis with safety signals from post marketing experience triggering further non-clinical investigations or a re-examination of existing data and feeding information back to the clinic. The success of translational research can thus include helping to keep a product on the market.

2.3 The respective roles of Ethics Committees and Regulatory Agencies

Recommendation: *The Institute should carry out a study to compare existing guidance documents relating to the roles of Ethics Committees (Institutional Review Boards - IRBs) and the remit of regulatory agencies and their advisory committees. The objective would be to stimulate discussions on the revision of key guidelines with a view to the adoption internationally of standardised practices.*

The Syndicates discussed the role and remit of Ethics Committees/IRBs in the face of an increasingly complex array of new medicines and therapeutic targets and greater involvement of ethics committees in technical issues, through their scientific advisors.

It was agreed that the there is a 'blurring' of the relative responsibilities of Ethics Committees and regulatory agencies in evaluating proposals for FTIM and early clinical studies. There is the danger of ethics bodies 'second guessing' the views of their scientific counterparts Companies reported:

- Ethics Committees, increasingly, raise questions on study design and initial dose levels;
- Agencies (less frequently) comment on the language in consent forms

The relationship between Ethics Committees and agencies is becoming increasingly complex and does not appear to be clearly articulated in written guidance. Hence the recommendation for preliminary work to be carried out in order to highlight the issues and encourage further action at an appropriate level.

It was noted that the Duff Report[1] had recommended the establishment of specialised centres for FTIM studies on high-risk compounds (see below) and it was suggested that there might also be a case for having separate guidelines and standards that apply to specialised Ethics Committee for considering FTIM and early trials on higher risk products.

Specialised clinical settings for early clinical development

In his Workshop presentation[c], Dr Ian Hudson had referred to the recommendation in the Duff report[1] that Phase I clinical trials on high risk products should be carried out only in duly accredited and inspected centres.

[c] *Lessons from TGN1412: the Impact on Phase I Clinical Trials* Presentation by Dr Ian Hudson, Director, Licensing Division, MHRA, UK

It was noted that the MHRA is developing an accreditation scheme in accordance with this recommendation and that CROs undertaking FTIM studies are likely to come under increasing scrutiny.

Whilst the concept of establishing specialised facilities was welcomed there was concern that, by taking action at a national level, Phase I trials could be driven out of the UK. The recommendation should therefore be considered for action at an EU level.

Note: The introduction to the Duff Report includes the statement '*Our recommendations are offered to the UK authorities and sponsors of first-in-man trials in the UK, but we believe it is important that agreement is sought at EU and international level, to ensure that equal protection is afforded to clinical trial participants worldwide'..*

Box 4

Expert Scientific Group on Phase One Clinical Trials (Chaired by Professor Gordon W Duff)[1]

Recommendation 22.

The feasibility of developing specialist centres for phase one clinical trials of higher risk agents and advanced medicinal products should be explored.

The development of a national inspection and accreditation system for clinical centres that undertake first-in-man studies of higher risk agents should be encouraged. The accreditation should be open to all centres that fulfill defined criteria, in both the public and private

2.4 Good Practices for early clinical studies

2.4.1 Implementation of regulatory guidelines

Recommendation: *The implementation of new regulatory guidelines needs to be monitored to ensure that definitions of 'potential high-risk' substances are interpreted consistently and that the scope of the guidelines is not allowed to 'creep' and impose unnecessary burdensome requirements on an increasing range of new products.*

Whilst the guidance set out in the Duff Report[1] and the EMEA draft guidelines[3] was welcomed there was concern about finding the right balance between the need to ensure research subjects are adequately protected, but at the same time, that early development of new medicines is not hindered.

Definition of a 'high risk' compound

Expert Scientific Group on Phase One Clinical Trials (Chaired by Professor Gordon W Duff)	***EMEA Draft Guidelines on Requirements for First-In-Man Clinical Trials for Potential High-Risk Medicinal Products***
Scope of the Recommendations, page 3 Our remit covers three categories of medicines that may have a higher potential for risk of harm to volunteers during the first human exposures, or where risk may be more difficult to evaluate in pre-clinical development. The categories are: Biological molecules with novel mechanisms of action; New agents with a high degree of species-specificity; New agents with immune system targets.	*4.1 Definition of potential high-risk investigational medicinal products* Medicinal products are defined as potential high-risk medicinal products when there are concerns that serious adverse reactions in first-in-man clinical trials may occur. These concerns may be derived from particular knowledge or uncertainties on (1) the mode of action, and/or (2) the nature of the target, and/or (3) the relevance of animal models

There was discussion about the need for caution in defining potential high-risk compounds and ensuring that any definitions are interpreted with flexibility. There were concerns that, over time, 'scope creep' would result in a larger and larger number of new compounds being subject to additional scrutiny. In the UK, this includes referral to the Expert Advisory Group (EAG) set up by the Commission for Human Medicines (CMI) before a clinical trial authorisation can be issued for FTIM studies.

The Duff report (see above) refers specifically to biological molecules but small rather than complex molecules can present similar safety hazards. Similarly, the term 'novel' needs boundaries if the scope is to be limited. It was suggested that there are 'Degrees of Novelty' which must be considered in the overall assessment of higher risk.

Other concerns related to the definition of 'potential for risk' (in both the above definitions) which needs further discussion and can extend beyond immunogenic potential to

other irreversible hypersensitivities and potential damage to the test subject. Written definitions, however, are no substitute for the need for companies to exercise due diligence in assessing the risks of new medicines before proposing FTIM studies.

It was also felt that agreeing definitions by consensus building was a better option than, for example, using the EU Clinical Trial Facilitating Group (CTFG) as a 'supreme court', above the national CT authorities, for providing binding advice on the classification of new agents.

2.4.2 Routine screening for cytokine release

Recommendation: *The assessment of cytokine release should become part of the routine preclinical in vitro screening requirements for new agents.*

The adverse events experienced with TGN1412 resulted from a so-called 'cytokine storm' and it was reported that reliable tests are available for screening for cytokine release.

There was discussion of whether TGN1412, itself, should be used as a positive control for such tests but this proposal was rejected. There was, however, regret that samples of TGN1412 were not available for further study.

Pre-clinical testing

In the light of the TGN1412 incident, the question 'What is the right amount of preclinical data?' was discussed and the following observations made:

- Conventional testing programmes, as followed by major research-based companies remain valid but the 'checklist' mentality must be avoided;
- Even where no animal models exist, current requirements will suffice but there must be a review of the totality of preclinical data acquired across species using a 'common sense' approach, exploring all avenues and not making any assumptions.
- There may, however, be concerns about agents developed by small venture capital enterprises that do not have the experience and background in preclinical development;

2.4.3 Risk Management

Recommendation: *Risk Management plans must be initiated at a much earlier stage and become a 'living document' from first-in-man studies and throughout a product's lifecycle.*

Risk management should not be regarded only as part of the review and assessment process for a new medicine. Throughout its development the team should be addressing and reviewing the questions:

- What do we know about safety?
- What do we *not* know about safety?
- What *should* we know about safety?

The general need of a fully integrated safety assessment of all first-in-human compounds was emphasised including all published and unpublished data on similar compounds. The 'red flag' should should be raised, in particular, when a murine analogue is available.

2.4.4 Scientific Advice

Recommendation: *Companies should seek early Scientific Advice from agencies more frequently and regularly engage in dialogue at a pre-IND stage.*

Whereas pre-IND meetings are offered by FDA it may represent a new role for many regulators, especially if they are asked to advise on the FTIM stage. The discussions raised the following points on the role of regulators in this new area:

- It is in the public interest to have better protocols as this would, ultimately improve the availability of new drugs.

- New concepts, e.g., in relation to translational studies, may not be familiar to regulators and mutual understanding of the concepts may need to be developed between industry and regulators.
- Is the role of scientific advice just to assist the development of new medicines or to prevent unnecessary studies?
  - Potential dangers were perceived in becoming involved in ethical questions of whether or not a study that produces some additional scientific knowledge is 'necessary';
  - The question of reducing animal studies can become a political issue but safety in humans cannot be compromised in this cause.

2.5 Other discussion points

2.5.1 Volunteers vs. Patients

On the question of whether healthy volunteers or patients should be used in FTIM studies, the following points were made:

- The body of data and knowledge about the molecule and about the disease to be studied should drive decision;
- In considering benefit and risk, the healthy volunteer can never be expected to benefit from a study and risk alone must be considered
  - Patients may derive some benefit from a novel treatment for a life-threatening condition
  - In circumstances where there are known toxicities, e.g., cytotoxicity/mutagenicity studies should only be conducted in patients;
  - Longer-term risk to healthy volunteers may not always be obvious, for example if an agent alters the immune system this may have consequences if the individual intends to travel.
- The downsides of using patients are that the homogeneity of data may be prejudiced, and operational efficiencies may be compromised (e.g.,difficulty in recruitment and high costs). There are, however, benefits in the possibility of a better understanding of the effects (pharmcodynamics) in relation to the pre-existing condition.

2.5.2 Use of other technologies

Although no specific recommendations were made, the Syndicate discussions reviewed other technologies that might be employed to address concerns over FTIM studies:

- Imaging techniques such as Positron Emission Tomography (PET) with microdosing, if appropriate
- Pharmacogenomics and application of other 'omics' techniques;
- Use of pharmacodynamic biomarkers
- Use of nanotechnology

2.5.3 Assurance of full disclosure by companies

The sponsor of a new medicine has the responsibility of carrying out a full and thorough evaluation of existing literature as well as a comprehensive review of 'checks and balances' from all the data acquired in the preclinical research.

The question was discussed of how agencies can be assured that this has been carried out and the following possibilities were reviewed:

- Continue to rely upon self-policing by industry, as at present
- Regulators could require the nomination of an accountable person and a signed statement by the sponsor
- Specific additional requirements could be included in clinical trial application requirements.

It was agreed that additional regulatory requirements were not required at this stage but that it is an aspect of which agencies should be aware when reviewing and updating guidance, at a later stage.

Addendum

Translational research, discovery medicine and clinical pharmacology.

The following references were proposed, subsequent to the workshop, as a source of discussion on the relationship between the different disciplines:

Clinical pharmacology or translational medicine and therapeutics: reinvent or rebrand and expand?

G A FitzGerald
Clinical Pharmacology & Therapeutics 81, 19 - 20 (14 Dec 2006) Point/Counterpoint

Translational Research: Moving Discovery to Practice

E A Zerhouni
Clinical Pharmacology & Therapeutics 81, 126 - 128 (14 Dec 2006) Public Policy

Clinical pharmacology: the science of therapeutics

S A Waldman, N B Christensen, J E Moore, A Terzic, SA Waldman
Clinical Pharmacology & Therapeutics 81, 3 - 6 (14 Dec 2006) Editorial

Annex 1

WORKSHOP PROGRAMME

SESSION 1: THE CHANGING FACE OF THE DISCOVERY/DEVELOPMENT INTERFACE	
Chairman's Introduction	**Professor Sir Colin Dollery** *Senior R&D Consultant, Glaxo SmithKline, UK*
Translational medicine and research: Why are these becoming critical to early development?	**Dr Bruce Littman,** *Vice President, Global Translational Medicine, Pfizer Inc, USA*
Phase I clinical trials: Science and regulatory framework	
Lessons from TGN1412: the Impact on Phase I Clinical Trials	**Dr Ian Hudson** *Director, Licensing Division, MHRA, UK*
First use in humans: Ensuring safety without stifling research	
Industry Perspective *What are the questions that TGN 14 12 raised?*	**Dr Mary Ellen Cosenza** *Executive Director, Regulatory Affairs, Amgen Inc, USA*
Regulatory Perspective *on behalf of the CHMP First in Man Task Force*	**Dr Eric Abadie** *Vice Chair, Committee for Medicinal Products for Human Use (CHMP) , EMEA*
Effective strategies in the preclinical stage to enhance success in the clinic	**Dr Frank Sistare** *Executive Director, Laboratory Sciences and Investigative Toxicology, Merck & Co, USA*
Microdosing and exploratory INDs	**Professor Colin Garner** *Chief Executive Officer, Xceleron, UK*
SESSION 2: STRATEGIES, SCIENCE AND TECHNOLOGY	
Chairman's Introduction	Prof Hans-Georg Eichler *Senior Medical Officer, European Medicines Agency (EMEA)*
Translating Research for human health	**Dr Christos Papageorgiou** *Vice President, SCPPS, Global Preclinical Development, Science & Medical Affairs, Sanofi-Aventis, France*
Is translational science a new regulatory discipline?	**Professor Bruno Flamion** *Chairman, EMEA Scientific Advice Working Party*
Learn and Confirm: A new paradigm for drug development	**Dr Evan Loh,** *Vice President, Clinical Research and Development, Wyeth, USA*
Laboratory to clinic - What does the future have in store?	
Clinical Pharmacologist Viewpoint	**Dr Phil Barrington** *Senior Clinical Pharmacologist, Lilly Research Laboratories, UK*
Preclinical Toxicologist Viewpoint	**Herman Van Cauteren** *Senior Vice President/ Global Head, Global Preclinical Development, Johnson & Johnson, Belgium*
Regulatory viewpoint	**Prof Gunnar Alvan**, *Director General, Medical Products Agency, Sweden*