European Medicines Agency

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OVERVIEW OF COMMENTS RECEIVED ON THE DRAFT GUIDELINE "REQUIREMENTS FOR FIRST-IN-MAN CLINICAL TRIALS FOR POTENTIAL HIGH-RISK MEDICINAL PRODUCTS"

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	Association for Clinical Pharmacology and Therapeutics (EACPT)	The United Kingdom
2	Centocor Research & Development (Centocor)	The United States
3	European Clinical Research Infrastructures Network (ECRIN)	Italy
5	Bristol-Myers Squibb BMS	The United States
6	The BioIndustry Association (BIA)	The United Kingdom
7	University College of London	The United Kingdom
8	Pharmadanmark	Denmark
9	University of Glasgow (UoG)	The United Kingdom
10	The European Association for Bioindustries EuropABiO	Belgium
11	European Biopharmaceutical Enterprises (EBE)	Germany
12	Federation of European Cancer Societies	The United Kingdom
13	Robert Reinhard, Member, Community Advisory Group, San Francisco Dept of Public Health Research Section (CAG)	The United States
14	FDA	The United States
15	IPOPI	The United Kingdom
16	Merck Sharp & Dohme (Europe) Inc. (MSD)	Belgium
17	The Academy of Medicinal Sciences (AMS)	The United Kingdom
18	Department of Clinical Pharmacology and Centre for Human Drug Research Leiden University Medical Centre (CHDR)	The Netherlands
19	Europeans for Medical Progress Trust (EMPT)	The United Kingdom
20	CPME	Belgium
21	German Association for Applied Human Pharmacology (AGAH)	Germany
22	Foundation for the Evaluation of Ethics In Biomedical Research (FEBBR)	The Netherlands
23	Cancer Research	The United Kingdom
24	European Association of Nuclear Medicine (EANM)	EU
25	Nirmala Bhogal FRAME	The United Kingdom
26	Galderma R&D (Galderma)	France
27	Johnson & Johnson	The United Kingdom
28	JPMA Kazuhiko Nakajima	Japan
29	The European Forum for Good Clinical Practice (EFGCP)	Belgium
30	Association of Clinical Research Organizations (ACRO)	The United States
31	AMGEN	The United Kingdom

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32	EFPIA	Belgium
33	International Council on Animal Protection at the ICH (ICAPI)	International
34	International Federation of Associations of Pharmaceutical Physicians (IFAPP)	The Netherlands
35	Millenium Pharmaceuticals (MP)	The United States
36	NDA Regulatory Science LTD (RS LTD)	The United Kingdom
37	Parenteral Drug Association (PDA)	Germany
38	PhRMA/Pre-Clinical Leadership Committee (Drusafe)	The United States
39	ROCHE (ROCHE)	The United Kingdom
40	Schering-Plough Corporation (SPC)	The United States
41	Swiss Agency for Therapeutic Products – Swissmedic	Switzerland
42	Takeda	The United States
43	Safety Pharmacology Society (SPS)	The United States
44	French Club Phase 1 (FCP)	France
45	Good Clinical Practice Alliance (GCPA)	Belgium
46	The Biotechnology Industry Organization (BIO)	The United States
47	Association of British Pharmaceutical Industry – ABPI	The United Kingdom
48	Institut Catala' d'Oncologia (ICO)	Spain
49	Rottapharm SpA	Italy
50	The GCP Committee of the British Association of Research Quality Assurance (BARQA)	The United Kingdom
51	Institute for Drugs and Medicinal Devices (BfArM	Germany
52	The Association of Research Ethics Committees (AREC)	The United Kingdom
53	Wyeth Pharmaceuticals (WP)	France
54	The Medical Research Council (MRC)	The UnitedKingdom
55	Eurocrof	France
56	University College Hospital London (UCLH)	The United Kingdom
57	Richmond Pharmacology LTD (RP LTD)	The United Kingdom
58	Anapharm	Canada

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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW
EACPT: The draft appears to be very useful to elevate the safety of first-in-man trials. A major problem is based on the definition of "high risk medicinal product". Once a product is considered to be at high risk, a large battery of additional studies and approval processes will be launched. The definition must follow clear and narrow guidelines.
Centocor Research & Development: The draft guideline is equally applicable to all investigational medicinal products. Consideration should be given to re-focusing the guideline to a 'points to consider' document on risk management strategies and dose-setting for first-in-human clinical trials. The emphasis of the guideline should be more focussed on risk mitigation strategies through the integrated analysis of all pre-clinical data and appropriate design of clinical trials. This would remove the need for a definition of "high risk"; whilst still addressing appropriate risk management strategies.
European Clinical Research Infrastructures Network ECRIN: ECRIN has to acknowledge that it is clearly written, gives a brilliant overview of a very complex issue, and that we are very happy for the guideline to recognise the need for randomisation and involvement of placebo. The introduction lacks concrete examples of what did go wrong in past examples, with references to the literature description of the cases. There are not too many cases (the Northwich Park Phase I unit in 2006, the SFBC unit in Miami, Florida in 2005, the death of a volunteer in Dublin in 1985,etc.). There are certainly many more cases, most of which have been settled by handsome payments to the trial participants outside the court. So it will be hard to grasp them all. The EMEA experts should agree about the reasons of each case and then verify that the Guideline addresses these issues effectively. Most of the recommendations in these guidelines would not have prevented the cases, and therefore there is a risk that by not ranking the proposed measures in order of priority as a function of dramas of the past, a proper guideline may not prevent them from rehappening.
Bristol-Myers Squibb – BMS: The draft guideline provides a reasoned framework for carefully assessing the potential high-risk of a particular investigational compound (lines 75 through 105). The case-by-case approach is understandable for these rare products; however its inherent uncertainty leaves a degree of vagueness which, without further refinement or additional opportunities for timely and more specific guidance, may not provide the intended assistance to sponsors in transitioning from non-clinical to early clinical development, particularly regarding their planning of how, when and where to conduct the First-in-Human (FIH) study. For example, as review/approval of a CTA is a national CA responsibility, it is not clear that the current draft guideline provides sufficient detail to ensure a reasonable degree of harmony in the interpretation of individual cases. Will national guidelines be issued to clarify CA approaches? Would a European level survey or feedback mechanism of CA assessments be conceivable to review how the guideline is implemented in practice (e.g. based on specific mechanisms, targets, class effect, etc.), possibly in the form of topic related Question and Answer documents, thereby allowing for updates as experience and knowledge evolve. As noted in lines 24 to 28, information for assessing a product as high-risk or not comes from various sources and at various times, requiring iterative review. Advice on how to obtain flexible access to scientific advice (national or CHMP) when trying to identify such products would be a useful supplement to the guideline.

BioIndustry Association – BIA:

The BIA supports the development of the guideline on requirements for first-in-man clinical trials for potential high risk medicinal products. The guideline will be of great help to all sponsors (commercial and academic). However certain sections provide too general guidance that may be of little use to applicants. In addition, there is a lack of illustrative examples to provide practical guidance to all applicants in dealing with issues relating to transition from non-clinical to early clinical development, particularly in respect of assessing risks associated with a given product.

Many of the points in the guideline apply in general to all first-in-man studies of any new product, whether it is classified as high risk or not. We recommend that the scope of the guideline be changed to include all new products. It is proposed to have a section on high-risk investigational medicinal products setting out the points specific to those classes of products, which are considered as high-risk. Moreover, there should be greater differentiation between new chemical entities and biological products, in particular those sections relating to quality aspects and non-clinical requirements. A further specific distinction should also be made for monoclonal antibodies, especially between those acting by an antagonistic mechanism from those activating immune processes (i.e. agonists) for which there are specific safety issues that warrant further consideration.

Whilst we support in general the proposal to allow sponsors to decide whether or not a new product is characterised as "potential high-risk", according to certain criteria, we have some concerns over these criteria as currently proposed in the draft guideline. If the criteria are not defined precisely, there is a potential for misapplication. If the definition of high-risk products is applied too widely this could have a detrimental effect on innovation. The view of the bioindustry sector is that this will create an excessively burdensome regulatory environment that will be damaging to the development of innovative medicines. We need to strike a balance between ensuring the safety of trial subjects and making the European Union an attractive place for cutting-edge biomedical research.

Therefore, it would be helpful to have a definition of "high risk medicinal products" based on objectively justified criteria, or conversely the criteria for characterising a product as not being of high-risk. Clarity on the approach to risk assessment would be welcomed. It would be useful to provide examples to illustrate the scope of the guideline. The guideline does not address the special circumstances surrounding the development of oncology products, where there is a general acceptance of risk in first-in-man trials. In addition, whilst generally volunteers in Phase I trials would not be expected to derive any therapeutic benefit, cancer patients could derive some benefit, particularly where the drug may be a "last resort" for these patients.

With regard to quality aspects, this guideline should not be used to increase expectations regarding the characterisation of investigational medicinal products, which will increase costs and cause further delays. It should be noted that the general principles provided in the Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigation Medicinal Products in Clinical Trials would be appropriate for assuring quality of high-risk IMPs whilst recognising that this guideline applies principally to chemically defined drug substances.

We welcome the opportunity to submit these observations and comments and hope they are helpful in improving this guideline with greater clarity. We believe that the first-in-man clinical trials guideline is important in establishing a clear, efficient process for both applicants and regulatory agencies.

University College London:

The UK report of the Expert Scientific Group on Phase one Clinical Trials chaired by Professor Gordon Duff contained the following:
"We recommend that regulatory authorities and the pharmaceutical industry should consider ways to encourage and expedite the collection of information on unpublished pre-clinical studies and phase one trials, and explore the feasibility of open access to this database".

This is addressed to some extent by EUDRAvigilance module of EUDRA and by other pharmacovigilance databases which contain data about serious adverse reactions. However they do not address the need for collecting preclinical, pharmacokinetic or pharmacodynamic data according to the guidelines in the EMEA document being considered.

A database would potentially be valuable to regulators in considering applications and to those developing new drugs. This issue is being pursued by the FDA, the US National Cancer Institute caBIG programme, the pharmaceutical industry, academic medicine and developers of reporting standards with the CRIX initiative (http://crix.nci.nih.gov/). Standards for submission of data to regulators are being developed so that data can be compared with greater validity than before. While data can remain confidential there is merit in sharing as much as possible to optimise safety and accelerate drug development.

There appears to be a real opportunity for collaboration between the EU and US in this area which could enhance safety and mitigate the cost implications of the current EMEA proposals. The UK National Cancer Institute Informatics Initiative (Director, Robin Clark) (www.cancerinformaics.org.uk) is coordinating the active development of standards for data reporting in UK cancer trials and has strategic partnerships with the caBIG programme and with the European Bioinformatics Institute to ensure compatibility and avoid duplication. The standards being developed in the cancer field are seen as a prototype for other areas of human healthcare and will be broadly applicable. However, to the best of my knowledge, the issues raised in the present EMEA Guidelines are not all being considered in the present collaborations between the US and Europe. There has, though been debate about them at international scientific meetings over the last 6 months.
It would be very constructive and cost-effective if the EMEA would consider consultations with the other parties concerned to accelerate the creation of well constructed and compatible databases of data relevant to "first in man" clinical trials.

Pharmadanmark – PPS:

In order to strengthen the safety of subjects participating in first-in-man studies Pharmadanmark welcomes this draft guideline made by CHMP. As the development of new medicines increasingly involves testing of active medicinal substances of a more complex nature and/or biological origin a stronger focus on safety is needed when testing such products in humans. Pharmadanmark finds it very positive that this guideline provides a detailed and structured overview of the many factors that need to be considered before initiating a first-in-man clinical trial in healthy volunteers with a potential high-risk investigational medicinal product.

Royal Statistical Society – University of Glasgow:

This report contains many sensible recommendations. Nothing, however, is said about the issue of informed consent nor in general as to what sort of risk information the sponsor should share with subjects in the trial. Nothing is said about statistical analysis in this guideline. However, if the results from such a trial are to be used they will need to be analysed and different designs will be suitable for different intended analyses and vice versa. Not considering the intended analysis would be unthinkable in the case of a phase III trial. The fact that this has not been mentioned here is indicative of a mentality that this guideline will do nothing to dispel: the unfortunate belief that phase I studies are not really serious experiments and that from the scientific point of view no care needs to be taken in their design because in general they will not receive public scrutiny. It is also unclear at what the EMEA actually expects will change as a result of the advice in this guideline. The report is much stronger in terms of general recommendations than it is in terms of operational advice. This is, to some extent, inevitable given that it is a guideline. However, even making allowance for this more detailed procedural advice could have been given.

The European Association for Bioindustries EuropaBio:

EuropaBio welcomes the initiative of addressing the requirements of first-in-man clinical trials for potential high-risk medicinal products. EuropaBio however wishes to raise the concern that some aspects of this guideline will delay first-in-man clinical trial initiation. EuropaBio notes the specificity of vaccines, blood-derived products and other imunotherapies. EuropaBio believes that the guideline is not always adaptable to such products and would welcome specific guidance on these products at the relevant points within this guideline. EuropaBio suggests that a formal classification of products as "high risk" or "not high risk" take place based on a standardized dossier submitted by the sponsor to the EMEA. This procedure should take place as early as possible, preferably after the results of pharmacology studies are obtained.

A dedicated Committee within National Agencies would be useful to review and approve this specific Phase I CTA and to assess efficiently the amendments required by the guideline. A European Steering Committee should be put in place at the EMEA to ensure harmonized application of this guideline across Member State and monitor its implementation and development

Overall this is a well written paper that is generally e.g. consistent with the UK Expert Scientific Group Report on Phase One Clinical Trials (Duff Report). It should be welcomed if it leads to a level playing field across the EU. Given the multiplicity of potential interpretations of what may constitute a higherrisk investigational medicinal product (IMP), appropriate communications for a first-time-in-human proposal should be encouraged between Sponsors and Regulators.

It is proposed that the definition of "higher-risk" agent be aligned with that used in the Duff report (and "higher risk" rather than "high risk" be used throughout the draft CHMP guideline):

Any agent whose effects might cause severe physiological disturbance to vital body systems
Species specificity of an agent making pre-clinical assessment difficult
Agonistic or stimulatory actions on the immune system
The potency of an agent e.g. compared with a natural ligand
Multifunctional agents e.g. bivalent antibodies, FcR binding domains
Targets in systems with potential for large biological amplification in vivo
Agents that have a steep dose-response in pharmacological effects and/or toxicity

The paper uses mixed terminology to refer to an Investigational Medicinal Product (IMP) – e.g. line 24 & 63 "medicinal products". The term is clearly defined in lines 16 and 17 and avoids the need for distinction between a biological and a small molecule/chemical. It is recommended that the term IMP be used throughout for clarity. It should be made clear which comments refer specifically to the development of small or large molecules. For small molecules, it should specifically state "for small molecules targeting the immune system and with agonist activity".

There is no mention of the use of surrogate molecules in preclinical experimentation to mitigate the limitations of cross-reactivity and availability of preclinical models. The authors should consider including a section on such use.

The document does not particularly address oncology first in human trials where many compounds are higher risk and the first in human dose selected is based typically on the SD10 i.e., 1/10 dose (based on surface area) that causes severe toxicity or death in 10% of rodents. In addition first in human trials are generally designed as multiple rather than single dose in patient populations.

European Biopharmaceutical Enterprises (EBE) – The comments below are made by Fresenius Biotech GmbH.:

It is acknowledged that after the experiences with TGN 1412 there is a need to define for new medicinal products the appropriate data that is needed for the transition from non-clinical to clinical development and how these products should be tested in first-in-man studies. A balance between the need to safeguard clinical trial subjects on the one hand and the need for continued development of innovative medicines on the other hand is important. An environment promoting clinical development is key to ensure public health by generating new treatments with the potential to address unmet medical needs. It is also acknowledged that there are medicinal products that need special attention before they can proceed to first-in-human studies.

The proposed depth of understanding of an IMP described in this guideline is considerably greater than what is typically provided for a CTA (or IND). Compliance with this guideline could greatly increase both time and resources necessary to filing clinical trial applications and generate significant data that is potentially difficult to interpret and is of questionable value.

Overall this is a well written paper and generally consistent with the UK Expert Scientific Group Report on Phase One Clinical Trials (Duff Report). Given the multiplicity of potential interpretations of what may constitute a higher-risk investigational medicinal product (IMP), appropriate communications for a first-time-in-human proposal should be encouraged between Sponsors and Regulators.

The document is written with the underlying assumption that the first in man study will normally be conducted in healthy volunteers. Considerations should be given to studies in patients, since first in man studies will, in certain settings, will be conducted in patients (e.g. cancer trials), and the appropriate risk benefit evaluations in these populations *vis a vis* healthy volunteers.

The overall rationale for investigating the mechanism of action and quantitative pharmacology of a molecule seems sound and thorough.

It is proposed that the definition of "higher-risk" agent be aligned with that used in the Duff report (and "higher risk" rather than "high risk" be used throughout the draft CHMP guideline):

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- Species specificity of an agent making pre-clinical assessment difficult
- Agonistic or stimulatory actions on the immune system
- The potency of an agent e.g. compared with a natural ligand
- Multifunctional agents e.g. bivalent antibodies, FcR binding domains
- Targets in systems with potential for large biological amplification in vivo
- Agents that have a steep dose-response in pharmacological effects and/or toxicity

It should also be clarified if it is the sponsor/applicant or the national competent authority responsible for the review of the respective CTA to finally decide on the risk level. For the latter the same decision rule needs to be applied consistently across all EU member states (CTA's are still handled nationally).

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It should be made clear which comments refer specifically to the development of small or large molecules. For small molecules, it should specifically state "for small molecules targeting the immune system and with agonist activity".

There is no mention of the use of surrogate molecules in preclinical experimentation to mitigate the limitations of cross-reactivity and availability of preclinical models.

The authors should consider including a section on such use. The document does not particularly address oncology first in human trials where many compounds are higher risk and the first in human dose selected is based typically on the SD10 i.e., 1/10 dose (based on surface area) that causes severe toxicity or death in 10% of rodents. In addition first in human trials are generally designed as multiple rather than single dose in patient populations.

However, the concern is that drug development and progress in medical science is adversely affected by putting a "high risk stamp" on a potentially highly promising medicinal product. This may make it more difficult to recruit patients or healthy volunteers.

Limitations of the current MABEL concept should be discussed in more detail.

Federation of European Cancer Societies:
This excellent document is very general in its language and could be improved by adding specific examples or indicating specific areas where, for example, patients Would be more appropriate than healthy volunteers.

Community Advisory Group, San Francisco Dept of Public Health Research Section:
Please consider revising the title – and throughout - to "First-in-Human…" a suggestion made to consider that even during first use trials there may be a theoretical potential for gender specific differences that may be of importance.

IPOPI:
What are the expectations of such a trial? Are there already anticipated responses from a first-in-man trial before the start? Are adequate antidote/reversible measures in place?

Merck Sharp & Dohme (Europe) Inc.:
Merck agrees overall with the proposed general recommendations and considerations for the initiation of first in man studies with medicinal products considered high risk based on limited information obtained from non-clinical studies or uncertainties regarding the mode of action and effect on the target. However, the document is too general, open to interpretation and does not provide specific guidance. Much of what is stated and recommended would be standard practice and standard considerations for FIM studies in general. There are not clear definitions of the criteria for what a high risk molecule is and importantly what a high risk molecule is not. Specifically, the differences in requirements or considerations for a high risk vs. standard molecule are unclear in Sections 4.2., 4.3 and 4.4. Most of what is written is a consideration or requirement for any FIM study.
Research has been performed successfully for a very high percentage of molecules under the current standards. There are however circumstances for which mechanism of action of the molecule or the relevance of preclinical evaluations to predict human toxicity raise concern. A guidance that defines those limited circumstances and any additional measures to be considered in those circumstance is important.

The Academy of Medical Sciences (AMS):

This document addresses the major concerns that have been recently been raised about design and conduct of first-in-man clinical trials. We support the rationale and broader approach taken to assessment of safety and design and conduct of trials as a basis for minimising risk to participants. The principal of presenting structured data about the target, and the *in vitro* and animal models, and relating this to the clinical trials design is a good basis for improving safety.

However, the guidelines are somewhat generic and antibodies, unlike other proteins and drugs, are special in that they can react with many aspects with physiology (e.g. complement, Fc receptors, antigen targets), thus antibodies may require special consideration. For example, engineering of Fc regions would eliminate binding to Fc receptors; if antibodies are being used to block function or act as an agonist, then there is no reason not to neutralise the Fc function.

The UK report of the Expert Scientific Group on Phase one Clinical Trials chaired by Professor Gordon Duff contained the following: 'We recommend that regulatory authorities and the pharmaceutical industry should consider ways to encourage and expedite the collection of information on unpublished pre-clinical studies and phase one trials, and explore the feasibility of open access to this database.'

This is addressed to some extent by EUDRAvigilance and by other pharmacovigilance databases that contain data about serious adverse reactions. However, these do not address the need for collecting preclinical, pharmacokinetic or pharmacodynamic data according to the guidelines presented in this EMEA document.

A database would potentially be valuable to regulators in considering applications and to those developing new drugs. This issue is being pursued by the FDA, the US National Cancer Institute caBIG programme, the pharmaceutical industry, academic medicine and developers of reporting standards with the CRIX initiative (http://crix.nci.nih.gov/). Standards for submission of data to regulators are being developed so that data can be compared with greater validity than before. While data can remain confidential there is merit in sharing as much as possible to optimise safety and accelerate drug development.

There is an opportunity for collaboration between the EU and US in this area, which could enhance safety and mitigate the cost implications of the current EMEA proposals. The UK National Cancer Institute Informatics Initiative (www.cancerinformaics.org.uk) is coordinating the active development of standards for data reporting in UK cancer trials and has strategic partnerships with the caBIG programme and with the European Bioinformatics Institute to ensure compatibility and avoid duplication. The standards being developed in the cancer field are seen as a prototype for other areas of human healthcare and will be broadly applicable.

The issues raised in the present EMEA Guidelines should be considered in the present collaborations between the US and Europe; it would be very constructive and cost-effective if the EMEA would consider consultations with the other parties concerned to accelerate the creation of well constructed and compatible databases of data relevant to "first in man" clinical trials.

Department of Clinical Pharmacology and Centre for Human Drug Research Leiden University Medical Centre (CHDR):

The recommendations in this guideline are useful. However, the guideline in it s current form may do a disservice to rational and safe drug development. The main reason is that the guideline tries to dichotomise high-risk and non high-risk compounds, which is impossible. In fact, the considerations and recommendations put forward should be used for all drug research in humans.

1. What exactly makes the distinction between 'potential high risks' and 'non-high risk' compounds? It may be impossible to discern compounds for which there is or is not 'a concern that SAE … may occur'. Unless the definition of high risk compounds is clear cut, this guideline does not add to already existing guidelines. We state that such a distinction is impossible to make.
2. The guideline suggests that there are low risk compounds. In fact, most new drugs explore novel mechanisms of action, animal models are rarely fully predictive of the effects of the compounds in man. Therefore, classifying drugs as low risk may increase the risk for participants in trials, because it may result in performance of trials with less stringent rules than warranted.

All recommendations in this guideline are worthwhile, but are already part of existing guidelines. So, we strongly recommend to not issue this guideline in its current form.

Europeans for Medical Progress Trust (EMPT):

We welcome the recognition that 'high-risk' products require human, in preference to animal, data. However, we are concerned that the focus is limited to perceived 'high-risk' products, when there is little cause for complacency regarding 'conventional' medicinal products. Whilst acknowledging that the TGN1412 trial was exceptional , the fact remains that significant numbers of volunteers in phase one clinical trials are injured or killed by 'conventional' products. According to an article in Science (Vol 288, Issue 5468, 951-957, 12 May 2000): "Although it's a shock when a patient dies in a toxicity test, says a clinician who has supervised many such trials, it is not unusual. "If you were to look in [a big company's] files for testing small-molecule drugs," he insists, "you'd find hundreds of deaths."”

In light of these facts, it seems prudent to suggest an independent scientific review of the clinical relevance of animal tests, as recommended by the House of Lords Select Committee on Animals in Scientific Procedures Report in 2002 (Volume 1, p71)*, as part of a study evaluating the ability of a battery of the latest methods (microdosing, human tissues, computer models etc) to predict human outcomes.

*also recommended by The Animal Procedures Committee in their review of the animal procedures cost-benefit assessment (June 2003), The Nuffield Council on Bioethics in their inquiry into the ethics of research involving animals (May 2005), and The Weatherall Report into the use of non-human primates (December 2006).

Standing Committee of European Doctors (CPME):

CPME welcomes the opportunity to comment on this document from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP).

CPME acknowledges that a number of ethical and regulatory issues have arisen as a result of unexpected and severe adverse reactions in the first human trials of pharmaceutical products, especially those with the capacity to interfere with the subjects' immune systems.

Of course, one of the uncertainties affecting better regulation in this area is the question of when a medicinal product can be categorised as "potentially high-risk", given that animal trials may give no indication that human use will produce disproportionate effects. We would agree that particular care should be taken with products introduced in Phase-1 trials that have the potential to fundamentally interfere with physiological responses, but at the same time the precautionary principles suggested should not be too widely applied to research in, and the eventual product licensing of, the majority of medicines, a process adequately covered by existing protocols and Directives.

The suggested criteria for classifying products as of "potential high-risk" is necessarily speculative and cautious, but CPME would agree that particular care should be applied to substances in which sufficiently consistent animal-based results are absent, where there is evidence of variability in dose/response, and when there is a lack of evidence concerning the outcome of trials using compounds of similar type.

We support the requirement that animal studies should illustrate a consistent dose/response relationship prior to first trials in humans, and also the recommendations concerning the need for additional safeguards for first dosages, using the "MABEL" model described.

We support the precautionary approach taken to dose increments. In particular, although many high-risk products may trigger rapid side-effects, it is important that sufficient time elapses between dose changes to ensure that there are no unexpected or delayed reactions.

CPME notes that, although the paper concentrates on clinical and pharmacological issues, a major concern relating to the risk to subjects must be the ethical aspects of trials using high risk products. These include the need for:

- a well-prepared information sheet for research subjects, emphasising the background to existing animal studies, and the particular precautions that will be taken in the first human trials
- a specific commentary that the product being tested is a high-risk compound, with a higher level of uncertainty than is usual
- a more detailed explanation than is usual about the mode of action of the product, and the steps to be taken in the event of unexpected adverse reactions
- a sufficient period of time to be provided for a decision by participants whether to take part, and the opportunity for concerns to be shared with experts not associated with the trial itself.

We suggest that these, and other ethical issues, become part of the document, in order to emphasise the particular rights of participants when exposed to high-risk compounds.

CPME would be interested in taking part in the EMEA stakeholder meeting that will follow the consultation on the proposals.

AGAH (German Association for Applied Human Pharmacology)

This is a general comment applicable to the title of the guidance, the footnote, and several locations in the text: We propose to delete the term "potential" in "… potential high-risk medicinal products". Our understanding is that the possibility of safety problems is already implicit in the term "high-risk". This draft guidance appears to be quite general. We understand that an exact definition of different risk categories is not easy because such a classification depends on many individual factors. However, we propose that the guideline should be more specific and more obliging in terms of giving recommendations and instructions to sponsors and investigators. Consider to define biologic mechanisms of actions which belong to the highest risk category as a rule of thumb.

Different types of risks should be discussed and taken into account in the planning of clinical studies:

- immediately apparent risks versus delayed risks

- reversible vs. irreversible reactions, duration of possible reactions

- risks which can be easily identified and diagnosed vs. risks which are difficult to identify and diagnose

- possible reactions easily treatable vs. reactions difficult to treat

Foundation for the Evaluation of Ethics in Biomedical Research (BEBO)

1. This Guideline is supposed to focus on potential High-Risk Medicinal Products (PHRMP). However, the definition of PHRMP (lines 66-67) is vague. Moreover, it is unclear whether a PHRMP must comply whit one, two or all three of the conditions mentioned in lines 68-69, and/or whether further considerations apply.
2. A medicinal product is defined as PHRMP when there are concerns that serious adverse reactions in FIM trial may occur (lines 66-67). However, it is the experience of the Independent Ethics Committee of our Foundation (accredited by the Dutch authorities and specialized in FIM trials that one cannot predict or presume when and with what type of compound serious adverse reactions occur in FIM trials.
3. Thus, one may also define any FIM study as being of potential high risk. This appears to be corroborated by Section 4.1., where lines 75-76 state that "the Sponsor should discuss the following criteria for **all** (emphasis added) FIM trials in their clinical trial authorization application". Furthermore, large parts of the present text are relevant for all FIM studies.
4. The present draft does not address the qualifications and/or possible role of the Independent Ethics Committee (IEC) involved in reviewing the protocol and in monitoring the conduct of the study.
5. The present draft does not address microdosing studies (Phase 0). Are the recommendations in the Guideline also valid for microdosing studies or do other and/or additional considerations apply. Furthermore, to what extent can microdosing be used to identify PHRMP's.

Cancer Research UK

The definition of "First-in-Man" is not explained. Does first-in-man mean the very first time the product is given to man or does it include new indications, doses and schedules?

The definition of high risk trials seems to have diverged from that in the Duff report. The definition needs to be consistent across European regulatory agencies and therefore the definition used in the guidance should match that in the Duff report.

The guidance is written with a very strong focus on healthy volunteer clinical trials. There is no mention of how the guidance fits in with existing guidances on patient clinical trials and in particular cancer and HIV patient clinical trials. The guidance concentrates on the assessment of risk alone rather than the assessment of risk-benefit necessary in patient clinical trials.

The guidance does not acknowledge that toxicity may be the end point of a trial. This guidance equates serious adverse reactions with a medicinal product being high risk and this may not necessarily be the case, e.g. a trial of a cytotoxic cancer therapeutic agent.

In several sections the guidance is written with an assumption that all drug targets are receptors.

The "quality aspects" section discusses the importance of product comparability between non-clinical and clinical studies, however the stage of non-clinical research and development at which this comparability is required is not discussed. It is important that it is clarified whether this refers to all non-clinical work or only the pivotal toxicology studies.

The "Site of the clinical trial" section has a considerable potential for a negative impact on academic clinical trials and European clinical research in general.

"Immediate access to facilities for the treatment of medical emergencies" requires clarification. It is important that any regulation of the site of clinical trials is not overly restrictive and is consistent across the member states.

The UK report of the Expert Scientific Group on Phase one Clinical Trials chaired by Professor Gordon Duff contained the following recommendation:

"We recommend that regulatory authorities and the pharmaceutical industry should consider ways to encourage and expedite the collection of information on unpublished pre-clinical studies and phase one trials, and explore the feasibility of open access to this database". Can this issue be addressed in this guideline?

Committee on Drug Development of the European Association of Nuclear Medicine (EANM)

Umbrella Organization

The European Association of Nuclear Medicine (EANM) is the umbrella organization of Nuclear Medicine in Europe and represents the sector towards the European Institutions. It was founded in 1985 as a professional non profit medical association, serving as a communication platform for clinical and research excellence in Nuclear Medicine. There are two membership branches of the society: one being 34 national societies (member states of the Council of Europe), the other being individual members (3.474 members), comprising physicians, radiologists, chemists, radiopharmacists, physicists and technologists.

Scientific Strength

Presently there are 11 committees representing the most important sub-specialties of Nuclear Medicine: Cardiology, Dosimetry, Drug Development, Molecular Imaging, Neurology, Oncology, Paediatrics, Physics, Radionuclide Therapy, Radiopharmacy and Technologists. These committees are furthermore the scientific pillars of the association and important cooperation partners for related fields such as Oncology, Radiology, Cardiology, Neurology, Paediatrics and Molecular Imaging. The official journal of the EANM, the "European Journal of Nuclear Medicine & Molecular Imaging" (journal impact factor in 2005: 3.88), is known for its scientific quality and serves as a communication tool for the cutting-edge research findings and Guidelines written by the EANM Committees.

Professional Infrastructure ensuring Continuity

Since 2001 there is an Executive Secretariat and Educational Facility in Vienna, which ensure the administrative workflow of the whole association and of the educational branch in particular: The European School of Nuclear Medicine (15 teaching courses per year at the Educational Facility in Vienna, 3 seminars per year in Central and Eastern Europe) is an integral part of the EANM. Moreover, the congress management department is a core unit of the Executive Secretariat, which is in charge of the organization of the annual scientific congress (EANM'07 Copenhagen: Oct. 13 – 17, 2007) usually gathering around 4,200 participants for a complete spectrum of state-of-the-art scientific sessions in Nuclear Medicine.

General Comment:

The strong impact of nuclear imaging on diagnostic and therapeutic decisions has paralleled its development as clinical and pharmacological research tool for in vivo assessment of physiology, pathophysiology and biochemistry. Relevant processes, such as metabolism, receptor binding and enzymatic reactions, can be detected and quantitated non-invasively into humans. Many of these applications can qualify as surrogate end-points able to support early phases of candidate drug testing, provide data on ADMET and dose/response issues.

Furthermore, a wealth of expertise has been accumulated on the synthesis, control of radiolabelled drugs and radiotracer and their use in vivo in both humans and animals to assess species-specificity and animal model validation. Use of validated animal models and early assessment of drugs into humans are thought to be a major resource to reduce risk and attrition, improve safety of studies and reinforce the ability of sponsors in making proper decisions on drug candidates. The introduction of exploratory phases before phase-I clinical studies, based on micro-dosing approach, is expected to strongly reduce the time and resources expended on clinical trials as well as enhance their ability to reach more robust data on drug candidates, while ensuring a higher degree of protection of volunteers. High sensitivity of nuclear imaging is expected to be the key point to achieve such result.

Issues above have been recently addressed by document CPMP/SWP/2599/02Rev1 (Position paper on non-clinical safety studies to support clinical trials with a single micro-dose) and document CHMP/SWP/91850/2006 (Concept paper on the development of a CHMP Guideline on the non-clinical requirements to support early phase 1 clinical trials with pharmaceutical compounds).

We believe that the integration of concepts from the above-mentioned documents may be functional to the scope of the Guideline.

FRAME:
The draft guideline is a platform for the development of detailed guidelines for the testing of medicinal products with novel or complex mechanisms of action that requires some elaboration. Worked examples appended to the document and decision-making strategies upon which investigators can base their decision to characterise a new medicinal product as high risk would be particularly useful.

GALDERMA R&D:
This guideline seems particularly adapted to systemic administration of medicinal products. As a company involved only in dermatological products, mainly applied directly on the target organ, we would like to express concerns in our day life work, especially that first-in-man clinical trials in our field are most of the time on patients and not on healthy volunteers and that systemic exposure is expected to be low as the pharmacological effect is targeted on the application site, the doses administered for first-in-man trials are microdoses and/or the sizes of application areas are minizones, specially with new chemical entities.

Johnson & Johnson:
We support the notion that it is important that information on pharmacological effects should be taken in to account, in addition to toxicological data, when determining safe starting doses in humans for the first clinical trial. Indeed, this is important for all development programs and should be a routine part of the assessment of the preclinical data when plans are made for the transition from preclinical to clinical development. Information on the dose and exposure range that gives pharmacological effects carries especially high weight when the drug target is novel and highly species specific. It would be helpful if the guidance could give greater clarity as to how the data generated from pharmacology studies should be applied to determine the safe starting dose in humans.

Overall it would be more helpful if this guidance could apply to the broad range of development programs where there is a gradation of certainty in predicting risk. It should be the aim of every program to minimize risk to human subjects and thus we suggest that compounds should not be categorized simplistically as either "low" or "high" risk. The guidance can focus on the approach to identify a safe starting dose and the procedures to assess, manage and mitigate risk on the basis of the full integrated preclinical data that are assessed and applied on a case by case basis. Many of the measures in the draft guidance suggested for first clinical trials should be standard for all first in human trials. Others, such as long-term follow up, should be applied on a case by case basis when the risk of longer term effects may be difficult to predict or unknown. Additional risk management measures should be applied according to the data and level of information for a specific investigational drug. Such an approach would serve the safety of human subjects better than the use of an ill defined "high risk" terminology. Another aspect of the use of the “high risk” terminology. Another aspect of the use of the “high risk” terminology might well be a bias with respect to the ability to recruit subjects for clinical trials opposing current EU efforts to stimulate pharmaceutical research and development in the region.

Based on above considerations it is considered more appropriate to delete references to higher risk in the text and to adjust the title of this guidance into:
“GUIDELINE ON RISK ASSESSMENT AND RISK MITIGATION FOR FIRST-IN-MAN CLINICAL TRIALS”

JPMADrug Evaluation Committee:
JPMA appreciates that this draft guideline provides a new insight to prevent such a serious adverse event caused by anti-CD28 antibody. We reviewed carefully the document and would like to make the following suggestions that may refine the document to be implemented more effectively and efficiently.

We are concerned about the confusion that this document might be applied to as many medical products as originally expected, although it would be very helpful for the prevention of clinical serious adverse event caused by a high-risk medical product. Thus, further knowledge and experiences should be accumulated before the concept is generalized as a guideline. Therefore, it should be a “points to consider” rather than a guideline.

EFGCP, the EUROPEAN FORUM FOR GOOD CLINICAL PRACTICE:

EFGCP is impressed with the quality of this draft guideline as a thorough reflection of most of the published recommendations made after the TGN 1412 event are integrated in this document (precautions to apply between doses/ cohorts, dose escalation scheme, stopping rule, etc…). However the introduction lacks concrete examples of what did go wrong in past examples, with references to the literature description of the cases. There are not too many cases (the Northwick Park Phase I unit in 2006, the SFBC unit in Miami, Florida in 2005, the death of a volunteer in Dublin in 1985, etc.). The EMEA experts should agree about the reasons of each case and then verify that the Guideline addresses these issues effectively. Most of the recommendations in these guidelines would not have prevented the cases, and therefore there is a risk that by not ranking the proposed measures in order of priority as a function of dramas of the past, the Guideline only stifles translational research, as described in the specific comments section below.

However, EFGCP wants to emphasize that - as the safety of participants in first-in-human trials and the ethical aspects in this stage of drug development are of their great concern – a stronger representation of these aspects should be included in this document. This guideline concentrates very much on the scientific and technical aspects of FiM trials but does not sufficiently consider ethical aspects like information to subjects, indemnity coverage requirements and medical safe-guards during and after the study performance. For example, with regard to paragraph 4.4. Clinical Requirements, some more guidance should be given in terms of qualifications/ certification of investigators and site personnel (see below specific comments). At several occasions it is too often referred to as 'appropriate' (appropriate training, appropriate facilities). In our opinion a Phase I unit should be able to anticipate each type of life threatening events. The conceptual issue is that adequate therapeutic facilities should immediately be available. We are also very much concerned that the required level of experience and qualification of investigators responsible for FiM trials are not specified in the guideline. Considerations should be given to the request for a training programme (with diploma) for Phase I investigators, the establishment of qualification checklists for ethics committees' review of the facility and investigator suitability and an accreditation system for Phase I units.

In general EFGCP underlines the importance of this guideline document in order to move from the non-clinical testing to early clinical development.

Association of Clinical Research Organizations (ACRO):

- Clinical research organizations (CROs) assist pharmaceutical, biotechnology and medical device companies with the conduct of thousands of clinical trials each year, and are a key participant in the development of new medicinal products. The Association of Clinical Research Organizations (ACRO) represents this key segment of the clinical research enterprise, and our member companies conduct research in more than 60 countries while employing more than 40,000 professionals worldwide. ACRO thanks the European Medicines Agency (EMEA) for issuing the above-referenced Guideline in draft, and we appreciate the opportunity to provide our comments to the Committee for Medicinal Products for Human Use (CHMP).

- In several instances, we note, the Guideline offers a general statement applicable to all first in man (FIM) trials, not just those with potential high-risk medicinal products (PHRMPs); for example, section 4.1 states, "the Sponsor should discuss the following criteria for all first in man trials in their clinical trial application." ACRO suggests that either the title of the Guideline should be altered to reflect general applicability to FIM trials or the contents clarified so that recommendations relating to studies with PHRMPs are clearly distinguished from statements relating to FIM studies in general.

For such an important guideline relative to the safety of subjects in the first trial in humans, we believe it essential that the recommendations offered by the EMEA be stated in sufficiently clear language that differences of interpretation between the various competent authorities of the EU Member States will be minimized.

AMGEN:

We agree in general with the premises presented in the document as it does reflect current practice in most settings, but modification is necessary. Firstly, the introduction should be reframed to focus on conduct of safe clinical study and not innate safety of the investigational medicinal product (IMP). As such, reference to high-risk IMP should be removed from the document. Secondly, as the document does generally reflect current practice in drug development, this would be best suited as a 'Points to Consider' document, rather than as a 'Guidance' document, with a focus on Risk Mitigation. Thirdly, the titles for sections 4.3 and 4.4 should be renamed to Non-clinical and Clinical Considerations, respectively. It should also be made clear that the examples presented are merely illustrative. This would prevent the document from being viewed as a check list. Lastly, more alternatives to dose selection for FTIM studies should be presented to guide the best method for the IMP.

Overall this is a well written paper and generally consistent with the UK Expert Scientific Group Report on Phase One Clinical Trials (Duff Report). Given the multiplicity of potential interpretations of what may constitute a higher-risk investigational medicinal product (IMP), appropriate communications for a first-time-in-human proposal should be encouraged between Sponsors and Regulators.

It is proposed that the definition of "higher-risk" agent be aligned with that used in the Duff report (and "higher risk" rather than "high risk" be used throughout the draft CHMP guideline):

- Any agent whose effects might cause severe physiological disturbance to vital body systems
- Species specificity of an agent making pre-clinical assessment difficult
- Agonistic or stimulatory actions on the immune system
- The potency of an agent e.g. compared with a natural ligand
- Multifunctional agents e.g. bivalent antibodies, FcR binding domains
- Targets in system with potential for large biological amplification in vivo
- Agents that have a steep dose-response in pharmacological effects and/or toxicity

The paper uses mixes terminology to refer to an Investigational Medicinal Product (IMP) – e.g. line 24 & 63 "medicinal products". The term is clearly defined in lines 16 and 17 and avoids the need for distinction between a biological and a small molecule/chemical. It is recommended that the term IMP be used throughout for clarity. It should be made clear which comments refer specifically to the development of small or large molecules. For small molecules, it should specifically state "for small molecules targeting the immune system and with agonist activity".

There is no mention of the use of surrogate molecules in preclinical experimentation to mitigate the limitations of cross-reactivity and availability of preclinical models. The authors should consider including a section on such use.

The document does not particularly address oncology first in human trials where many compounds are higher risk and the first in human dose selected is based typically on the SD10 i.e., 1/10 dose (based on surface area) that causes severe toxicity or death in 10% of rodents. In addition first in human trials are generally designed as multiple rather than single dose in patient populations.

EFPIA:

EFPIA supports the creation of a new guideline on First In Man (FIM) clinical trials for medicinal products. The draft guideline reflects good science and decision-making. It is a good summary of what EFPIA considers to be standard good clinical practice in the conduct of clinical trials in early development in general and of first-in-human trials in particular.

On collecting the comments from various stakeholders in response to the draft guideline, it was quickly seen that the major problem with the draft guideline was the differentiation of 'high-risk' investigational medicinal products (IMP) from the rest. Assigning a compound to one category versus the other could be viewed as being arbitrary. Risk is related to the doses administered in the clinical trials - not the IMP itself- and to the clinical trial design.

Therefore it is EFPIA's view that the classification of some medicinal products as high-risk medicinal products, as proposed in the draft CHMP guideline, may lead to a situation that impacts negatively on conducting clinical development in Europe. Rather than the classification of medicinal products as high risk, EFPIA believes that it is the clinical trial design that leads to acceptable or unacceptable risk versus benefit to human subjects in first-in-human trials. Therefore, the emphasis of the guideline should be repositioned to risk mitigation strategies through the integration of all non-clinical data and appropriate design of clinical trials. Therefore, it is proposed that the emphasis of the guideline should be repositioned to risk mitigation strategies through the integration of all non-clinical data and appropriate design of clinical trials; this is explained further in a specific document (see appended document).

In case the concept of a potential high-risk investigational medicinal products remains in the guideline, then the definition should be made more specific in order to avoid inappropriate classification and to support consistent approaches into the EU Member States.
It is EFPIA position that many points require clarification to avoid risk of misinterpretation, lack of flexibility and a more conservative interpretation; this could imply unnecessary hurdles for drug development without leading to gains in safety when this guidance will be applied in practice.

Given these major concerns, EFPIA do support the need for appropriate communications for a FIM guideline. EFPIA do expect that the June workshop organised by EMEA will help clarifying the issues, including with whom and when these can be discussed and finding a common way forward so that clinical research is optimised and maintained in Europe

General comments

The document is written with the underlying assumption that the first in man study will normally be conducted in healthy subjects. Considerations should be given to studies in patients, and the appropriate risk versus benefit evaluations in these populations vis-à-vis healthy volunteer. However, even in healthy subjects it is not possible to decrease the risk of the trial to zero. Effort should be made to emphasize that the appropriate metric is the minimization of risk in the healthy volunteer, and balancing that risk versus the potential benefit to the intended population if the IMP is successful

The document does not particularly address oncology first in human trials where many compounds are higher risk and the first in human dose selected is based typically on the SD10 i.e., 1/10 dose (based on surface area) that causes severe toxicity or death in 10% of rodents. In addition first in human trials are generally designed as multiple rather than single dose in patient populations. It would be recommended that the final guideline explicitly states that there are already existing guidelines in place to cover oncology products entering patients with metastatic cancer- which are not therefore the subject of this guideline.

The guideline might consider addressing gender differences, as there are anecdotal reports of first dosing in females revealing devastating serious adverse reactions for the first time. No mention of gender is made in the document.

International Council on Animal Protection at the ICH (ICAPI):

These comments were prepared by Drs. Gill Langley and Katy Taylor on behalf of the more than 30 million supporters of **International Council on Animal Protection at the ICH (ICAPI)**, whose organisational members include the British Union for the Abolition of Vivisection, the European Coalition to End Animal Experiments, Eurogroup for Animals, Humane Society International, PETA Europe Ltd., Animal Alliance of Canada, Doris Day Animal League, Japan Anti-Vivisection Association, and the Physicians Committee for Responsible Medicine.

We would like to note that we are not responding to all sections of the guideline; only those that relate to pre-clinical studies and their extrapolation.

We would like to express our support for the cautious approach that is taken in this document with regard to the relevance of animal models and the emphasis on the need to demonstrate concordance with human *in vitro* data where relevant. This guideline represents a more realistic and critical approach to the application of pre-clinical animal data, which is essential.

We would, however, like to stress that the utmost caution should be applied when determining if a medicine is likely to be 'high-risk'. Given the limitations of animal models, particularly for biologicals, extrapolation from animals is inherently risky, in all cases. It is important therefore that, in the absence of strong evidence to the contrary, *all* drugs should be treated as potentially high risk. The Duff Report itself also suggested that "a thorough assessment of risk should be made and a clear scientific case provided when risk of harm is assessed as being low…When there is significant doubt, higher risk should always be assumed." (Expert Scientific Group on Phase One Clinical Trials: Final Report, 30th November 2006, HMSO). It is clear that TGN1412 should have been considered a 'high-risk' medicine and therefore all measures must be taken to ensure that this oversight does not happen again. Only by ensuring the same high quality evidence and maximum use of human-based data for all new medicines can this be achieved. 'Absence of evidence' is not 'evidence of absence', i.e. absence of evidence that pre-clinical animal data is likely to be unreliable is not the same as evidence that pre-clinical animal data *is* likely to be reliable. Whilst there was little evidence of any inherent problem with the animal models for TGN1412, neither was there substantial specific evidence that the animal models *were* reliable and in hindsight it was clear that they were not. Regulators should set the barriers high with respect to proving the relevance of animal models and always adopt a precautionary principle. For all investigational drugs, rigorous evidence (such as systematic reviews) should be provided to support claims as to the relevance and predictability of the animal model used, together with as much human-based data as is scientifically, ethically and practically possible.

IFAPP International Federation of Associations of Pharmaceutical Physicians:

Recommendations on planning the actual first-in-man trial are suggested to be augmented in order to avoid both overexposure of subjects (i.e. too expose the same cohort to too many dose-levels) and potentially dangerous dose-leaps (e.g. in alternating cohort designs)

Definition of high risk product is relatively vague and open for discussion. Therefore the sponsor will have to pay particular attention to the discussion why/why not a product is to be considered high risk.

MILLENNIUM PHARMACEUTICALS, INC.:

Millennium's major concern regarding this draft guideline is the clarity and definition of the term "high-risk". The guideline lists many factors to be considered, but is not clear how to make a decision based on these considerations, especially in a quantitative way. In addition, there is no clear explanation of how to evaluate a new chemical entity.

The guideline is understandably more appropriate for biological products/proteins without the inclusion of small organic molecules. In consideration of this, we seek clarification on the following: How many small molecule drugs on the market have full knowledge of MOA? Should all cytotoxic anti-cancer agents be excluded? Should the scope of small chemical products be more defined or specific with examples and reference?

NDA REGULATORY SCIENCE LTD.:

The criteria to follow in the development and regulatory review of applications for first-in-man clinical trials of high-risk investigational medicinal products (IMPs) have been published for consultation within a very short time period after the publication of the *Duff-report* which is highly welcome taking into account their urgent need. NDA Regulatory Science Ltd. has increasingly observed that new IMPs and in particular biopharmaceuticals are more and more developed by SMEs. These rather small companies thus carry the whole burden of the early development stages including the complete pre-clinical development. Innovative approaches are increasingly followed in drug development requiring gradually more case-by-case decisions and risk-mitigation considerations already at a very early stage of drug development. These innovative approaches also increasingly include attempts to accelerate drug development. Expeditious entry into clinical trials and fast performance of clinical trials are of major interest to drug developers. The guideline calls for particular attention to understand the molecule under development in all of its attributes, to accept its potential to be of high risk and to follow particular regulatory principles. These principles to follow in drug development applicable throughout the EU have been described in this guideline for the first time.

The drafting group might also consider recommending on how and where and in what level of detail to insert information into the existing structure of the IMPD in order to provide guidance on how the information required for potential high-risk IMPs should be presented to the national agencies in charge of the approval of the FTIM-CTA. Criteria to be followed in the benefit-risk evaluation performed by the sponsor and by the agency would also be of great interest.

The Parential Drug Association (PDA):

1. Title and references throughout should be to “First –in-human” rather than first in man. (Find and replace throughout the document)
   Reason: consistency with the ICH CTD Guideline.
2. As biological products are also included (see scope section) some of the latter statements in section “4.2 Quality Aspects” need additional commentary. For specifics, refer to the table below.
3. The use of GLPs is referenced in the document although there is a need to reference specific GLP guidelines (e.g. OECD).

PhRMA – Pre-Clinical Leadership Committee (DruSafe):

The document is well written and provides timely regulatory insight into an important area that should offer significant benefit to industry. Whilst the guidance contains positive suggestions to improve safety of clinical studies in high-risk medicinal products, it contains elements, such as the proposal to recommend involvement of an IDSMB, which may prove impractical and serve no beneficial purpose. The guidance would also benefit from additional emphasis on those aspects that are specific to high-risk products.

Because there are many terms that are based on experience and therefore are somewhat subjective, application of the guidance may be difficult for those inexperienced in developing new medicines. For example, subjective terms such as "acceptable safety", "case-by-case", and "limited relevance" are used in section 4.1. Moreover, requests to provide more specific details of the extent of comparability needed across species would potentially make the document too restrictive and limit its effectiveness for the majority of sponsors. A few exceptions are noted below in 'Specific Comments'.

In some sections the guideline is a relatively high level document and many points require clarification, otherwise there is a risk of misinterpretation and that the most conservative, versus the most appropriate, interpretation of any stakeholder may delay advancement of innovative new medicines. A more detailed definition of "high risk medicinal products" and conversely what is clearly "low risk" (and in each case why they would be designated so) would be helpful. Examples throughout would be useful to clarify the intent of the guideline.

It is proposed that the definition of "higher-risk" agent be aligned with that used in the Duff report:

Any agent whose effects might cause severe physiological disturbance to vital body systems
Species specificity of an agent making pre-clinical assessment difficult
Agonistic or stimulatory actions on the immune system
The potency of an agent e.g. compared with a natural ligand
Multifunctional agents e.g. bivalent antibodies, FcR binding domains
Targets in systems with potential for large biological amplification in vivo
Agents that have a steep dose-response in pharmacological effects and/or toxicity

The paper uses mixed terminology to refer to an IMP – e.g. line 24 & 63 "medicinal products". The term is clearly defined in lines 16 and 17 and avoids the need for distinction between a biological and a small molecule/chemical. It is recommend that the term IMP be used throughout for clarity. It should be made clear which comments refer specifically to the development of small or large molecules. For small molecules, it should specifically state "for small molecules targeting the immune system and with agoinst activity".

There is no mention of the use of surrogate molecules in preclinical experimentation to mitigate the limitations of cross-reactivity and availability of preclinical models. The authors should consider including a section on such use.

The document does not particularly address oncology first in human trials where many compounds are higher risk and the first in human dose selected is based typically on the SD10 i.e., 1/10 dose (based on surface area) that causes severe toxicity or death in 10% of rodents. In addition first in human trials are generally designed as multiple rather than single dose in patient populations.

The document makes a critical point in the Introduction, "Decisions on strategies for development of a new medicine and the experimental approaches used to assemble information relevant to the safety of FIM clinical trials must be science based, made and justified on a case by case basis."

The guidance might consider addressing gender differences in Phase 1. No mention of gender is made in the document.

ROCHE:

The overall rationale for investigating the mechanism of action and quantitative pharmacology of a molecule seems sound and thorough. However the scope of this guideline needs further clarity in terms of the definition of "high-risk medicinal products".

The definition of "high-risk medicinal product" is somewhat ambiguous as any drug that is not a generic or a me-too would fall into this category. A definition which includes the type of risk which could be of concern in single dose administration, such as drugs which have potential to over-stimulate the immune response, would be more useful. It should also be clarified if it is the Sponsor or the concerned national competent authority to finally decide on the risk level. For the latter the same decision rule needs to be applied consistently across all EU member states, which further increases the need for more concrete definition of "high risk".

Limitations of the current MABEL concept should be further defined within the guideline. The concept of the MABEL is potentially troublesome because a) it is based on extrapolation and could therefore be subject to subjectivity and b) it is not clear how the MABEL concept should be used to determine the starting dose (the guideline states that other safety factors can be applied).

The proposed depth of understanding of an IMP described in this guideline is considerably greater than what is typically provided for a CTA (or IND). Compliance with this guideline could greatly increase both time and resources necessary to filing clinical trial applications and generate significant data that is potentially difficult to interpret and is of questionable value.

Finally, the document is written with the underlying assumption that the first in man study will normally be conducted in healthy volunteers. Considerations should be given to studies conducted in patients, and the appropriate risk benefit evaluations in these populations vis a vis healthy volunteers.

Schering-Plough Corporation (SPC):

The intent of this document is to assist sponsors in the transition from pre-clinical research to first-in-man clinical studies for investigational medicinal products. However, the document does not consistently qualify the investigational status of the medicinal product. Therefore, we would recommend that any reference to "medicinal product" throughout the document as well as in the title of the guideline include the qualifier "investigational."

Swissmedic, Swiss Agency for Therapeutic Products, Toxicology Unit:

The Toxicology Unit of Swissmedic has reviewed and discussed your draft guideline. We generally agree with the scope, the content and the approaches described in this guideline, which we believe will become a very important document for the near future.
We have identified some specific points, which we would like, however, discuss directly at the EMEA Workshop on 12 June 2007 in London.

TAKEDA:

A well written guideline which provides useful recommendations for conduction of FIH studies with potentially high risk medicinal products. Further clarification around the definition of a potential high risk product is key.

Safety Pharmacology Society (SPS):

It is clear that as an industry we need to assess the safety of high risk medicinal products by identifying potential safety issues early. The Safety Pharmacology Society membership welcomes the introduction of guidance to assist in this process and to ensure that this is done that this is done consistently prior to first in man studies. Our membership, in general, have noted that while the categories for consideration in assessing which medicinal products are high risk are clear and justifiable, the detail behind these categories is focused on the absence of relevant information rather than demonstration of a detailed knowledge of the pharmacology of the medicinal product and a demonstration of this knowledge applied to define the relevance of animal models to human. Additionally, our members have noted this is an area in which our experience will evolve quickly and the guidance should make allowance for this.

French Club Phase 1:

This guidance provides a comprehensive attempt for guiding the design and conduct of First-in-man single ascending dose studies of potentially high risk compounds. A major point is the definition of potential high risk medicinal products. According to the way it is currently written, almost any new innovative compound can be interpreted as being a potential high risk compound. Therefore, this is a need for revisiting and better specifying the definition. Addition of examples may be useful. It is the primary responsibility of the sponsor to determine if is compound may be considered as potentially high risk. It should be useful to also clearly specify if regulatory authorities may also reclassify the drug (it should probably be possible) and if IRB can also reclassify the drug as high risk . Even if this guidance is currently a draft , it is already used and interpreted by some IRB.

Good Clinical Practice Alliance GCPA:

The Good Clinical Practice Alliance – Europe (GCPA) wishes to express its appreciation to the Committee for Medicinal Products for Human Use (CPMP) of the European Medicines Agency (EMEA) for bringing forth this draft 'Guideline on Requirements for First-in-man Clinical Trials for Potential High-risk Medicinal Products'. The guideline addresses a major concern today regarding the safety and well-being of research participants within the European Union and globally. Following on the implementation of Directive 2001/20/EC, it has become evident that insufficient regulatory guidance and engagement exist regarding phase I or first-in-man clinical trials in the European Community. In particular, a number of Member States used the occasion of the implementation of Directive 2001/20/EC to increase their competitive advantage in the European market place for phase I clinical trials. Following the full implementation of the EU Directive on GCP, the events of the TeGenero 1412 phase I clinical trial demonstrated a lapse in oversight for phase I studies, even if improved oversight may not have fully prevented the events of this particular trial. In particular, the fact that the proposal for this trial had been presented to two separate regulatory agencies and that it was eventually carried out in the Member State that was 'first to the post' raises serious public concerns.The GCPA welcomes the assistance this guideline will provide in defining risk for first-in-man clinical trials from both non-clinical and clinical perspectives. Clarifying risk, and how it can be limited and properly addressed in phase I studies, is critically important. This guideline is researched and considered regarding the definition of risk.The GCPA believes that the guideline should be addressed, not solely to sponsors, but to all parties needing to be in a position to identify risk in first-in-man studies and make decisions regarding the validity of the science and ethics of proposed studies, including sponsors, researchers, regulators, patients & their organisations, and members of ethics committees.

The GCPA considers that the draft guideline might better be addressed to all first-in-man studies. Defining and differentiating high-risk chemical and biological entities, as the draft guideline demonstrates, is complex and requires consideration of a broad range of issues and possibilities. These issues and possibilities apply, however, to all first-in-man studies. Thus, the guideline might prove stronger and more useful if it was presented for consideration of all first-in-man studies and then assisted the reader in both identifying high-risk chemical and biological entities as well as strategies for decision-making regarding the risk. As the draft guideline now stands, it presents considerations valid for all first-in-man studies without establishing clear criteria for either when 'the conventional non-clinical programme provides an acceptable safety estimate [sic] for a first administration in humans'and when high-risk attenuates the chemical or biological entity proposed for a first-in-man clinical trial. The GCPA considers that the guideline could be enhanced by providing criteria to distinguish subjects not expressing the condition the chemical or biological entity is intended to address and patients. With regard to the latter, the guideline might provide for specific considerations for different patient populations (e.g., children, following on the EU Regulation 1901/2006; patient populations experiencing rare or neglected diseases).The GCPA considers the term 'medicinal product' to be inappropriate in characterising chemical and biological entities proposed for testing first-in-man. Such terminology is misleading for patients and possibly for the medical community as well. The GCPA, however, regrets that the draft guideline limits itself to identifying risk and does not go far enough in assisting sponsors, researchers, regulators, patients & their organisations, and members of ethics committees in understanding their proper roles in managing the risk and, most importantly, decision-making regarding the science and ethics of risk.

Directive 2001/20/EC requires both competent authorities and ethics committees to provide public assurances regarding the science and ethics of proposed clinical trials: '2. A clinical trial may be undertaken only if, in particular: (a) the foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients. A clinical trial may be initiated only if the Ethics Committee and/or the competent authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored . . . .' However, in many Member States, and specifically across Member States, the relationship between the decisions taken by regulators and those by ethics committees remain vague, as well as the individual and shared competencies in the decision-making processes. The European citizen cannot be assured full protections in clinical trials if there is vagueness or hindrance in the decision-making between responsible parties having an oversight function. While regulatory oversight and ethical review remain largely a competence of the individual Member States, Community-level discussion and guidance would be beneficial to all, most particularly, the individual European who finds himself/herself a subject of a first-in-man clinical trial.

The GCPA would, thus, ask the CHMP to consider providing an additional section (4.5) on regulatory and ethical review responsibilities for risk management and risk decision-making in first-in-man studies. We would be pleased to assist in providing an outline or preliminary draft for such a section.

Finally, the GCPA wishes to conclude by pointing to the timeliness of this proposed guideline. Due to financial, market, and patient pressures, there is an increasing emphasis by sponsors on accelerating the development of molecules from bench to market. The ongoing European attempts to streamline legislation and procedures testify to these pressures, often felt particularly acutely in the decision-making processes concerning the move to first-in-man studies. Globally the pressure on such decision-making and risk analysis is also growing, particularly with a view toward the United States' Food & Drug Administration's Critical Path Initiative and US legislation forthcoming in 2007. It also shows itself in the increasing globalisation of phase I clinical trials, and specifically in the documented rogue patient recruitment activities in Eastern Europe by certain Community-based CROs. The European Union needs to strengthen its competitive edge in this highly pressurised and global market of first-in-man studies. The best way to do this is by providing public assurances of the sound scientific and ethical basis for the first-in-man studies approved and carried out within the Community. This proposed guideline should assist Europe in moving closer to the needed public assurances.

Association of British Pharmaceutical Industry – ABPI:

The publication of this draft guidance is welcomed as an opportunity to clarify the requirements for first-in-man clinical trials. The draft guideline highlights some of the key points to consider when taking an IMP into clinical testing and this is an appropriate style to adopt. Indeed, the guideline is equally applicable to all IMPs and consideration should be given to re-focus the guideline to a points to consider document on risk management strategies and dose-setting for first-in-man clinical trials. Some new IMPs can be classified as highly novel molecules which show a high degree of species specificity and with little or no prior knowledge of the risk/benefit ratio in man. These molecules require special attention in defining and communicating the risk management strategy. The emphasis of the guideline should be more focussed on risk mitigation strategies through the integrated analysis of all pre-clinical data and appropriate design of clinical trials. This would remove the need for a definition of "high risk"; whilst still addressing appropriate risk management strategies.
Two key areas need to be covered by the guideline:

1. **The dose/concentration-response relationship for toxicity and pharmacology.** The aim of the preclinical data is to characterise the mechanism of action and the shape and steepness of both the toxicological AND pharmacological dose/concentration-response relationships utilising data that are normally generated for all potential candidate drugs (see Figure 1). The suggestions provided in the guideline to characterise concentration-response relationships should be seen as such and not as an exhaustive checklist of endpoints. This approach to safety assessment, which takes account of the pharmacological as well as the toxicological profile of the IMP, emphasises the importance of the involvement of experienced safety scientists by both sponsor and regulator, preferably those with knowledge of toxicology, immunology and/or the relevant pharmacology.

2. **Risk management in relation to the risk profile of the IMP** Using all the available data, the sponsor should justify the design of the clinical study (starting dose, dose escalation, clinical population etc) based on the risk profile of the IMP. Limitations of the preclinical animal species / models for predicting human safety should be addressed and where there is limited confidence in the predictive value of the available preclinical data this should be reflected in risk mitigation strategies for the design of the clinical trial e.g. cautious starting dose and dose escalation, choice of clinical population etc. Depending on the risk profile of the IMP and clinical population, the starting dose may be set above the Minimum Anticipated Biological Effect Level (MABEL), at the MABEL or at some fraction of the MABEL. For example, for an IMP with known pharmacology and mechanism of action and where there is reasonable confidence in the predictive value of the preclinical data (including in vitro human data), or where the clinical population justifies the adoption of a higher risk (e.g. for certain patient populations such as oncology) it may be possible to justify a starting dose above the MABEL. For an IMP with a novel mechanism of action and little or no prior knowledge about the target, a more conservative approach may be needed which involves a starting dose based on the MABEL or a fraction of the MABEL (to be justified by the Sponsor - see Figure 2). This approach recognises the need to assess potential toxicities associated with the pharmacology together with adverse effects that are not related to primary pharmacology.

It should be recognised that it may not be possible or appropriate to generate data to cover all the points addressed in the draft guideline in the section "preclinical requirements". Rather, the sponsor should consider the points discussed in this section of the guideline, and then justify on a case-by-case basis which data are appropriate for the purpose of characterising and dose/concentration-response relationship. Likewise in relation to the section on clinical requirements, the sponsor should justify the design of the first-in-man clinical study based on the risk-profile of the IMP and should address the points to consider in the IMPD.
Below is a list of specific comments on the guideline. If the guideline is re-focussed, as described above, those comments made in relation to "high risk" become less relevant.

SPECIFIC COMMENTS ON TEXT		
EMEA EXPLANATORY NOTE		
Following the external comments and the EMEA Workshop, the aim of guideline has been changed from "criteria to classify IMP as potential high risk MP" into "identification of factors influencing risk and providing strategies for risk mitigation and management". The title has also been changed accordingly. Therefore many of the comments related to the definition of high risk MP are not relevant anymore and will not be commented in detail. See in Annex the draft initially published as cross-reference to the comments.		
GUIDELINE SECTION		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
TITLE and EXECUTIVE SUMMARY		
Title (ABPI)	This guideline should be equally applicable to ALL new medicinal products (see general comments above). Special emphasis may be given to novel molecules which have not previously been tested in the clinic. It is suggested that the title should read "Points to consider document on risk management strategies and dose-setting for first-in-man clinical trials"	The intention of CHMP was a guideline document not a reflection paper ("points to consider" documents do not exist anymore.) Title and executive summary have been changed. See above.
1-6 (BIO)	This guideline should be re-focussed so that it is a points-to-consider document that covers all IMPs (see general comments above), while allowing for the diversity of molecules taken into FIH clinical trials. Special emphasis may be given to novel molecules which have not previously been tested in the clinic. The title should read "Points to consider document on risk management strategies and dose-setting for FIH clinical trials". The text of the guideline will need revision to be in line with the major comments above	

[1] Where applicable

2 (AGAH)	Whether or not a compound is to be considered a high-risk medicinal product is also of interest to the investigator. According to the German Medicines Act, the Principal Investigator has the ultimate responsibility for the safety of the subjects. "… to assist sponsors *and investigators* in the transition …"	Agreed, this guideline applies to all parties involved in such clinical trials. "Investigators " are mentioned in section 4 (Main guideline text).
2 (GCPA)	Would it not be beneficial if this guideline was intended not only to assist sponsors, but also researchers, regulators, patients, and ethics committee members. This guideline is intended to assist sponsors, researchers, regulators, patients & their organisations, and members of ethics committees in the transition from non- clinical to early clinical development.	
5 (EuropaBio)	"Potential" is missing in many places before "high-risk"	Not relevant anymore as definition high-risk has been removed. See above
5 (EBE)	"Potential" is missing in many places before "high-risk"	
3-6 (ABPI)	It provides criteria to classify some new IMPs as highly novel molecules which show a high degree of species specificity and with little or no prior knowledge of the risk/benefit ratio in man. These molecules will warrant special attention and it also gives guidance on quality aspects……for first-in-man clinical trials, including the calculation of the initial dose…..	
3-6 (BIO)	We suggest the alternate wording: "It provides criteria to classify some new investigational medicinal products (IMPs) as highly novel molecules which show a high degree of species specificity and for which there is little or no prior knowledge of the risk/benefit ratio in humans. These molecules will warrant special attention. It also gives guidance on quality aspects, non-clinical testing strategies and designs for first-in-human (FIH) clinical trials, including the calculation of the initial dose to be used in humans, the subsequent dose escalation and the management of risk.	
6 (EFGCP)	This guideline should not only cover pharmacological, toxicological,	Mentioned in the new guideline. More details given in the clinical section.

	quality and scientific aspects but put an equal emphasis on subject protection and clinical requirements. The following aspects should in principle be added: …the subsequent dose escalation, the management of risk *as well as the safeguard and protection of study participants, the suitability of clinical research units and the qualification of the clinical staff.*	
1. INTRODUCTION		
8 (EFPIA)	Though by far the predominance of initial clinical studies are in males, trials may be in women for certain diseases specific to women or may be in men and women with life threatening diseases. Recommended text change: suggest replacing "first in man" with "*first in* ***human*** (FIH)".	Done
8 (PDA)	Change from:…….consideration in Rationale: Clarity ……consideration when proceeding to……	See revised text.

8-10 (GCPA)	The 'paramount consideration' for first-in-man studies is to consider the pharmacodynamic and pharrnacokenetic responses in man to a chemical or biological entity. If safety was the 'paramount consideration' no such studies would take place. This paragraph should state clearly what transition is being discussed. The subjects are selected (in all cases where the research is scientifically and ethically sound) for the safety data they can potentially provide on the new chemical or biological entity. It is important to disclose this. Subjects in phase I studies may or may not be expected to derive a benefit (diagnostic, prophylactic, or therapeutic – depending upon the study).]Rewrite as follows: 'The safety of subjects participating in first-in-man clinical trials is the paramount ethical consideration in proceeding to introducing new chemical or biological entities for medicinal purposes into man. Such subjects are generally selected for their ability to provide a safety profile of the new chemical entity. These subjects may or may not be expected to potentially benefit from the intervention.'	
9 (IPOPI)	Such subject would not normally be expected to derive any therapeutic benefit. But in line1.20 reference is being made to healthy volunteers and Patients who might benefit I would delete that sentence	

9 (EFGCP)	In FiM trials there is never a therapeutic benefit for trial subjects expected. What should be expressed here is that the risk-benefit analysis has to be performed particularly carefully in FiM with high-risk drugs *Participation in this type of studies is by definition not providing any potential therapeutic benefit to the subjects. In clinical trials with high-risk drugs particular emphasis has to be put on provision of an acceptable risk-benefit ratio and an optimal protection of the subjects during and after the study performance.*	
9 (PDA)	Change From:……..such subjects would not normally Rationale: Clarity: It is normal to conduct phase 1 trials in patients as well as healthy volunteers. However, it is not the general practice. …..such subjects would not generally	
9-10 (EBE)	*"Such subjects would not normally be expected to derive any therapeutic benefit."* It should be considered that in certain areas, such as oncology or immunotherapy a trial participant may benefit from the treatment. For "medicinal products requiring special attention" it should be considered to enrol patients instead of healthy volunteers in first-in man-trials. see also comment to lines 268 – 269 Delete sentence: *"Such subjects would not normally be expected to derive any therapeutic* *benefit."*	

9-10 (AGAH)	The sentence does not add much value in this context (in a clinical efficacy trial, patient safety would also be important, and the identification of a high-risk medicinal product would have some implications as well). Delete: "… Such subjects … to derive any therapeutic benefit … "	
9-10 (EFPIA)	While subjects in FIM studies would not normally derive therapeutic benefit, this may not be true if the FIM studies were in patients, especially if the investigational product has a long duration of effect. An assessment of risk and benefit is an important part of the decision to test an IMP in man including the selection of FIH populations Add: ***"Such subjects would not normally be expected to derive any therapeutic benefit, so that this population requires special care with regard to risk assessment***." Recommended change, Add the following text at the end of line 10: ***"In cases where the first in human trial is in patients or a population that would be expected to derive benefit, an appropriate risk evaluation in the context of the concerns expressed in this guidance may justify other approaches."***	
9-10 (Roche)	"Subjects would not normally be expected to derive any therapeutic benefit" – it should be acknowledged within the guideline that some therapeutic benefits, especially following administration of monoclonal antibodies or chemotherapy IMPs to patients, would be anticipated. Delete the sentence starting with "*…Such subjects would not normally…*"	

9-10 (ABPI)	While subjects in FIM studies would not normally derive therapeutic benefit, this may not be true if the FIM studies were in patients, especially if the investigational product has a long duration of effect. It is therefore sometimes appropriate to incorporate potential benefit in the risk-benefit assessment. Such subjects would not normally be expected to derive any therapeutic benefit, although this may not be the case if patients are included in the trial and/or the anticipated duration of effect is sufficient to observe a therapeutic benefit. An assessment of risk and benefit is an important part of the decision to test an IMP in man.	
9-10 (BIO)	While subjects in FIH studies would not normally derive therapeutic benefit, this may not be true if the FIH studies were in patients, especially if the investigational product has a long duration of effect. We suggest the alternate wording "Such subjects would not normally be expected to derive any therapeutic benefit, although this may not be the case if patients are included in the trial and/or the anticipated duration of effect is sufficient to observe a therapeutic benefit. An assessment of risk and benefit is an important part of the decision to test an IMP in humans."	
9-10 (BIA)	Healthy volunteers would not normally be expected to derive any therapeutic benefit from first-in-man studies. However patients may receive benefit, particularly if the investigational medicinal product (IMP) has a long duration of action. Modify as follows: **Healthy volunteers would not normally be expected to derive any therapeutic benefit. However some therapeutic benefit may be observed in patients and/or where the duration of effect is prolonged in which case the balance between risk and potential benefit is important when making the decision to proceed to human trials.**	

12 (GCPA)	Such decisions need to be not only 'science-based' but also 'ethically sound and of medical importance'. (See our general comment above for the need to expand the discussion in this draft guideline on decision-making.) Perhaps the term 'medicine' in a first-in-man study is presumptuous and misleading for patients/subjects. (Correct throughout the text.) Rewrite as follows: 'Decisions on strategies for development of a new chemical or biological entity and the experimental approaches used to assemble information relevant to the safety of first-in-man clinical trials must be science-based, ethically sound, and of medical importance and justified on a case-by-case basis.'	Section reworded. Ethical considerations are mentioned in the clinical section.
Sec 1 (AGAH)	The introduction should be more precise. Expressions such as "Decisions … must be science-based, made and justified on a case-by-case basis" are quite general. Some purposeful statements should be included in the introduction describing the goal of this guideline and giving a short summary of the points that are to be considered. Consider the following structure: 1.) Statement on the need to identify high-risk medicinal products 2.) Mention that a definition of high-risk medicinal products is given in this guideline 3.) Short summary of the challenges 4.) Statement that the knowledge of the mode of action, the nature of the target, the relevance of animal models, and the results of non-clinical studies may provide hints for the identification of a high-risk medicinal product, and … 5.) .. in turn, specific aspects may have to be addressed during the non-clinical development programme if an investigational drug is already known to beat risk, and these aspects are described in this guidance. 6.) Safety aspects, identification of a safe starting dose and other design issues to be observed in first-in-man studies	Not agreed. Details given in the main guideline text (section 4).

	7.) Special implications on CMC issues Summary of the goal of this guideline / References	
14-15 sec 1 (J&J)	In line with remarks under general comments we argue whether it is appropriate to speak of high-risk products Quality requirements for all medicinal products are similar. However especially in case of first-into-man situations in combination with novel targets the absence of adequate pharmacological information may lead to special considerations.	Not relevant anymore. High-risk products deleted. See also quality section
14-15 (EFPIA)	The word 'quality' could refer to the chemical profile/content. It is not clear if this is what is intended, or if the word is meant to indicate that standards are not lower for high-risk drugs. Recommend clarifying 'quality'. Change for clarification: "Quality requirements for high-risk medicinal products are not different to other medicinal products." Recommended change: "**The physicochemical characteristics and content of the high risk medicinal products should be described. .** . " or reword to otherwise clarify intent. "*Quality requirements for high-risk medicinal products are **generally** not different to other medicinal products."*	
14-15 (ABPI)	The word "quality" could refer to the chemical profile/content. It is not clear if this is what is intended, or if the word is meant to indicate that standards are not lower for high risk drugs. Recommend clarifying "quality".	

15 (AGAH)	The sentence “Nevertheless, special consideration should be given to certain aspects” does not contain much information. Give some useful introductory information on special quality/CMC aspects. Maybe you would like to consider the following: “For high-risk medicinal products, a high degree of quality characterisation must be achieved at an early stage with regard to both drug substance and compound. Special demands on assay validation are applicable if biological activity is the basis for the assessment of potency and drug quantification. In case of very small nominal doses, appropriate measures should be taken to maintain accuracy of dosing. …”	
15 (PDA)	The following sentence is unclear regarding the intention: Nevertheless, special consideration should be given to certain aspects. Deleting the sentence	
16-19 (EFPIA)	This paragraph states one area where IMP’s could be considered high risk but does not consider how to deal with compounds of potential high-risk where targets are similar between humans and animals: a typical example would be a cytotoxic agent – would that not be covered by this guidance? It would be helpful to state here the full intent of the guidance. Furthermore it is not clear what is meant by ‘other factors’ The non-clinical testing and experimental approaches for first-in- man studies with novel IMPs that are species restricted (i.e. they show a high degree of species specificity) and/or there is little prior knowledge of the use of this class of molecules in man, raise particular difficulties. These molecules together with those with a known but acceptable risk in FIM studies require a defined risk management strategy. It would be useful to provide some examples of the "other factors".	It was decided not to give examples as all situations cannot be covered here. High-risk MP definition has been deleted. See above

18 (PDA)	Change from:…..may be reduced Rationale: Clarity …….is questionable particularly if the nature of the target is more specific to humans or……..	Paragraph has been reworded.
16-19 (RS-LTD)	The wording might be improved to make the paragraph more concise (e.g. “raise particular difficulties “ in line 17) The range of experimental tools used in non-clinical testing of potential high-risk investigational medicinal products may be limited in their ability to fully characterise the pharmacological and safety profile and the safe starting dose of the new molecule prior to entry into first-in-man studies. Furthermore, high-risk medicinal products may exert serious adverse reactions not due to inherent toxicity but due to their primary or secondary pharmacology which cannot fully be investigated in animal models due to its species specificity. Thus, mainly because of the species specificity of the target of interest and/or differences in effector functions among species the preclinical investigation of potential high risk medicinal products leaves a degree of uncertainty which needs to be supplemented by other risk-mitigating measures upon entry into first-in-man studies.	
16-19 (ABPI)	The non-clinical testing and experimental approaches for first-in-man studies with novel IMPs that are species restricted (i.e. they show a high degree of species specificity) and/or there is little prior knowledge of the use of this class of molecules in man, raise particular difficulties.	
16-19 (BIO)	We suggest the alternate wording “The non-clinical testing and experimental approaches for first-in-human studies with novel IMPs that are species restricted (i.e. they show a high degree of species specificity) and/or for which there is little prior knowledge of the use of this class of molecules in humans, raise particular difficulties.”	
19 (IPOPI)	What other factors?	

19 (ABPI)	Clarify intent of the guidance. Recommended change: provide some examples of the "other factors".	
20 (EFPIA)	Change: "… healthy volunteers…." To "… *healthy* ***subjects****…."*	Not changed, term widely used.
20-21 (Galderma)	In the field of dermatology, most first-in-man clinical trials are proof of concept or proof of efficacy conducted directly in patients and not in healthy volunteers	Patients are mentioned
21 (FECS)	This needs strengthening Delete "attention" and add "a critical decision is to decide upon calculation of the initial dose"	Agreed but sentence judged strong enough.
21-23 (EFPIA)	Clarify the grammar. Suggest: *"Attention should be given to the calculation of the initial dose to be used in humans, to* ***the calculation of*** *subsequent dose escalations,* ***to the*** *intervals between doses to different individuals, and the* ~~*management of risk*~~ ***to the data (e.g. clinical observations, PK) gathered. Managing the risks of what is known about the pharmacology, projected (human) and documented (non-clinical) toxicity, and the clinically observed or measured results of initial dosing are important to ensuring the safety of healthy subjects and patients."***	Partially reworded.
21-23 (RS-LTD)	Suggestion on wording Particular attention should be given to the calculation of the initial dose….and the mitigation and management of the risk of triggering serious adverse reactions upon administration of the IMP.	

21-23 (ABPI)	Clarify the grammar. Attention should be given to the calculation of the initial dose to be used in humans, to the calculation of subsequent dose escalations, to the intervals between doses to different individuals, and to the data (e.g. clinical observations, PK) gathered. Managing the risks of what is known about the pharmacology, projected (human) and documented (nonclinical) toxicity, and the clinically observed or measured results of initial dosing are important to ensuring the safety of volunteers and patients."	
24 (BIO,ABPI)	We suggest the alternate wording "In defining an appropriate early development programme, information needs to be …"	Not changed
24-25 (EFPIA)	It is recommended that the guideline specifically identify the Sponsor as having the responsibility to frequently review information in an iterative process to clarify that an additional regulatory approval of the information is not required. "*In defining an appropriate early development programme for high-risk medicinal products, information needs to be integrated from many sources and frequently reviewed* ***by the Sponsor*** *in an iterative process."*	
25 (RS-LTD)	Suggestion to insert Thus, from early on, a kind of mechanistic model of all actions and interactions known for the molecule from studies and literature should be developed, continuously followed up and complemented with data from investigations during development.	Not included
26-28 (RP LTD)	We would propose to include Investigators in the audience of the guideline. It is the Investigator who is ultimately responsible for the safety of the volunteers while they are under their care. Investigators with current practical experience in the conduct of complex Phase 1 trials should be involved early in the discussions about study design	Investigators are now mentioned in the main guideline text (section 4)

	and risk management so that adequate procedures can be specified in the study protocol. Include Investigators as well as Sponsors in the audience.	
29-30 (J&J)	1) If scientific advice by the EMEA is requested as referred to in these lines, would this be restricting any future possibilities to seek scientific advice by EMEA? 2) What would be the value/status of EMEA scientific advice on this topic in view of member state specific clinical trial legislation? 3) The timing to get a meeting may delay the onset of clinical studies	This is not a comment on the text, but on the SA procedure.
29-30 (ACRO)	In accordance with the Final Report of the Expert Scientific Group on Phase I Clinical Trials (the Duff report), which stressed the need for early discussion with regulators on potential HRMPs well in advance of submitting the clinical trial application (recommendation 5 of the report), this statement should be reworded to emphasize that sponsors <u>should</u> seek expert scientific advice from the relevant competent authority or EMEA well in advance of submitting the application. REPLACE (changed wording shown in bold): "Expert scientific advice on this topic **should** be requested from the relevant Member State Competent Authorities or the EMEA."	Not agreed. SA request is the decision of the sponsor and should be planned appropriately.
29-30 (EFPIA)	Scientific Advice It is not clear how scientific advice can be obtained without delay to the early development programme. Furthermore it is also unclear how scientific advice from Member State Competent Authorities will be achieved consistently. The mechanisms for review are potentially divergent across member states as evidenced by creation of a separate review mechanism within the UK MHRA.	

29-30 (MP)	Regarding Section 1 – Introduction the guidelines states "*Expert scientific advice on this topic may be requested from the relevant Member State Competent Authorities or the EMEA.*" The guideline recommends seeking expert scientific advice, but no information is provided regarding the appropriate procedure to obtain advice from the EMEA. The inclusion of a reference to the specific procedure for obtaining scientific advice would be helpful. We recommend the inclusion of a reference, which specifies the appropriate procedure to use to obtain scientific advice from EMEA.	
30 (PDA)	Addition of consultancy option. Rationale: this should be standard practice at the Member State Competent Authorities. Sponsors is offered to discuss non-clinical plans through first-in-human strategies with the Member State Competent Authorities upfront thus avoiding unnecessary delays at a later stage.	
33 (EFPIA)	It should be clarified, if the concept of single microdosing is applicable for high-risk IMPs as well (Position paper on non-clinical safety studies to support clinical trials with single micro dose CPMP/SWP/2599/02/Rev1).	Reference to this guideline has been added
34-40 (EFPIA)	As immunomodulatory compounds are considered to be potential high – risk medicinal products, the ICH S8 immunotoxicity guideline (CHMP/167235/2004) should also be mentioned as relevant guideline. This guideline presently focuses on aspects of unintended immunosuppression and immunoenhancement. It does not cover aspects of drug-induced hypersensitivity or autoimmunity that might even be more relevant for high-risk medicinal products. The weight-of-evidence approach serving as basic approach in the assessment of potential immunotoxicity is also recommended for application in this guideline. Please, add ICH S8 Immunotoxicity guideline (CHMP/167235/2004) to the list.	Agreed that ICH S8 might apply but only a small selection of guidelines is mentioned. Effects on immune system are mentioned with reference to ICH S7A.(section safety pharmacology)
40 par 1	Document CHMP/SWP/91850/2006 (Concept paper on the	"Position Paper on the non-clinical safety studies to support clinical trials

(EANM)	development of a CHMP Guideline on the non-clinical requirements to support early phase 1 clinical trials with pharmaceutical compounds) is considered to add relevant information to actors designing and performing early clinical trials Add new line: **Concept paper on the development of a CHMP Guideline on the non-clinical requirements to support early phase 1 clinical trials with pharmaceutical compounds CHMP/SWP/91850/2006**	with a single micro dose" has been added. Concept papers are not guidelines
41 (PDA)	Under "Quality Aspects" add references Rationale: Relevancy: ICH guidelines are referred to under non-clinical and clinical aspects Add reference to all ICH Quality guidances (Q1->Q9)	Quality references have been moved in section references. Only the main ones are mentioned.
2. SCOPE		
2. Scope (Drusafe)	Gene and Cell Therapy medicinal products are excluded and are covered by specific guidelines. The scope states that the guidance is applicable to both chemical and biological products. However, the specifics noted in sections 4.2 and 4.3 are often relevant for only biologics or only small molecular entities but no mention is made toward a distinction. As such, the scope of the document should be clarified. Vaccines should also be excluded. The guidance should state when it is applicable to only small molecules and when only to biologics. Alternatively, the guidance could be separated into two distinct parts.	The scope has been reworded and broadened. Vaccines should not be excluded.

52 (GCPA)	The Introduction as presented here would appear to apply to all first-in-man clinical trials. Aside from a reference to 'special attention' nothing specific to 'high-risk chemical or biological entities ('medicines') seems to be addressed in the Introduction. The next section on Scope suggests that this guideline concerns specifically 'high-risk entities'. Thus, this should be clearly addressed in the Introduction.	Not relevant anymore. Scope has been reworded. See explanatory note at the start of this overview.
53-56 (J&J)	Similar remark regarding the use of term high-risk products as for lines 14-15. This guideline particularly refers to medicinal products, including chemical and biological medicinal products. It specifically covers the first administration of a single dose of a product with a novel target/ mode of action and the initial single ascending dose phase of clinical development.	
54 (AGAH)	Chemical and biological medicinal products are a major objective in the context of this guideline. Replace "… *including* …" by "… *with special emphasis on* …"	

54-55 (BIA)	A misconception has been built up that all monoclonal antibodies are high-risk medicinal products. A further specific distinction should also be made for monoclonal antibodies, especially between those acting by an antagonistic mechanism from those activating immune processes (i.e. agonists) for which there are specific safety issues that may need to be addressed. For monoclonal antibodies, the immunological properties of the antibody will need to be described in detail: antigenic specificity, complement binding, Fc-mediated effector functions, and any unintentional reactivity and/or cytotoxicity toward human tissues distinct from the intended target. It may be possible therefore to use knowledge and previous experience in the risk assessment for a new monoclonal antibody. These aspects have been adequately covered in the existing European regulatory guidelines. Add the following sentence: This guideline particularly refers to high-risk medicinal products, including chemical and biological medicinal products. **Note: Not all monoclonal antibody therapeutics will meet the definition of potential high-risk medicinal products.** It specifically covers the first administration of a single dose…	
54 (EBE)	The reference to chemical" as distinct from biological IMP's goes beyond the Duff report which does not make this specific distinction except in the case of "species-specific small molecule agents when the detection of 'on-target' toxicity in animal studies may be unreliable". Omit the reference to "chemical" and "biological" – unnecessary	Meant to be explicit for clarity .
54 (Drusafe)	The reference to "chemical" as distinct from biological IMP's goes beyond the Duff report which does not make this specific distinction except in the case of "species specific small molecule agents when the detection of 'on-target' toxicity in animal studies may be unreliable".. Omit the reference to "chemical" and "biological" – unnecessary	

54 (EuropaBio)	The reference to “chemical” as distinct from biological IMP’s goes beyond the Duff report which does not make this specific distinction except in the case of “species-specific small molecule agents when the detection of ‘on-target’ toxicity in animal studies may be unreliable”. Omit the reference to “chemical” and “biological” – unnecessary	
54-56	The reference to “chemical” as distinct from biological IMP’s goes beyond the Duff report which does not make this specific distinction except in the case of “species-specific small molecule agents when the detection of “on-target” toxicity in animal studies may be unreliable”.. A misconception has been built up that all monoclonal antibodies are high risk medicinal products Omit the reference to “chemical” and “biological” “This guideline refers to all chemical and biological medicinal products and pays particular attention to those IMPs for which it may be difficult to assess the risk profile. It specifically covers…” Note: not all monoclonal antibody therapeutics will meet the definition of potential high-risk medicinal products.	
54-56 Cancer Research	First in Man studies in oncology are generally in patients and are often not single dose studies. Oncology studies should be either positively included or excluded from this scope of this guideline. If oncology studies are included they should be specifically addressed by the guideline.	Oncology studies are not excluded but need specific considerations that can be found in existing relevant guidelines. This is specifically mentioned at the end of section 4.3.6.
54-56 (EFPIA)	The guideline covers NCE and NBE, while the content is more focussed on NBE. Omit the reference to “chemical” and “biological”	Not relevant anymore. See above

54-56 (MP)	Regarding Section 2 – Scope, the guidelines states: *"This guideline particularly refers to high-risk medicinal products. It specifically covers the first administration of a single dose of a high-risk medicinal product and the initial single ascending dose phase of clinical development."* It is not clear whether the scope of this guideline is specific to confirmed high risk molecules or potential high risk molecules. The inclusion of additional information to clarify the scope of the guideline with respect to confirmed or potential high risk molecules would be helpful. We recommend the inclusion of additional information to clarify the scope of the guideline with respect to the differences between confirmed high-risk molecules and potential high-risk molecules.	
54-56 (SPC)	2. Scope The scope of this guideline specifically covers "first administration of a single dose" . . . "and the initial single ascending dose phase of clinical development." Since this guideline sets forth criteria uniquely associated with the initial introduction of an investigational agent in humans, and not during later drug development phases when sponsors have begun defining the safety profile based on human clinical data, the scope of the guideline should be written to preclude the further application of such criteria in later drug development or registration phases. Line 55-56 should be revised to read, "It specifically covers only the first administration of a single dose of a high-risk investigational medicinal product and the initial single ascending dose phase of clinical development and should not apply to later stage clinical development or registration."	
54-56 (BIO)	"This guideline refers to all chemical and biological medicinal products and pays particular attention to those IMPs for which it may be difficult to assess the risk profile. It specifically covers …."	
53-57	The scope states that the guidance is applicable to both chemical and biological products. The specifics noted in sections 4.2 and 4.3 are	Scope has been broadened and vaccines are not excluded.

(EFPIA)	often relevant for only biologics or only small molecular entities but no mention is made toward a distinction. As such, the scope of the document lacks clarity to applicability of the guidance. More precise criteria for classification are needed especially for NCEs. Additionally examples for high-risk NCEs would be helpful Could the authorities please indicate here whether vaccines are included and thus are covered by this guideline too? Gene and Cell Therapy medicinal products are excluded and are covered by specific guidelines. Vaccines should also be excluded. The scope of this guidance requires further clarification to assist the Sponsor in identifying medicinal products that may be potentially high-risk. **In addition, while gene and cell therapy medicinal products are specifically excluded, vaccines are neither included nor excluded from the guidance. Most of the specific principles outlined in the guidance pertaining to starting dose selection are not appropriate in determining starting dose for potential vaccine products.** It would be helpful to indicate if this guidance would also allow FIM studies on high risk products using a microdosing approach, and if exploratory FIM studies incorporating one or more high risk compounds can be conducted. By analogy the CHMP's Position paper (CPMP/SWP/2599/02/Rev 1) on microdose FIM studies states "The clinical trials covered by this Position Paper will be exploratory in nature (pre-phase I) and may be conducted with a single test substance or with a number of closely related pharmaceutical candidates to choose the preferred candidate or formulation for further development." "Biological" products are usually not considered to encompass drug substances of biotechnological origin. With reference to the sentence reading *'It specifically covers the first administration of a single dose…'* please further clarify that this is referring not only to the starting dose but also to the subsequent dose escalation steps in humans. "This guideline ~~particularly~~ refers to ~~high risk~~ ***all*** medicinal products,	

	~~including chemical and biological medicinal products~~ ***and pays particular attention to those IMPs for which it may be difficult to assess the risk profile.*** *It specifically covers …"* The guidance must state when it is applicable to only small molecules and when only to biologics. Alternatively, the guidance should be separated into two distinct parts. "*Gene- and cell therapy medicinal products* ***and vaccines*** *are excluded and are to be covered by* ***separate*** *guidelines."*	
55 (AGAH)	A short summary of all the aspects that are covered by this guideline should be given under "2. Scope". Replace "*It specifically covers …*" by "*Among preclinical aspects and quality aspects, clinical requirements with regard to first-in-man studies are concerned. More specifically, the guideline covers …*"	Scope has been reworded.
55 (PDA)	Change: from: "….the first administration" Rationale: Clarity. Phase I involves more than one volunteer and the high-risk continues until sufficient data is collected throughout phase I at least and not the first administration only …….the first time administration	

54-57 (WP)	The scope of this guidance requires further clarification to assist the Sponsor in identifying medicinal products that may be potentially high-risk. In addition, while gene and cell therapy medicinal products are specifically excluded, vaccines are neither included nor excluded from the guidance. Most of the specific principles outlined in the guidance pertaining to starting dose selection are not appropriate in determining starting dose for potential vaccine products. We recommend that the statement be revised to: *"This guideline particularly refers to high-risk medicinal products, including chemical and biological medicinal products. It specifically covers the first administration of a single dose of a high-risk medicinal product and the initial single ascending dose phase of clinical development* *The scope includes medicinal products acting (directly or indirectly) via the immune system with a novel target or a novel mechanism of action or having a potential secondary effect on the immune system via a mechanism of action, which is currently poorly characterised.* *The scope of this guideline also includes, more generally, medicinal products with novel active substances acting via a possible (or likely) species-specific mechanism or where animal data are unlikely to be predictive of activity in humans.* *Gene- and cell therapy medicinal products and vaccines are excluded and are to be covered by ~~specific~~ separate guidelines."*	

55 – 56 (EBE)	*"It specifically covers the first administration of a single dose of a high-risk medicinal product and the initial single ascending dose phase of clinical development."* It is suggested that the guideline focuses on the first administration of a "medicinal product requiring special attention". The dose escalation scheme should not be restricted to single ascending doses. The dosing schedule should be science-based and justified on a case by case basis. Change as follows: *"It specifically covers the first administration of a single dose of a high-risk* *medicinal product "medicinal product requiring special attention" and the* *initial single ascending dose phase of clinical development."*	
57 (MSD)	Gene and Cell Therapy medicinal products are excluded and are covered by specific guidelines. Vaccines should also be excluded.	
57 Cancer Research	Which guidances does this refer to? Are these existing guidances, currently in consultation or guidances yet to be released?	
2. Scope (Eucrof)	The guideline covers « the first administration of an initial **single** ascending dose ». From our point of view, the guideline has to cover the first administration of the initial **single** ascending dose and of the initial **repeated** ascending dose.	
3. LEGAL BASIS		
	No comments	
4.1 Definition High-Risk MP		
4.1 (BIA)	The risk here is that ANY first-in-the class compound will be caught in this definition.	Acknowledged. Therefore, the general approach of section 4.1 has been changed to a risk mitigation strategy, which identifies risk factors rather than

	The definition of high-risk medicinal product needs to be precise, and should be based on objectively justified criteria to remove any uncertainty in assessing whether a new drug candidate is characterised as high risk. It is suggested to keep specific for those classes of compound that have been demonstrated to be a real risk e.g. immunomodulating molecules with long durations of action.	defining a particular "high risk" compound. Such risk factors then enable for a case-by-case evaluation of novel compounds to identify if the precautionary scientific principles as laid down in this guideline might be applied. See explanatory note at the beginning. It is felt inappropriate to become too specific, e.g. focussing on immunomodulators with long-lasting effect only, since there might be novel compounds developed in future that have another mechanism of action but nevertheless pose a risk.
4.1 (Drusafe)	unique structures (e.g., fusion proteins) are overly broad and could add unnecessary delays where standard toxicological paradigms are quite adequate to evaluate risk for most products in these categories. The scope of the definition is particularly excessive given the one exceptional case where traditional testing may not have been adequate, and this conclusion itself is debatable given the available information. The scope if applied as is will significantly adversely impact novel therapeutic development, that would otherwise be safely conducted under existing guidance, to the detriment of the public. The "high-risk products" definition should be restricted to the types of agents that have shown significant unexpected toxicity; i.e., to modes of action where amplification of a signal could be predicted. Thus, antagonists would not routinely be considered high risk. Furthermore, the concern is whether animal models have appropriately assessed potential human risk for such products. Therefore, the definition of high-risk products based on MOA should include the additional dependency that there is either 1) evidence from animal models for the potential risk for serious, pharmacologically-mediated toxicity, or 2) an indication that the animal models do not exhibit pharmacological response expected in humans sufficiently to adequately assess the risk and other compounds have not been tested to derive an understanding of the potential risk	See above. The guideline text repeatedly states that for most novel compounds the "conventional" testing programme can be adequate. "Fusion proteins" as well as "bispecific antibodies" have been deleted, and a new example has been included that better reflects the intention of the wording. Part of the suggestion included, the other not since covered below "relevant animal model"
62-105 (MRC)	This definition is not precise and this reflects the wide range of risks and products that would fall into this category. It would be preferable to address the Guidance to all studies of first in man IMPs and then to describe a risk assessment process for evaluation of those studies. Risk	See above, risk mitigation strategy approach adopted.

[2] Expert Scientific Group on Phase 1 Clinical Trials. Final Report ig

	is a spectrum and there are several difficulties that the current approach will lead to. The most relevant of these to patient safety is the implication that studies are 'high' or 'not-high' risk which may lead to less vigorous safety assessments and planning without this having been fully justified by the investigator through risk-assessment an a case-by-case basis. In addition, the criteria given are rather vague and subjective. The MRC would favour the approach adopted by the MHRA and described in the Expert Report on the TGN1412 case(the Duff report)[2] in which the categories of potential higher risk were more succinctly described and the factors for subsequent risk assessment set out.	The criteria have been refined. The criteria of the Duff report are the following: ▪ Biological molecules with novel mechanisms of action; ▪ New agents with a high degree of species specificity; ▪ New agents with immune system targets. These criteria have been included already in the first draft. Some of these would not overcome the problem that is reflected in various comments, i.e. being too broad ("novel mechanism of action", "immune system target").
(AREC)	The Association supports the approach given in the guidelines. While it is the primarily the responsibility of sponsors to identify potential high-risk trials Ethics Committees and the appropriate national Regulatory Authorities should have mutual and effective communication strategies in place to identify such trials, and for the exchange and sharing of relevant information and advice relating to each others processes for scrutiny and approval. A written framework, such as a Memorandum of Understanding, can provide a useful framework for this two-way communication. It must be open to Ethics Committees to call for specialist advice at national level on such products before issuing an ethical opinion on the proposed trial.	This is a very important aspect, but, however, beyond the scope of this guideline, which is intended to be purely scientific.
63-64 (EFPIA)	Change to read: "*Sponsors should consider whether ~~the criteria and guidance for~~ **the definition of a** high-risk medicinal product ~~are applicable~~ **applies to the investigational new medicinal product** when planning a first-in-man clinical trial."*	In part included.
63 (GCPA)	Is it only sponsors that need to make these considerations? Should not others involved in clinical trials, as suggested in our comments above, also be considered.	It is the sponsor and the investigator who develops the product, and thus the primary risk mitigation responsibility is indeed up to them. However, these considerations will also be part of the regulatory assessment process.

	Does this paragraph not suggest that the criteria and guidance provided here is solely at the sponsor's discretion. Does 'potential high-risk' differ from 'high-risk'?	
Sec 4.1 (AGAH)	the points in 4.1 should be considered in any development, not only in "high risk" products. The term "high risk" should not suggest black and white.	Agreed. Therefore, the term "high risk" has been omitted from the guideline.
65 (FCP)	4.1 Definition of high- risk investigational medicinal products The use of serious adverse reactions is appropriate may be replaced by "severe drug-related adverse reactions" The definition should avoid to consider any new innovative compound as a potentially high-risk compound. The current definition seems too much seems too much general and almost any compound may fit within it. We suggest that the definition of a potentially high-risk compound includes the association of several criteria, particularly novelty AND poor predictability from animal models of activity or toxicity. In contrast, a new innovative compound with a new target organ with predictive models of activity and toxicity has no scientific reason to be considered as a high-risk compound. The only exception would be a new compound targeting the immune system with a potential stimulatory effect that should always be considered as a high-risk compound. It should be useful to provide some examples of high-risk medicinal products for which there is a clear consensus from regulatory authorities (agonist monoclonal antibodies, novel medicinal products that have stimulatory effects on the immune system mechanisms (especially if activate T cells), targets that by-pass control mechanisms , species specificity making pre-clinical risk-assessment in animal models difficult or impossible etc…) We recommend "when major drug-related safety concerns (or there are concerns that clinically important drug- related adverse events) in FIM	Included. See above. Included. Examples are not necessarily useful, since they might drive the reader's attention too much to specific product classes. The most famous example (TGN1412) has already been included (CD28 super-agonists). Would also be applicable to all novel medicinal products.

	clinical trials may occur" At the end of lines 77, we suggest to add "Any new medicinal product acting directly or indirectly through the immune system with a novel target or a novel mechanism of action should be considered as a potentially high-risk medicinal products. More generally , any medicinal product with novel active substances acting via a likely species-specific mechanism or where animal data are unlikely to be predictive in humans should be considered as a potentially high-risk product."	These ideas are valid, but already covered by the present text.
65 (EFPIA)	Change title This section is a very general definition and almost any compound would fit within this description. We suggest that the definition of high risk should be where there are concerns that serious adverse reactions could occur and there is significant uncertainty in predicting human effects from on-clinical studies. In addition to discussion of the relevance of animal models the sponsor should also discuss any additional methodology e.g. ex-vivo cytokine release models, that have been applied to investigate risk For better differentiation a definition for "NOT high risk investigational medicinal products" should be added. Title "***Identification of risk for investigational medicinal products***" Propose: '*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* ***and there is significant difficulty in predicting human effects from non-clinical studies***. These concerns…'	Scope changed, respective sentence has been deleted. Not agreed; a definition for "non-high-risk" bears the risk of a false feeling of safety. New concept is risk identification and mitigation, and thus such definition is now not necessary anymore. Agreed, included. Scope changed, respective sentence has been deleted.
65 (Drusafe)	Definition of 'high risk' This section is a very general definition and almost any compound would fit within this description. We suggest that the definition of high risk should be where there are concerns that serious adverse reactions could occur and there is	Redundant, see above.

	significant uncertainty in predicting human effects from preclinical studies. '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 and there is significant difficulty in predicting human effects from preclinical studies. These concerns…"	
65 (ABPI)	Change title Title "Identification of risk for investigational medicinal products" **This section would need to be re-written if this recommendation is accepted. The comments below refer to the existing text.**	Redundant, see above.
	In addition to discussion of the relevance of animal models the sponsor should also discuss any additional methodology e.g. ex-vivo cytokine release models, that have been applied to investigate risk	See section 4.3
65-105 (EFPIA)	While some criteria are given in section 4.1 to identify high-risk products, how are the authorities and a sponsor to agree on whether or not a product is high risk? The designation as high risk has a very large impact on safety programs, and if not identified early, could delay the entry into man by several years. Add a mechanism for obtaining agreement between the EMEA and the sponsor, or add more specific criteria for designation as high risk.	Agreed, and this is why the guideline recommends seeking scientific advice from authorities.
65-105 (Roche)	By reading this chapter, many people involved in R&D of biologics, may gain the impression that almost all biologics would adhere to the one or the other criterion that applies to "high-risk biologics". However, the outlined criteria seem to apply primarily to therapeutic antibodies that have the capacity to bind not only to the target structure (via the Fab portion) but also to several types of immune cells that carry particular types of Fc receptors (via the Fc portion). Otherwise it would not have been possible that TNF-alpha was the kinetically first cytokine to be induced by TGN1412, although T cells (the target cells of	Agreed, see above. In principle correct, but also other compounds like small molecule agonists for signalling receptors of the immune system can bear the same risks. Thus a focus on monoclonal antibodies only is felt inappropriate.

	TGN1412) are unable to secrete TNF-alpha. Likewise, mAb Campath, a humanized IgG1, has lost its capacity to induce cytokine release, upon transformation into an IgG4 type of mAb. Clarity should be provided on the definition of "high-risk" medicinal products. Alternatively, it should be made clear that the high-risk criteria outlined here, apply primarily to full-length therapeutic Abs, rather than to all biologics or to small molecules. It may be added that only in those cases, where non-mAb biologics have similar capacities as mAb, with respect to activating immune cells via Fc receptors (or other receptors) or cross-link target cells with unrelated immune cells, they may belong into the same high-risk category as the respective mAb.	Again, this is too specific for the guideline and would not cover some upcoming compounds where particular caution needs to be exercised.
65-105 (BIO)	Change section title in line with major comments above. The concept of "potential" high-risk products is vague. Who decides whether a product fits this designation and when? What data are necessary to facilitate this decision? Definitions could be different among sponsors, Phase I units and regulatory agencies. This section provides a very general definition of "high-risk" and almost any compound would fit under this definition. We suggest that the definition of high risk be eliminated or that it be simplified (e.g. an investigational medical product is "high risk" if there are concerns that serious adverse reactions could occur and there is significant uncertainty in predicting human effects from preclinical studies). Relevance of animal models: The terms "animal species" and "animal models" must be carefully distinguished. The former should be used when speaking of the species selected for safety testing, including discussions of relevant species. The latter term, animal models, should be reserved for those instances in which a spontaneous or induced animal model of human disease is used in safety testing. This document mixes the two concepts and thereby creates confusion.	Redundant, see above. Agreed, wording has been changed.

	Need to specify that *in vitro* bioactivity is important for defining species relevance. Lack of data from a relevant animal species does not increase intrinsic IMP risk but rather the uncertainty in the dose calculation. Therefore caution must be increased. What should be said is that, if no data are available one must proceed with caution. This document effectively creates two classes of products: those that are of potential high risk and those that are not. However, many of the recommendations in this document could be applied to almost any product being tested for the first time in humans, including both biologics and small molecules. They are sound practices for avoiding and or mitigating adverse events (AEs) or severe adverse events (SAEs). Therefore we reiterate here our comments from above that the guideline would be more useful if it were refocused to be a "points to consider" document that provides guidance on when and how to develop appropriate risk mitigation strategies through the integrated analysis of all pre-clinical data and the appropriate design of clinical trials. We also note that animal studies should never be relied on as "predictive". Rather, these studies are informative. Nonclinical programs that reveal safety concerns are not the studies one has to worry about. Rather it is those that do not reveal safety concerns; that is, those for which the target and/or MOA suggests possible AEs/SAEs but for which the nonclinical program does not reveal safety issues. The Section Title should read "Points to consider in defining appropriate risk mitigation strategies for a FIH clinical trial" **This section would need to be rewritten if the major comments from BIO are accepted.**	Discussed in section 4.3 Lack of a relevant animal model will significantly influence the risk inherent to a first-in-man trial, and this is also said in the guideline already. Partly agreed, see refined text. However, the document is intended to represent a guideline document, not a "points to consider" document. It should be understood that the term "predictive" does not mean "absolute" predictivity, as expressed in the sentence by "*sufficiently* predictive".
65-105	The definition of high-risk product needs to be more clearly defined so	Redundant, see above.

(Centocor)	that the intent of this guideline is met and that it does not get used as default guidance for all new investigational medicines. We realize this is difficult to do but, there needs to be a clear definition of how to differentiate potentially high risk products, both small molecular weight drugs and large molecular weigh proteins, from low risk products. Although we believe the intention of the draft guideline is to limited to the truly high risk investigational medicinal products, in our opinion the definition is too broad and potentially covers many classes of molecules that have been demonstrated to be low risk. The definition of high-risk focuses highly on biotherapeutics even though historically biotherapeutics have shown very low toxicity compared to small molecular weight drugs.	
66 (AGAH)	This should be given more precisely. Add: "… when there are concerns that *drug-related* serious adverse reactions …"	Scope changed, respective sentence has been deleted.
66 (CHDR)	The risk that SAE may occur is true for all compounds that are administered for the first time to humans and is thus not helpful to distinguish compounds.	Scope changed, respective sentence has been deleted.
66 (EFGCP)	This paragraph defines "potential high-risk medicinal products when there are concerns that serious adverse reactions in first-in-man clinical trials may occur". Comment: this should remain a temporary category until the first-in-man CTs have been completed with the medicinal product so labeled. A medicinal product for which the potential high-risk is not confirmed should loose this label at entering Phase II.	Scope changed, respective sentence has been deleted. (agreed.)
66 (ECRIN)	This paragraph defines "potential high-risk medicinal products when there are concerns that serious adverse reactions in first-in-man clinical trials may occur". This should remain a temporary category until the first-in-man CTs have been completed with the medicinal product so labelled. A medicinal product for which the potential high-risk is not	Scope changed, respective sentence has been deleted.

	confirmed should loose this label at entering Phase II. Also: considerations on potential Ventricular Prolongation of QTc are required.	
66-67 Cancer Research	For some medicinal products, the end point of the clinical trial is toxicity and the aim is to determine the maximum tolerated dose (MTD). To define a MTD the dose needs to be escalated until toxicity is observed i.e. serious adverse reactions. Consequently, the presence of serious adverse reactions does not necessarily relate to the product being high risk. Therefore the definition of high risk products should be changed accordingly, e.g. using the definition as suggested in the report of the Expert Scientific Group On Phase One Clinical Trials.	Scope changed, respective sentence has been deleted. This comment on the particulars of cancer drugs is acknowledged.
4.1 (EuropaBio)	Definition of compounds in scope should be considered more clearly, especially a need for definition of 'the novelty of the structure of the medicinal product' mentioned in line 89.	Agreed, wording has been changed.
66-67 (BIA)	The definition of high risk in terms of serious adverse reactions may potentially lead to a wide range of interpretations. We suggest that high risk medicinal products are defined as any agents that might cause severe physiological disturbances to vital body systems in first-in-man clinical trials.	This might be true, but such definition would be even broader. Part of the wording included.
66-69 (AMS)	The definition of high-risk could be very broad.	Redundant, see above.
66-69 (MSD)	The definitions are very broad and if conservatively interpreted almost any FIM study could be considered high risk. The definitions need to be specific and importantly also define what is not a high risk molecule. The definitions need to be specific and importantly also define what is not a high risk molecule.	Redundant, see above.
66-69 (Galderma)	A molecule already on the market does not respond to this definition as any new clinical trial, even by a new route of administration, is not a first-in-man anymore Already marketed molecules used by known or new administration routes are not considered as potential high-risk medicinal products	Agreed, implicitly included by the new scope of this section.
66-69 (Galderma)	A medicinal product for the topical route with an expected low systemic exposure and a large safety ratio cannot be considered as a potential high-risk medicinal product	Agreed, implicitly included by the new scope of this section.

	Are not considered as potential high-risk medicinal products non biological molecules administered by the topical route, assuming low systemic exposure and selective activity limited to the skin.	
66-69 (J&J)	Similar remark regarding the use of term high-risk products as for lines 14-15. Medicinal products that have particular knowledge or uncertainties on (1) the mode of action, and/or (2) the nature of the target, and/or the relevance of animal models may require additional non-clinical and clinical safety measures .	Redundant, see above.
66-69 (ACRO)	ACRO is concerned that the definition of a potential HRMP remains unclear. The document states (lines 66-69), "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." While we recognize the difficulty of providing a precise definition, this broad definition seems likely to lead to widely differing classification of products by varying Competent Authorities, and even individual reviewers. In revising the draft Guideline, ACRO urges the CHMP to consider focusing the Guideline and its new requirements for FIM trials of potential HRMPs on the medicinal product categories reviewed by the Expert Scientific Group. We believe the Guideline could then provide greater clarity for Sponsors, Competent Authorities, Ethics Committees, investigators, and others in regard to identifying potential HRMPs. From our perspective, the original and more narrow language of the Duff report, which defined potential HRMPs as: (1) biological molecules with novel mechanisms of action; (2) new agents with a highly species-specific action; and (3) new drugs directed toward immune system, was more useful in characterizing medicinal products with a potential to be high-risk in the context of a first-in-man clinical trial.	Redundant, see above. Widely differing classification and/or interpretation of risk is a general concern that is not solvable by this document. Solutions are e.g. discussion of IMPDs during a scientific advice meeting with Competent Authorities. See comments above. These definitions are also broad, and the concept is now to identify and mitigate risks.

66-69 (AMGEN)	With the present definition of higher-risk medicinal product, many new molecular entities will fit one or more of the criteria. Further, much of the data requested in the section would not generally be available for First Time in Man (FTIM) studies and pose unreasonable expectations. Should the term high-risk remain in the document? Refine the definition of higher-risk medicinal product to remove uncertainty of applicability to an IMP.	Redundant, see above.
66-69 (EBE)	With the present definition of higher-risk medicinal product, many new molecular entities will fit one or more of the criteria. Further, much of the data requested in the section would not generally be available for First Time in Man (FTIM) studies and pose unreasonable expectations. Refine the definition of higher-risk medicinal product to remove uncertainty of applicability to a candidate drug.	Redundant, see above.
66-69 (EFPIA)	With the present definition of higher-risk medicinal product, many new molecular entities will fit one or more of the criteria. Further, much of the data requested in the section would not generally be available for FTIM studies and pose an unreasonable expectation. Definition of potential high-risk medicinal products is wide (for example the understanding of the relevance of an animal model is not always absolute) and could be misinterpreted to need to apply to all novel FIM targets. The definitions are very broad and if conservatively interpreted almost any FIM study could be considered high risk. The definitions need to be specific and importantly also define what is not a high risk molecule. Clear examples would be helpful, as based on recent experience there can be different opinions between agency and sponsor. According to the MHRA and BfArM presenters at the DIA Euromeeting in March 2007, “high risk” would define only about 5-10% of first-in-man studies. Thus for most IMPs the current non-	Redundant, see above.

	clinical programs are adequate. It should be made clear that the first IMPs from a new drug class are not automatically regarded as "high risk". "***Assessing the potential risk for an IMP involves the identification of potential adverse events and the adoption of an appropriate risk management strategy***. *These concerns may be derived from…."* Suggestion to refer to description on the Dec 06 EWG publication. http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_073165.pdf Alternatively consider: "***High-risk medicinal products are defined as medicinal products for which there are concerns that unforeseen serious adverse reactions in first-in-man clinical trials may occur that cannot be predicted in nonclinical in vitro and in vivo testing using either pharmacological or toxicological models."*** "*For **most** new medicinal products, **including most IMPs of new drug classes**, the conventional non-clinical programme provides an acceptable safety estimate for a first administration in humans."* OR "*For **most** new medicinal products, the conventional non-clinical programme provides an acceptable safety estimate for a first administration in humans."* - followed later by the statement: ***"The first IMPs from a new drug class are not automatically regarded as "high risk."***	Agreed. Does not add new information. This is dangerous. The sentence has been reworded.
66-69 (MP)	Regarding Section 4.1 Definition of Potential High-Risk Investigation Medicinal Products, the guideline states: "*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."*	Redundant, see above.

	The definition of "high risk" provided in the guideline is not specific and appears to be applicable to all molecules that have not yet been dosed in humans. For clarity, we feel that a more specific definition of "high risk" should be included. For clarity, we recommend the inclusion of a more specific definition for the term "high-risk".	
66-69 (Drusafe)	With the present definition of high-risk medicinal product, many new molecular entities will fit one or more of the criteria. We recommend clarification of the definition of high-risk medicinal product to remove uncertainty of applicability to a candidate drug.	Redundant, see above.
66-69 (SPC)	4.1 Definition of potential high-risk investigational medicinal products All early phase studies have safety and tolerability as a primary focus. The ability to respond appropriately to unexpected events is a basic tenet of clinical research for all early phase studies. As currently drafted, the definition of "potential high-risk investigational medicinal product" is broader than the intended scope of the Guideline. This may lead to an unintended effect of including many (if not all) compounds instead of the relatively few that would fall within the narrowly-tailored description covering the intended special class of investigational drugs. "High-risk" should be defined in a manner consistent with sound scientific criteria that minimizes the risk of misinterpretation and clarifies the appropriate application for first-in-man studies. Also, please note application of observation above in General Comments section that the Definition of "potential high-risk investigational medicinal products" should clearly state "potential high-	Redundant, see above. Agreed, has been added.

	risk investigational medicinal product."	
66-69 (ABPI)	Assessing the potential risk for an IMP involves the identification of potential adverse events and the adoption of an appropriate risk management strategy. These concerns may be derived from…..	Redundant, see above.
66-69 (SPS)	The definition of "concern" is centred around either the specific knowledge that there is a risk or the absence of clear information in the pre-defined categories. It is suggested that it be indicated more clearly that it is a demonstration of a breadth and depth of the pharmacological knowledge of the medicinal product which should be provided. Medicinal products are defined as potential high-risk medicinal products when review of the available pharmacology results in concerns that serious adverse reactions in first-in-man clinical trials may occur.	Text slightly refined.
66-69 (EuropaBio)	With the present definition of higher-risk medicinal product, many new molecular entities will fit one or more of the criteria. Further, much of the data requested in the section would not generally be available for First Time in Man (FTIM) studies and pose unreasonable expectations. Refine the definition of higher-risk medicinal product to remove uncertainty of applicability to a candidate drug.	Redundant, see above.
66-77 (Takeda)	**Definition of a high risk medicinal product** Additional clarification of the definition is required given the single dose nature of the FIH study. Examples of specific drug types (e.g. biological or immunological agents) drug classes (e.g. hormonal therapies) or mechanisms of action (PPAR's or COX-2's) which are of potential concern to the regulatory agencies should be identified. Guideline must provide enough clarification around the definition to ensure the regulatory agency and Sponsor concur on the classification Furthermore, clear delineation should be in place regarding the requirements for FIH studies as compared to studies of longer duration for chronic use conditions. PPAR's or COX-2's are not known to	See also above, the guideline should avoid directing the reader too much by providing examples. Study requirements for longer term use are beyond the scope of this guideline. It is referred to other guidelines, e.g. EWP or ICH guideline.

	exhibit any safety concerns on single dosing whereas both have recognised adverse event profiles on chronic administration. Additional clarification around high risk medicinal products on single administration.	
68 (IPOPI)	It there is such a conviction about the potential high risk of a human trial, why proceed with the trial until more information has been gathered on non-humans.	Rather that stopping the development of compounds, the ideal regulatory route for a novel compound with potential risks should be to obtain all necessary information before commencing the first-in-man study and apply adequate precautions.
68 (PDA)	Change: “on” Rationale: clarity / English regarding	Word changed.
68-69 (EFGCP)	This paragraph states that concerns may be “derived from (…) uncertainties about (1) the mode of action, and/or (2) the nature of the target, and/or (3) the relevance of animal models.” Comment: all three reference criteria for judging uncertainties are notoriously controversial subjects: modes of action of drugs are usually not fully clarified at the beginning of Phase I. The level of clarification of the mechanism of action (cellular, sub-cellular, molecular) never gives complete certainty about the mode of action of a medicinal product. Many physiological effects of medicinal products have been discovered before their mode of action could be even studied: e.g., aspirin was found to be a platelet aggregation inhibitor before it was discovered that aspirin blocks cyclooxygenase (COX). Also, medicinal products very frequently if not always multiple modes of actions, and one may be elucidated regarding the mode of action in the putative indication for the new medicinal product, whereas the other which is not even suspected may be associated with high risk. It would be wrong to (1) require a deep level of elucidation of a broad band of modes of actions of lead compounds before they go in first-in-man CTs as this	Redundant, see above. This is partly agreed. The guideline does not require to solve all possible uncertainties or factors of risk, which could indeed take a very long time, but rather to identify and characterise these risks reasonably well and apply adequate precautions for the clinical trials.

	would delay drug development potentially by months or rather years, and (2) require the lack of uncertainty regarding our knowledge of the mechanism(s) of actions, since elucidating mechanisms of action is a never-ending process. Mutatis mutandis, these observations apply to the nature of targets and animal models. Targets may be identified at sub-cellular level, e.g., at receptor level in the brain, and yet the precise role of the receptor may not yet be elucidated. By definition, animal models are only models, and therefore subject a priori to uncertainty. If there were no uncertainty left, the medicinal products would not have to be tested in man. Therefore, it is to be feared that an overcautious connection of risk with these uncertainties will lead to paralysis.	
68-69 (ECRIN)	This paragraph states that concerns may be "derived from (…) uncertainties about (1) the mode of action, and/or (2) the nature of the target, and/or (3) the relevance of animal models." All three reference criteria for judging uncertainties are notoriously controversial subjects: modes of action of drugs are usually not fully clarified at the beginning of Phase I. The level of clarification of the mechanism of action (cellular, sub-cellular, molecular) never gives complete certainty about the mode of action of a medicinal product. Many physiological effects of medicinal products have been discovered before their mode of action could be even studied: e.g., aspirin was found to be a platelet aggregation inhibitor before it was discovered that aspirin blocks cyclooxygenase (COX). Also, medicinal products very frequently if not always multiple modes of actions, and one may be elucidated regarding the mode of action in the putative indication for the new medicinal product, whereas the other which is not even suspected may be associated with high risk. It would be wrong to (1) require a deep level of elucidation of a broad band of modes of actions of lead compounds before they go in first-in-man CTs as this would delay drug development potentially by months or rather years, and (2) require the lack of uncertainty regarding our knowledge of the mechanism(s) of actions, since elucidating mechanisms of action is a never-ending	Redundant, see above.

	7process. Mutatis mutandis, these observations apply to the nature of targets and animal models. Targets may be identified at sub-cellular level, e.g., at receptor level in the brain, and yet the precise role of the receptor may not yet be elucidated. By definition, animal models are only models, and therefore subject a priori to uncertainty. If there were no uncertainty left, the medicinal products would not have to be tested in man. Therefore, it is to be feared that an overcautious connection of risk with these uncertainties will lead to paralysis, although for that to happen we got to be able to mutate all the greed genes simultaneously.	
69 (FECS)	Item 3, the relevance of animal models Add "this is particularly difficult where cancer is concerned"	Comment not understood; the testing of relevance is generally not any different for cancer drugs (regarding safety).
69 (AGAH)	Concerns may also be derived from findings of non-clinical studies (those findings may be interrelated to the question whether or not a model is appropriate or whether or not a finding is species-specific). Add: "… and/or (4) the results of non-clinical studies."	Agreed, included elsewhere (subsection "mode of action").
70-74 (EFGCP)	This paragraph states that for high-risk medicinal products conventional non-clinical programmes do not provide an acceptable safety estimate. Since it is not possible to flag high-risk compounds, this requirement risks being interpreted practically as requiring more non-clinical research on all lead compounds. The words "acceptable safety estimate" introduce a medico-legal responsibility issue which is a moving target since it depends on who will judge the acceptability. This will lead scientists in the field of preclinical programmes and in Phase I to blame each other for being insufficiently conservative, hence the preclinical phase may become longer for all lead compounds because of increased responsibility to demonstrate safety beyond doubt and Phase I specialists may request more animal work before taking the responsibility of a first application in man.	Wording has been changed. The comment is acknowledged, however, for novel compounds like TGN1412 a more detailed non-clinical programme before filing an IMPD for a first-in-man study might indeed be required on a case-by-case basis. Based on regulatory experience, some IMPDs for clearly risky compounds were filed that lacked essential data. This should be avoided, and this again underlines the recommendation to seek scientific advice from Competent Authorities.

70-74 (EFPIA)	The importance of making sure that the non-clinical programme is relevant for human testing is highlighted but where there is less confidence greater caution in initiating clinical trials is warranted. **Suggest replacing this paragraph with the following: "***Special considerations of the non-clinical programme conducted before the first-in-man study to sufficiently assess the predictive value of the models for the effects, especially serious adverse reactions that may occur in human studies. In case that there are doubts about the relevance of non-clinical studies for human studies, the transition from non-clinical to clinical testing requires particular precautions to minimise risks."*	Wording partly included.
71 (PDA)	Change "safety estimate for a list administration in humans" Rationale: Clarity Safety model for estimating risk prior to first administration in humans	Wording partly included.
71 (PDA)	Add the word "potential" before high-risk medicinal product Rationale: Clarity and consistency. This should be a global change in document.	Not relevant anymore, "high risk" has been omitted from the guideline.
71-73 (AGAH)	Consider the interspersed phrases and changes in italics to be more precise. "However, for high-risk medicinal products this *conventional non-clinical* programme might not be sufficiently predictive of serious adverse reactions in man, and *that is why additional requirements may have to be observed not only in the non-clinical development programme, but also in the first clinical studies*."	In contrast to other comments, thus original wording kept with some amendments to enhance clarity.
74 par 4.1 (EANM)	Direct comparison of non-clinical to clinical testing represents a major advantage to ensure robustness of conclusions in translational research. Micro-dosing approach may be largely contributing to such a result.	

	Add at the end of existing sentence: **and in vivo assessment of active molecule behaviour using highly sensitive modalities (such as Positron Emission Tomography) may be advisable**	Judged as too specific for this guideline. Reference to the "Position Paper on the non-clinical safety studies to support clinical trials with a single micro dose" has been added.
74 (PDA)	After "testing" and prior to "therefore requires……add text as shown. Rationale: Clarifies that there is no need for the special precautions mentioned here for products outside this category For these types of products	Sentence has been deleted and replaced.
74 (PDA)	Add text prior to "special precautions to minimize…." Rationale: improved clarity The implementation of	Sentence has been deleted and replaced.
75-76 (J&J)	The guideline recommends that the criteria for all first-in-man trials be discussed in the clinical trial authorisation applications. However, it is not clear where in the CTA application this discussion should appear. We propose that it be included in the Overall Risk and Benefit Assessment section of the IMPD. Add underlined text: *The Sponsor should discuss the following criteria for all first-in-man trials <u>in the Overall Risk and Benefit Assessment section of the IMPD</u> in their clinical trial authorisation application.*	Wording taken into account.
75-77 (EFPIA)	The consequence for an IMPD of a product defined as high-risk should be clarified in an additional section 'Regulatory aspects'. Although this guideline is specifically targeted for "first-in-man" clinical trials for potential high-risk medicinal products, it is not clear whether the statement "The Sponsor should discuss the following criteria for all first-in-man trials in their clinical trial authorisation application" implies that for all entry into human studies, one has to justify whether the IMP is classified as high-risk product. "The Sponsor should discuss the following criteria for all first-in-man trials in their clinical trial authorisation application."	Indeed, for any novel compound it should be deliberated whether a risk mitigation strategy as described in the guideline is necessary, however, it is expected that for most compounds this might not be necessary.

	Since this guideline only applies to "potential high-risk IMPs" (see chapter 2 "Scope"), the criteria should only be discussed for these drugs and not for "<u>all</u> first-in-man trials". Since the typical pharmacological characterization of biologics and small molecules differ significantly both with regard to available methodology and issues to be addressed (example: tissue cross reactivity), this should be stated in this guidance. It should be clarified, that all three criteria should be evaluated in an integrated assessment, i.e. in particular situations were only one criterion is applicable, this should not mean that the IMP is automatically defined as high-risk. **Will there also be a section added to the CTA application form and EUDRACT database to allow a statement by the Sponsor on proposing the classification "high risk" and "non-high risk"? It would be helpful to have a specific mechanism defined and where responsibility for making such definition identified – is it the sponsor or the authority?** Add the sentence: ***<u>"Especially, fundamental differences between biologics and small molecules should be taken into account."</u>*** Add: ***<u>"The sponsor should provide an integrated risk-assessment based on the following criteria when deciding whether or not a new medicinal product is of potential high-risk. (There might be situations where only one but a very important criterion of the three may lead to designation as a high-risk medicinal product. In other situations only a combination of two or three (but not a single valid criterion alone) leads to this designation depending on the type of product, knowledge available and relevance of the criteria concerned.</u>*** ***<u>E.g. the absence of a relevant animal model does not mean that – by default – all substances where such a model is missing are defined as high-risk.")</u>***	Not felt necessary, since this is common knowledge. Agreed, but not relevant anymore, since strategy has changed.
75-77	Although this guideline is specifically targeted for "first-in-man" clinical trials for potential high-risk medicinal products, it is not clear	See above.

(Roche)	whether the statement "The Sponsor should discuss the following criteria for all first-in-man trials in their clinical trial authorisation application" implies that for all entry into human studies, one has to justify whether the IMP is classified as high-risk product.	
76-77 (JPMA)	**Since the definition of "high-risk" is substantially broad, most of investigational medicinal products currently under clinical development might fall in the category of high-risk potential medical product. However, the true high-risk medical product that needs careful FIM may not be so many.** **Add the following sentence after the sentence of Line 76-77, "The decision should be made on concern basis".**	Redundant, see above.
77 (PDA)	Change"…..of potential high risk" Rationale: Clarity ……..to be classified as constituting a potential high risk	Redundant, see above.
78 (AMS)	Mode of action: with products known to be agonist to the immune system, extra caution is needed, as cytokine release is particular to the white cell (immune) system and not to other tissues. Due care should be taken to monitor this possibility by following biomarkers at the initial lowest first dose used.	Agreed, but guideline should not focus on immunologicals only.
78 (AMGEN)	Expectations expressed relative to knowledge of mode of action of a candidate drug would apply to any new target and is counter to a desire for innovative therapies and is a disincentive to bring first-in-class molecules to human study.	Agreed, first sentence amended.
78 (EBE)	Expectations expressed relative to knowledge of mode of action of a candidate drug would apply to any new target and is counter to a desire for innovative therapies and is a disincentive to bring first-in-class molecules to human study.	Redundant, see above.
78 (EuropaBio)	Expectations expressed relative to knowledge of mode of action of a candidate drug would apply to any new target and is counter to a desire for innovative therapies and is a disincentive to bring first-inclass molecules to human study.	Redundant, see above.

78-83 (MP)	Regarding Section 4.1 Definition of Potential High-Risk Investigation Medicinal products – Mode of Action, the guideline states: *"Consideration should be given to the novelty, plausibility and extent of knowledge of the proposed made of action. This includes the nature and intensity (extent, amplification, duration, reversibility) of the effect of the active substance on the target and the type of dose response (linear, non linear, U-shaped, bell-shaped). Previous exposure of human beings to compounds that have related biological mechanisms should also be considered."*	
	The term "consideration" seems to be very broad, which may not be helpful regarding chemical medicinal products, as the majority of anti-cancer/cytotoxic agents will generally meet the definition of MOA. The inclusion of specific references for cases of toxicities for small chemical medicinal products at the first dose levels selected based on all the MOAs would be helpful for clarification.	Not agreed, specific references are not part of such guidelines. However, the wordings have been refined.
	The guideline is unclear on how previous human experience should be determined for compounds that have a related biological mechanism. We feel that more specific examples would be beneficial for a clear understanding of how to determine "high risk" or "non high risk" based on previous experience.	Not agreed, it is felt that reference to previous exposure to similar compounds should be clear. Determination of high-risk vs. non-high-risk not relevant anymore.
	We understand that the suggestion in this guideline is to provide a PK profile assessment for the molecule in the CTA. We consider this to be a difficult task for a molecule that has not yet been dosed in humans.	Wording clarified.
	For clarity, we recommend the inclusion of specific references for cases of toxicities for small chemical medicinal products at the first dose levels selected based on all of the MOAs. We also recommend the exclusion of all anti-cancer/cytotoxic small molecules as they should be included under different guidelines.	See above.
	We recommend the inclusion of more specific examples or a decision tree to help explain how to determine "high risk" or "non high risk" based on previous experience.	
	Please consider early development situations (molecules not yet dosed	

	in humans) when suggesting the inclusion of PK profile assessments in the CTA.	See above.
78-105 (EFPIA)	Definitions of high-risk products based on novel mechanisms, pleiotropic effects, or unique structures (e.g., fusion proteins) are overly broad and if conservatively interpreted almost any FIM study could be considered high risk. This would add unnecessary delays where standard toxicological paradigms are adequate to evaluate risk for most products in these categories. The scope if applied as is will significantly adversely impact novel therapeutic development that would otherwise be safely conducted under existing guidance, to the determent of advancing novel medicines. Furthermore these definitions leave it open to potential divergent interpretation by different competent authorities. The "high-risk products" definition should be restricted to the types of agents that have shown significant unexpected toxicity; i.e., to modes of action where amplification of a signal could be predicted. Thus, antagonists and small molecular chemical agents would not routinely be considered high risk. Where the MOA is the basis for definition of high risk it should also include the additional criteria that there is either 1) evidence from animal models for the potential risk for serious, pharmacologically-mediated toxicity, or 2) an indication that the animal models do not exhibit pharmacological response expected in humans sufficiently to adequately assess the risk and other compounds have not been tested to derive an understanding of the potential risk	Redundant, see above.
78-105 (Takeda)	**Mode of Action, Nature of Target and Relevance of Animal Models** The guideline implies that full knowledge of the mode of action, nature of the target and relevance of the animal model should be available at the time of FIH. However, there are likely to be instances where the	The guideline provides flexibility, since - the concept now is a risk mitigation strategy - the guideline already in the draft version repeatedly stated that decisions

	mode of action or downstream biological effects are not fully understood at the time of FIH. The guideline should, therefore, provide flexibility to allow discussion of these criteria in the relevant sections of the IMPD in the presence and absence (if justified) of specific data. The overall classification of a new molecule as a potential high risk medicinal product will be derived from the totality of the existing data, precedent, class etc. and thus mode of action, nature of the target and relevance of animal models should be considered alongside all other relevant parameters	have to be made on a case-by-case basis. Thus, the comment is agreed with.
78-91 (ICAPI)	*4.1 Definition of potential high-risk investigational medicinal products: Mode of Action* We draw attention to the list of situations where a new medicine may be considered high-risk in the Duff Report (p4). Also, mode of action, nature of the target and relevance of animal models should be given appropriately numbered subheadings.	Definitions of Duff report were taken into account.
79 Cancer Research	What is meant by plausibility in this statement?	Deleted since apparently unclear and covered by "extent of knowledge"
79 (RS-LTD)	Suggestion to insert prior to first sentence The target in man should be discussed in detail.	Put to text, but sub "Nature of the target".
79 (PDA)	Delete plausibility Rationale: Clarity. Too vague and not scientific wording.	See above.
79 (PDA)	Change "proposed" Improve clarity by "supposed"	Agreed
79 (BIA)	**Mode of action**	Part of the suggestions have been included.

	Where a mode of action of the new entity is novel, it may be possible to use both internal and external knowledge to provide a rationale for the underlying mechanism of action, and not just previous human exposure to compounds that have related biological mechanisms. Reference should be made to cytokine release syndrome. We suggest that this is revised as follows: Consideration should be given to the novelty, plausibility and extent of knowledge of the proposed mode of action **or related modes of action.** Add: **- Molecules that target a biological amplification cascade or cytokine release.**	
79-80 (SPC)	<u>Mode of action</u> The novelty of drug target has increased during the last several years. If novelty of the target is a primary criteria for evaluating the target this will represent a large group of compounds coming into clinical development. As the pool of human biology has decreased, the extent of information for new drug targets has declined, so many of the new drug targets have very limited knowledge. This change is reflected in both the extent of published literature on the drug target and a higher likelihood that this literature will be more removed from direct human experience. In many circumstance, Health Authorities are in a better position to determine the perceived risk of a drug target based on their past target-related experienced than those developing the drug. The extent of filing information will usually be based on publicly available information and will result in worst case planning – extensive information. If human studies are embarked upon to ascertain additional information, some additional human risk will also be entailed. Before filing the clinical trial authorization, the extent of information required may be best determined well before filing to assure an appropriate dossier and to	Redundant, see above. see recommendation for Scientific Advice.

	minimize both HA workload and additional risk to human subjects. A more precise definition of drug target of greatest concern is required.	
79-82 (EFPIA)	Could the document please clarify whether they consider only the effect of the active substance of relevance or whether also the effect of metabolites should be taken into account? It is indicated that the type of dose response should be considered. However, for vaccines and for locally acting products PK is not always of relevance. Could the document please indicate what considerations apply in such a case?	Certainly the active principle is meant, which represents for some compounds active metabolites. "Active substance" therefore replaced. Text has been refined. Special cases like vaccines or locally acting products would be covered by the "case-by-case" philosophy of the guideline.
80-82 (AGAH)	Consider the interspersed phrases and changes in italics to be more precise. "This includes the nature and intensity (extent, amplification, duration, reversibility) of the effect of the active substance on the target *and subsequent mechanisms, if applicable,* and the type of dose response *which may be* linear *within the dose range of interest, or* non-linear (*e.g., plateau with a maximum effect, over-proportional increase,* U-shaped, bell-shaped)."	Proposal included in revised draft.
81 (RS-LTD)	Suggestion to add …the effect of the active substance on the <u>specific</u> target and <u>non-targets</u> and the type of dose response…	Proposal included in revised draft.
81 (PDA)	Change: Active substance Rationale: Consistency in terminology: ICH Q7A uses "API" for chemical and biologically active pharmaceutical substances. Active pharmaceutical Ingredient	Text changed, see comment above.
81 (Drusafe)	All dose-response are inherently nonlinear and highly dependent on the dosing design, i.e., range, placement and amount. In the context of safety/tolerability, the	Proposal included in revised draft.

	steepness of the dose-response should be considered as well as the shape. Suggest addition: '….and the type and steepness of dose response….'	
81 (BIO)	All dose-responses are inherently nonlinear and highly dependent on the dosing design, i.e., range, placement and amount. In the context of safety/tolerability, the steepness of the dose-response should be considered as well as the shape. We suggest that "and steepness" be added so that the text reads: '….and the type and steepness of dose response….'	Redundant, see above.
82 (RS-LTD)	How should previous exposure to human beings to compounds with related biological mechanisms be considered?	Any available data (from mode of action to safety in humans) should be used (e.g. literature) as it might give relevant information.
82-83 Cancer Research	Clarification of "previous exposure" is required. For example does this solely refer to exposure in clinical trials or should occupational or environmental exposure also be considered?	
82-83 (EFPIA)	In cases where the target mode of action is known in humans, this will give additional information on potential safety issues – or lack thereof *"Previous exposure of human beings to compounds that have related biological mechanisms should also be considered.* ***Furthermore, information on potential safety risks or the lack thereof can be taken when deficiencies of a specific mechanism in humans are known****."*	Agreed, wording included in the revised guideline text.
82-154 (EFPIA)	Certain products can have paradoxical responses depending on the concentration. There is more than one reference to U- and bell- shaped dose-responses, and whilst this is important to understand the dose range, it is also important to focus on the steepness of the dose-response.	Redundant, see above.

	"… (***steepness and shape of the curve***, *linear, non-linear, U-shaped, bell- shaped)"*	
82-154 (ABPI)	Certain products can have paradoxical responses depending on the concentration. There is more than one reference to U- and bell- shaped dose-responses, and whilst this is important to understand the dose range, it is also important to focus on the steepness of the dose-response. … (steepness and shape of the curve, linear, non-linear, U-shaped, bell-shaped)	Redundant, see above.
83 (AGAH)	These are other important aspects. Add: "In any case, the existence of additional targets should be taken into account. If other targets are known, the related physiologic effects should be characterized if deemed to be necessary for the overall safety assessment. The variability of the dose-response observed in *ex-vivo* models and animal studies should also be considered which is particularly important for investigational compounds that may have a narrow therapeutic index. In this context, the existence of polymorphisms in human drug metabolism which might put individual subjects at risk should also be taken into account."	Wording considered for revised guideline.
83 (PDA)	Delete "considered" Rationale: improved clarity …….discussed in the application where relevant.	Wording considered.

84 (PDA)	Delete: "mechanisms" Rationale: Clarity – follows on better from previous paragraph and paragraph heading Modes of action	Agreed.
84-91 (EBE)	*The definition of a* "high risk" *mechanism appears rather vague and difficult to interpret. We understand the difficulty and risk in too narrowly or specifically defining how one identifies a* "high risk product*", but would welcome some guidance on how to best work with regulatory agencies to come to agreement on how to define proposed products and mechanisms as* "high risk".	Redundant, see above.
84-91 (EFPIA)	A pleiotropic mechanism alone should not be considered as evidence of high risk, unless the consequences of such a mechanism are not known and cannot be assessed properly. Depending upon your understanding of "pleiotropic" and "ubiquitously expressed" many compounds will qualify. Steroids and their receptors would certainly fit in this definition; are they going to be considered high risk from now on? For clarity to reader the authorities are asked to provide a more precise example would be helpful. Sentence should read: *"A pleiotropic mechanism, e.g. leading to various physiological effects, or targets that are ubiquitously expressed ~~as often seen in the immune system~~* ***if the physiological consequences of target interaction in the human cannot be properly assessed****."*	Agreed, but it is felt that the current wording of the guideline's attitude (case-by-case, risk mitigation) is now sufficiently clear that not every compound targeting a pleotropic mechanism is automatically "high-risk".
84-91 (Roche)	The definition of a "high risk" mechanism appears rather vague and difficult to interpret. We understand the difficulty and risk in too narrowly or specifically defining how one identifies a "high risk product", but would welcome some guidance on how to best work with regulatory agencies to come to agreement on how to define proposed products and mechanisms as "high risk".	Redundant, see above
85 (PDA)	Add text after "physiological effects"	Wording included in revised text.

	Rationale: Clarity. Improves emphasis Or a cascade effect	
85 (Roche)	It is not clear what "pleiotropic mechanism" means here. Rephrase: *"A MoA that involves a target molecule which is connected to multiple signalling cascades (target with pleiotropic effects),…"*	Wording included in revised text.
85-86 (SPC)	Pleiotropic mechanism and wide expression are loose concepts and could represent a large fraction of drug targets. A more precise description of high-risk drug targets is required. Potentially illustrative positive and negative examples of new drug targets could communicate the intent of the guideline better and clarify its use.	Redundant, see above.
88 (AGAH)	This is another important example for a mechanism which should be considered as high risk. Add: "- any mechanism which has the potential to induce a cascade of reactions leading to an amplification of the effect that might not be controlled by a physiologic feedback mechanism (e.g., in the immune system or blood coagulation system).	Wording considered.
88 (AMGEN)	Reference to "supra-agonists". Change to: "super-agonists". Add the words: - *"Molecules with known or expected downstream effects such as involved with amplification cascades or cytokines release."*	Included.
88 (Drusafe)	Reference to "supra-agonists"	Redundant, see above

	Should be “super-agonists”? Include: - Molecules with known or expected downstream effects such as involved with amplification cascades or cytokines release	
88 (ABPI)	Suggested additional text under “The following mechanism could be considered as high risk” Molecules that target a biological amplification cascade or target the production of cytokines	Redundant, see above
88 (EuropaBio)	Reference to “supra-agonists”. Change to: “super-agonists”. Add the words: - *“Molecules with known or expected downstream effects such as involved with amplification cascades or cytokines release.”*	Redundant, see above
78-94 (MSD)	Definitions of high-risk products based on novel mechanisms, pleiotropic effects, or unique structures (e.g., fusion proteins) are overly broad and if conservatively interpreted almost any FIM study could be considered high risk. This would add unnecessary delays where standard toxicological paradigms are adequate to evaluate risk for most products in these categories. The scope of the definition is particularly excessive given the one exceptional case where traditional testing may not have been adequate, and this conclusion itself is debatable given the available information. The scope if applied as is will significantly adversely impact novel therapeutic development that would otherwise be safely conducted under existing guidance, to the determent of the public. Furthermore, the concern is whether animal models have appropriately assessed potential human risk for such products.	Redundant, see above

	The "high-risk products" definition should be restricted to the types of agents that have shown significant unexpected toxicity; i.e., to modes of action where amplification of a signal could be predicted. Thus, antagonists and small molecular chemical agents would not routinely be considered high risk. The definition of high-risk products based on MOA should include the additional dependency that there is either 1) evidence from animal models for the potential risk for serious, pharmacologically-mediated toxicity, or 2) an indication that the animal models do not exhibit pharmacological response expected in humans sufficiently to adequately assess the risk and other compounds have not been tested to derive an understanding of the potential risk	
85 (CHDR)	Pleiotropy is more a rule than an exception and whether this is clear from the pre-clinical experiments heavily depends on the assumption that the compound would exert more effects.	Agreed, but covered by text on relevant animal models.
85-86 (AMS)	Statements such as "targets that are ubiquitously expressed" should be viewed with caution. Many targets are very widely expressed and this could end up with too many things being captured as high risk.	Agreed, but it is felt that the current wording of the guideline's attitude (case-by-case, risk mitigation) is now sufficiently balanced.
85 (EBE)	*It is not clear what* "pleiotropic mechanism" *means here.* Rephrase: *"A MoA that involves a target molecule which is connected to multiple signalling cascades (target with pleiotropic effects)…"*	Redundant, see above
87 (CHDR)	All drugs bypass physiological mechanisms (for instance loop diuretics).	Correct, wording refined.
87–88 (EBE)	*" – A mechanism that bypasses physiological control mechanisms, e.g. CD3 or CD28 (supra-)agonists."* Binding of a molecule to CD3 is not considered as bypass mechanism. CD3 should be deleted as an example. Change as follows: *" – A mechanism that bypasses physiological control mechanisms, e.g. ~~CD3 or~~ CD28 (supra-)agonists."*	Arguable from an immunological perspective (CD3 triggering can activate T cells).

88 (EBE)	Reference to *"supra-agonists"*. Change to: "super-agonists". Add the words: - *"Molecules with known or expected downstream effects such as involved with amplification cascades or cytokines release."*	Redundant, see above Wording adapted.
88 (EFPIA)	Suggested additional text under "The following mechanism could be considered as high risk" Reference to "supra-agonists" Molecules that target a biological amplification cascade or target the production of cytokines Should be *"**super-**agonists"?*	Redundant, see above
89 (PDA)	Add "molecular" before the word "structure" Rationale: Clarity Molecular structure supposed	Agreed and added.
89 (PDA)	The use of the term "medicinal product" is not consistent. Rationale: Clarity. The guideline should be consistent with the wording in the ICH guidelines. Suggestion: "medicinal product" is replaced by "drug product"	Agreed, but should be "active substance". Changed in the revised draft.
89-90 (EBE)	*"(…) for example new type of engineered structural format like bispecific antibodies or novel fusion proteins."* Current experience does not support that bispecific antibodies should	Agreed, has been reworded.

	be listed as an example for “high-risk medicinal products”. Delete “bispecific antibodies”: *“(…) for example new type of engineered structural format like bispecific antibodies or novel fusion proteins.”*	
89-90 (EFPIA)	Definition of compounds in scope should be considered more clearly, especially a need for definition of 'the novelty of the structure of the medicinal product' mentioned in line 89. The examples provided in this paragraph should be replaced with some that are more adequate and specific to outline the concern. Novel fusion proteins could include pegylation or Fc modifications of marketed or well known proteins. We believe the guideline is referring to fusions of two proteins each with its own pharmacology. ***S**ponsors should also discuss the novelty of the structure of the **active ingredient(s) of the** medicinal product,”* Provide more clarity on what’s considered ‘novel’ to exclude protein modifications directed toward increasing the half-life of existing therapies	Agreed, has been reworded.
90 (Drusafe)	Novel fusion proteins could include pegylation or Fc modifications of marketed or well known proteins. We believe the guideline is referring to fusions of two proteins each with its own pharmacology. Provide more clarity on what’s considered ‘novel’ to exclude protein modifications directed toward increasing the half-life of existing therapies	Redundant, see above.
90 (Roche)	mAbs engineered or modified at the Fc portion should also be explicitly mentioned here, as the nature of the Fc portion seems to be a key contributor for all mAbs that have been triggering severe types of	Included with revised wording in the revised draft, however, more general and not focussed on mAbs since some Fc modified mAbs have already been tested clinically.

	cytokine release, as yet (see above). Rephrase: *"…engineered structural format like bispecific antibodies, novel fusion proteins or antibodies engineered or modified at the Fc part…"*	
90 (BIO)	Novel fusion proteins could include pegylation or Fc modifications of marketed or well known proteins. We believe the guideline is referring to fusions of two proteins each with its own pharmacology. Provide more clarity on what's considered 'novel', to exclude protein modifications directed toward altering the biodistribution of existing therapies.	Redundant, see above.
89-91 (IFAPP)	Engineered medical products might carry more than average potential of being high-risk Suggest moving this item as a third type of example of potentially high-risk medicinal product in the same paragraph	Preferred as not a third bullet point, since this is not a "mechanism of action", but a modulator thereof.
92 (EACPT)	Following the definitions, should any new medicinal product affecting new identified targets, or targets never affected before be considered as "high risk medicinal product"?	Redundant, see above.
92 (EBE, Roche)	*It should be mentioned that primarily (not exclusively) targets of the immune system belong to the high-risk category, since those targets are primarily able to trigger signalling events leading to cytokine secretion. Noteworthy, all mAb that induced cytokine release syndrome did recognize targets on immune cells (anti-CD3: T cells, anti-CD52: T, B cells, monocytes; anti-CD20: B cells; anti-CD28: T cells).* Add 3rd bullet point (line 100): *- the extent to which the target molecule is expressed in / on cells of the human immune system*	In revised draft included in the first bullet point (mode of action)

92-97 (AGAH)	The nature of the target and its regulation mechanisms relate back to the type of reaction as described under "Mode of action". That means it may not always be an independent factor. Add: "These factors may have an impact of the biological effect and the type of reaction."	Included in the revised draft.
92-99 (EFPIA)	Nature of the target might have impact on the risk categorisation. Many CNS-active compounds would qualify since little is known on the relationship between the biology of their targets and the physiological or pharmacological effects, neither in the normal nor in the diseased state(s) but should not necessarily be classed as high risk.	Agreed, but it is felt that the current wording of the guideline's attitude (case-by-case, risk mitigation) is now sufficiently balanced.
93 (EBE)	*"Irrespective of the mode of action, the nature of the target itself might impact on the risk inherent to a first administration to humans, and sponsors should discuss (…)"* The impact is closely connected to mode of action. Change "Irrespective" to "Dependent on": *"Irrespective to Dependent on the mode of action, the nature of the target itself might impact on the risk inherent to a first administration to humans, and sponsors should discuss (…)"*	This was not the intention; wording slightly changed for clarity.
95-97 FRAME	Characterisation of the nature of the target should include assessment of target density at specific sites in healthy subjects and different patient groups. Hence, the draft guideline should include a lack of knowledge of target density as a potential source of uncertainty. The extent of the knowledge on the structure, tissue distribution, cell specificity, regulation, **density** and biological function**…..and how it might vary between individuals in different populations of healthy subjects and patients**	Text included. "Density" might not be clear, therefore modified wording.

95-99 (SPC)	Nature of the target The work requested here could be substantial. For many new drug targets, human physiology has been minimally defined due to lack of appropriate probe to more fully explore the physiology. The translation from animal to human for the species restricted drug targets is among the larger challenges. A dossier of available knowledge can be prepared from existing literature and limited supplemental human studies. Additional human characterization studies prior to NME availability would be difficult.	The text appears to have been misunderstood. The degree of characterisation necessary (and possible) is a case-by-case decision, but this degree is a factor contributing to the estimation of risk. It is self-evident that knowledge from literature is part of the overall concept.
98 (EBE)	*"- the relationship between the biology of the target, and the physiological or pharmacological effects, in both normal and pathological states."* In case of absence of relevant animal models physiological effects can not be determined in non-clinical studies. Add "if possible": *"- the relationship between the biology of the target, and if possible the physiological or pharmacological effects (…)*	Text has been amended in order to direct to the "case-by-case approach".
98-99 Cancer Research	Could the meaning of this statement be further clarified?	See above
98-99 FRAME	*Ex vivo* and *in vitro* studies on comparable cell types, from the test species and from people representative of different potential phase 1 trial subject groups, might provide information about possible variability between subject groups and sources of uncertainty arising from preclinical animal studies. ..the relationship between the biology of the target, and the physiological and pharmacological effects, in both normal and pathological states **in so far as this information can be practically**	Not included, since this is self-evident.

	and ethically obtained.	
89 and 93-99 (CAG)	I believe you are referring also to the structure of the product in relation to the structure of the target cell, potentials for down regulationor blocking of significant switches and the importance of understanding principles of structural biology in the design of products? It may be useful to elaborate and clarify that understanding if so with the following lines 93-99	Text in this section clarified.
99 (EFPIA)	Clarify Suggested additional text under "Sponsor should discuss the following aspects accordingly" ***-"Polymorphisms of the target in relevant animal species and humans, and the impact of polymorphisms on the pharmacological effects of the medicinal products."***	Included in the revised draft.
100 (EFPIA)	Clarify what would constitute "a relevant species" e.g. for mAb would homologue protein target + same tissue cross-reactivity w/human tissues qualify? More details would be helpful. Relevance of animal models – it would be very helpful to have a discussion on the use of surrogate molecules at this point in the document. Data generated using a surrogate molecule may be highly relevant and useful. Even if there is binding to the non-human primate target, more relevant information may be generated using a surrogate in the rodent system.	Beyond the scope of this section; considerations on "relevance" are found in section 4.3.3.
100 (BIO)	Relevance of animal models: The terms "animal species" and "animal models" must be carefully distinguished. The former should be used when speaking of the species selected for safety testing, including discussions of relevant species. The latter term, animal models, should be reserved for those instances in which a spontaneous or induced animal model of human disease is used in safety testing. This document mixes the two concepts and thereby creates confusion.	

	Line 100: The title should read "Relevance of animal species and models"	Has been included.
100-105 (MP)	Regarding Section 4.1 Definition of Potential High Risk Investigation Medicinal Products – Relevance of Animals Models, the guideline states: *"The Sponsor should compare the available animal species to humans taking into account the target, its structural homology, distribution, signal transduction pathways and the nature of pharmacological effects. If available animal models are of limited relevance to study properly the pharmacological and toxicological effects of the medicinal products, it should be considered as high-risk."* We believe that this statement is appropriate for biological products/proteins, but not be necessary for chemical medicinal products, as small molecules are generally adequately tested in animal species (one rodent and one non-rodent species). In addition, as a statement is made regarding available animals models of limited relevance, we feel that the opposite situation should also be included by stating – *"If available animal models are relevant to study the pharmacological and toxicological effects of the medicinal product it should not be considered high-risk."* *We also believe that toxicity should be the primary concern, regardless of similarity of targets in animals and humans.* We recommend that this paragraph should be limited to biological products. We also recommend the inclusion of the following statement: *"If available animal models are relevant to study the pharmacological and toxicological effects of the medicinal product it should not be considered high-risk."*	In principle correct. However, novel species-specific chemical substances would not be covered if reference was made to biological products only. In light of the revised concept of a risk-based approach, the distinction between "high-risk" and "non-high-risk" is not necessary.
101 – 103 (EBE)	*"The Sponsor should compare the available animal species to humans taking into account the target, its structural homology, distribution, signal transduction pathways**,** and the nature of pharmacological effects."*	Agreed, included in the revised text in the first bullet point (Mode of Action).

	As the non-clinical evaluation of the risk to humans for medicinal products with high species-specificity is much more difficult, (see line 180-182) experience from previous exposure of human beings to compounds that have related biological mechanisms is very important and should clearly be considered. Change as follows: *"The Sponsor should compare the available animal species to humans taking into account the target, its structural homology, distribution, signal transduction pathways, and the nature of pharmacological effects and experience from previous exposure of human beings to compounds that have related biological mechanisms."*	
101-103 (EBE)	This section is somewhat confusing since it suggests that the best animal model for a pharmacological action (and the exaggeration of it) would be the best model for toxicological effects, which are based on different mechanisms of action.	"Pharmacological effects" refers to actual activity of the compound, since binding and sequence homology alone are not sufficient to conclude on the relevance of the target species. Pharmacological effect is usually a prerequisite for toxicological effects (e.g. penetration into the cell and consequent effects)
101-103 (BEBO)	Add: metabolic routes/metabolites formed	Included in cross-referred section 4.3.1.
101-103 (EFPIA)	To create such data for all available species will imply an effort not justified by the information gained. What is needed, is a proper justification of the selected animal model according to the state of the art. Mention should be made that correction for potency may be required. The role of transgenic animals with humanized target structures as potential surrogates should be discussed here The sponsor should justify the relevance of the chosen animal model for humans taking into account the target, its structural homology, distribution, signal transduction pathways, the nature of the pharmacological effects and the relative potency.	The guideline does not say that such efforts should be undertaken for all animal species available. The search for an animal species is a directed approach, starting e.g. with sequence homology/comparisons of the target structure. What the guideline says is that such sequence comparisons are not sufficient to conclude on the animal species, and that further data are necessary in order to justify the relevance of the target species. Is discussed in section 4.3, therefore not included here. Agreed, included.

101-103 (IFAPP)	The comparison of available animal species should be outlined in more detail The sponsor should compare the available animal species taking into consideration their age and gender and eventual species differences (e.g. how old/what gender have the studied animals compared to the intended population?)	Is discussed in section 4.3, therefore not included here. This is a very specific aspect, which is not detailed in this general chapter (although on a case-by-case basis indeed potentially relevant).
101-103 (ABPI)	Mention should be made that correction for potency may be required The sponsor should compare the available animal species to humans taking into account the target, its structural homology, distribution, signal transduction pathways, the nature of the pharmacological effects and the relative potency.	Redundant, see above.
101-103 (BIO, Centocor)	Need to specify that *in vitro* bioactivity is important for defining species relevance.	Agreed, included in the revised draft.
101-103 (BIA)	**Relevance of animal models** The guideline should not be seen as a definitive list of information required, rather a series of points to consider when making the assessment of relevance of animal species for non-clinical studies. We propose that this is revised as follows: The Sponsor should compare the available animal species to humans taking into account**, for example,** the target, its structural homology, distribution, signal transduction pathways**, ~~and~~** the nature of the pharmacological effects**, the relative potency and tissue expression in a disease state.**	Text revised, however "for example" not felt appropriate, since most of the information should be available. Again, this is a case-by-case decision. Potency is mentioned later in chapter 4.3.6, "estimation of the first dose in human".
104 (AMGEN, EBE)	Animal models are always of limited relevance. Qualify the degree of relevance, or characterize as "questionable	Text of this section now modified.

	relevance" indicating that confidence in the animal model as predictive is negligible.	
104 (EFPIA)	Tissue expression of target may depend on the disease state in an animal model. For instance, its expression may be present at a low level in a non-diseased animal but may increase in a diseased state. The definition of high risk is broad and is likely to be interpreted in a wide variety of ways. The MHRA started with 3 areas that seem easier for different stakeholders to grasp: biologics with novel MOA, new agents with a high degree of species-specificity and new agents with immune system targets. The lengthy experience with NCE would seem to warrant some separation from biologics. We would recommend that the guideline adopt the 3 categories previously defined by the Expert Working Group in the UK to create a more straightforward definition of "high-risk". EMEA could consider a procedure for rapid consultation (faster than the Scientific Advice Procedure) to confirm risk category selection, where the phase 1 study would be conducted in more than one Member State. An exception should be made for agents including biologics targeting adventitious agents (Bacteria, fungi, viruses etc.), where orthologue reactivity in any tox species is excluded After line 105 - It could be useful to provide some clarity on how to define whether a compound is <u>not</u> of high-risk. Add ***"<u>and tissue expression in a disease state</u>"*** after "…. *pharmacological effects"* Where animal models are of limited relevance to adequately study the pharmacological and toxicological effects of the medicinal product, it should be considered as high-risk. Previous exposure of humans and animals to IMPs that have related biological mechanisms should be discussed. If animal models are of limited relevance due to the high species-specificity of a medicinal product, then the use of homologous	Redundant, see above. Beyond the scope of the guideline. Furthermore, the guideline recommends scientific advice. Too specific, and covered anyway by the "case-by-case" and risk mitigation strategy. Please refer to section 4.3.

	proteins (i.e. surrogate antibodies) or the use of relevant transgenic animals expressing the human animal models are of limited relevance to study properly the pharmacological and toxicological effects of the medicinal product, it should be considered as high-risk and special care should be undertaken in order to qualify and quantify the potential risk emerging from human studies with this compound At the end of Section 4.1 (Definition of potential high-risk investigational medicinal products) the following text is suggested: ***"A medicinal product could be considered not to be of high-risk if it can be established that:*** • ***It does not target a pleiotropic mechanism, for example a ubiquitous cell-mediated receptor or an immune system component that bypasses physiological control mechanisms*** • ***There are other molecules that have been or are being tested, the activity of which is associated with the same receptor, that is they share the same mechanism of action (i.e. this is not a new MOA)*** ***There is comparable tissue binding in animal (to be used in predicting in vivo effects in human) and human".***	Text revised. Redundant, see above.
104 (PDA)	Change: "if" Rationale:: Clarity "where"	Text revised.
104 (PDA)	Delete: "to study properly" and replace with new text Rationale: clarity "for through investigation of"	Text revised.
104 (EuropaBio)	Animal models are always of limited relevance.	Redundant, see above.

	Qualify the degree of relevance, or characterize as "questionable relevance" indicating that confidence in the animal model as predictive is negligible.	
104-105 (EBE)	*"If available animal models are of limited relevance to study properly the pharmacological and toxicological effects of the medicinal product, it should be considered as high-risk."* As the non-clinical evaluation of the risk to humans for medicinal products with high species-specificity is much more difficult (see line 180-182) experience from previous exposure to humans to compounds that have related biological mechanisms is very important. If information of previous human exposure is available from a compound with a related mechanism of action, the new compound should not be considered as "medicinal product requiring special attention". Change as follows: *"If available animal models are of limited relevance to study properly the* *pharmacological and toxicological effects of the medicinal product, it should be considered as high-risk "medicinal product requiring special attention". This applies to medicinal products with a novel mode of action where no experience from previous exposure to humans is available*	Redundant, see above.
104-105 (EBE)	For biologics, many do not work in rodents, which are the standard models for disease. More specific language regarding the types of limitations may be necessary. Use of a surrogate molecule (homologous protein) in the animal models of disease should still be appropriate (otherwise, the majority of mAbs would be in the higher risk category). NOTE: define use of homologous in this setting. Experience from previous exposure to humans of compounds that have related biological mechanisms is very important. If information from a compound with a related mechanism of action, the new compound should not be considered as a higher risk product.	Please refer to section 4.3

	Add the words: *''If available animal models are of limited relevance to study properly the pharmacological and toxicological effects of the medicinal product (or surrogate), it should be considered as higher-risk. This applies to medicinal products with a novel mode of action where no experience from previous exposure to humans is available.''*	Text now revised.
104-105 (EMPT)	There is abundant evidence to suggest that available animal models are of limited relevance to study properly the pharmacological & toxicological effects of any medicinal product. To give a few examples: Hackam & Redelmeier in their systematic review of the most highly cited animal studies in 2006 concluded that "Finally, poor replication of even high-quality animal studies should be expected by those who conduct clinical research" (*Journal American Medical Assoc.*, October 11, 2006, Vol 296, No. 14 1731-1732). "Relative lack of severe toxicity in animal models should never be construed as a guarantee of safety in man, as the story of thalidomide taught us." Michael Goodyear, *British Medical Journal*, 2006; 332:677-678. "The published data base is inadequate to make proper judgements, & the best guess for the correlation of adverse reactions in man & animal toxicity data is somewhere between 5% & 25%." *Animal Toxicity Studies: Their Relevance for Man*, Chapter 7, Clinical Toxicity- could it have been predicted? Post-marketing experience, Ralph Heywood, 1989. On this basis, relying on animal tests as pre-clinical models, every new drug could potentially be considered high risk.	Text now revised.
104-105 FRAME	All animal models are of limited relevance since by definition they are models. In some cases, animal models can be useful for defining off-target effects without being of direct relevance. Whether an investigative medicinal product is classified as high risk may also involve a consideration of whether studies on a species-specific surrogate to an investigative medicinal product yields	Text now revised.

	information that can be used in clinical trial design. If the relevance, reliability and reproducibility of information from studies on animal models for assessing specific elements of the pharmacological and toxicological effects of the medicinal product or of a species-specific surrogate has not been established or proven, the product should be considered as high-risk.	
104-105 (J&J)	Suggestion to rephrase: If available (pharmacological and toxicological) test results are of no or very limited relevance to study properly the exaggerated pharmacological effects of the medicinal product this should be reflected in appropriate non-clinical and clinical safety measures.	Text now revised, should be covered.
104-105 (EFGCP)	If animal models are of limited relevance. The Guideline should give a more precise reference, because if experts writing the guidelines cannot come up with workable solutions, there probably aren't. In practice, different parties will need to implement the Guideline in a way which allows consensus: ethics committees, sponsors, patient associations, the Phase I unit, all must know what "limited relevance means", otherwise there will be chaos as the parties quarrel about the meaning of the limits of reasonableness.	There is international consensus on the definition of a relevant animal model (ICH guideline S6, which is also referred to in the guideline). The revised guideline text elaborates more on criteria for demonstration of relevance which should help drug developers.
104-105	For biologics, many do not work in rodents, which are the standard models for disease. Use of a surrogate molecule (homologous protein) in the animal models of disease should still be appropriate (otherwise, the majority of mAbs would be in the higher risk category). NOTE: define use of homologous in this setting. Add the words: *"If available animal models are of questionable relevance to study properly the pharmacological and toxicological effects of the medicinal product (or surrogate), it should be considered as higher risk."*	Redundant, see above. "Homologues" means "surrogate molecule" in this respect.

104-105 (ICAPI)	*4.1 Definition of potential high-risk investigational medicinal products: Relevance of animal models* It should be noted that all animal models are of limited relevance to the human situation, to a greater or lesser degree. This is true whether for on-target effects (e.g. poor predictivity of animal models for stroke treatments - Annals of Neurology 2006, 59: 467-77 and HIV vaccines - Curr Drug Targets Infect Disord 2005, 5: 193-201) or toxicology (e.g. Reg Toxicol Pharmacol 2000, 32: 56-67 – rodents predicted acute human effects in only 43% of cases). Increasingly, systematic reviews of the predictivity of animal experiments for human medicines have revealed species differences in efficacy, safety and/or poor design (Br Med J 2004, 328: 514-7, Br Med J 2007, 334: 197-200). With regard to the predictive power of animal studies for the immunogenicity of recombinant proteins in humans, specialists have written that "…animal studies, even those conducted in non-human primates, have limited predictive power" (Curr Opin Mol Ther 2004; 6; 10-6) The FDA have recently estimated that 92% of drugs that enter clinical trials ultimately fail to reach the market, primarily because of poor efficacy or safety profiles in humans (FDA. Challenge and Opportunity on the Critical Path to New Medicinal Products, 2004). Therefore, although severe adverse effects in Phase I trials are uncommon, it is incorrect to assert that preclinical animal tests are an accurate predictor of safety or efficacy in humans. They usually provide little more than a rough screen. More severe events are also often reported in later trials or during post-market surveillance (e.g. recently; torcetrapib, avimopan, tesaglitazar). Less reliance on animal tests and greater emphasis on human-based, pre-clinical data may have prevented these. Sometimes there are conflicting reports of similarities between and within species in the literature that may affect the quality of the evidence that an animal model is relevant. For example, for TGN1412 receptor structure, although the Sponsor claimed the CD28 binding epitopes were identical between macaque and human, others had previously reported that there are differences of up to 4% (Immunogenetics 2001. 53; 315-28.). Others since the trial have also highlighted differences in receptor structure that may have been	Redundant, see above.

	relevant (Nature 2006. 441; 282; Alt Lab Anim 2006; 34; 225-39). It is important therefore that the relevance of animal models is defended by a thorough literature review and, preferably, by a systematic review. As suggested by the Duff report (recommendation 3), unpublished pre-clinical data for all drugs should be collated in a searchable database, to develop a useful body of information to prevent duplicative animal studies and to enhance patient safety. The proposed database should be widely accessible. The judgement as to the degree to which animal models are of 'limited relevance' is to some extent subjective. All such judgements must be made with extreme caution, not just for potential 'high-risk' medicines. Regulators should set the barriers high with respect to proving the relevance of animal models. It must never be assumed that lack of evidence of problems is the same as positive evidence of predictivity.	
104-105 (Drusafe)	The definition of high risk is broad and is likely to be interpreted in a wide variety of ways. The MHRA started with 3 areas that seem easier for different stakeholders to grasp: biologics with novel MOA, new agents with a high degree of species specificity and new agents with immune system targets. MOA should be considered and biologics should not be singled out in a definition of high risk products. We recommend that the guideline adopt the 3 categories previously defined by the Expert Working Group in the UK to create a more straightforward definition of "high-risk". EMEA could consider a procedure for rapid consultation (faster than the Scientific Advice Procedure) to confirm risk category selection, where the phase 1 study would be conducted in more than one Member State. An exception should be made for agents including biologics targeting adventitious agents (Bacteria, fungi, viruses etc.), where orthologue reactivity in any tox species is excluded. Suggested additional text. "If available animal models are of limited relevance to adequately study the pharmacological and toxicological effects of the medicinal product, it should be considered as high-risk. Previous exposure of humans and animals to compounds that have related biological mechanisms should be discussed. If animal models are of limited relevance due to the high species-specificity of a	Redundant, see above.

	medicinal product, then the use of homologous proteins (i.e. surrogate antibodies) or the use of relevant transgenic animals expressing the human protein are strongly recommended".	
104-105 (Roche)	Lines 104-105 make a statement that appears overly broad. All animal models of toxicity and pharmacology have limitations on their relevance in predicting effects in humans. More specific language regarding the types of limitations may be necessary.	Redundant, see above.
104-105 (ABPI)	Clarify Where animal models are of limited relevance to adequately study the pharmacological and toxicological effects of the medicinal product, it should be considered as high-risk. Previous exposure of humans and animals to IMPs that have related biological mechanisms should be discussed. If animal models are of limited relevance due to the high species-specificity of a medicinal product, then the use of homologous proteins (i.e. surrogate antibodies) or the use of relevant transgenic animals expressing the human protein are strongly recommended".	Redundant, see above.
104-105 (BIO)	Lack of data from a relevant animal species does not increase intrinsic IMP risk but rather the uncertainty in the dose calculation. Therefore caution must be increased. What should be said is that, if no data are available one must proceed with caution. This document effectively creates two classes of products: those that are of potential high risk and those that are not. However, many of the recommendations in this document could be applied to almost any product being tested for the first time in humans, including both biologics and small molecules. They are sound practices for avoiding and or mitigating adverse events (AEs) or severe adverse events (SAEs). Therefore we reiterate here our comments from above that the guideline would be more useful if it were refocused to be a "points to consider" document that provides guidance on when and how to develop appropriate risk mitigation strategies through the integrated analysis of all pre-clinical data and the appropriate design of clinical trials.	Redundant, see above.

	We also note that animal studies should never be relied on as "predictive". Rather, these studies are informative. Nonclinical programs that reveal safety concerns are not the studies one has to worry about. Rather it is those that do not reveal safety concerns; that is, those for which the target and/or MOA suggests possible AEs/SAEs but for which the nonclinical program does not reveal safety issues.	
104-105 (ECRIN)	If animal models are of limited relevance…. The Guideline should give a more precise reference, because if experts writing the guidelines cannot come up with workable solutions, there probably aren't. In practice, different parties will need to implement the Guideline in a way which allows consensus: ethics committees, sponsors, patient associations, the Phase I unit, all must know what "limited relevance means", otherwise there will be chaos as the parties quarrel about the meaning of the limits of reasonableness. The alternative is to conduct systematic reviewing of animal literature and then decide on an animal-by-animal and by drug-by-drug basis what works comparably in man. One should also work for registration of all animal experimental protocols and registration of all animal research data, just as we are doing for human research. In any case take into consideration age and gender, and eventual species differences.	Redundant, see above.
104-105 (EuropaBio)	For biologics, many do not work in rodents, which are the standard models for disease. Use of a surrogate molecule (homologous protein) in the animal models of disease should still be appropriate (otherwise, the majority of mAbs would be in the higher risk category). NOTE: define use of homologous in this setting. Add the words: *"If available animal models are of questionable relevance to study properly the pharmacological and toxicological effects of the medicinal*	Redundant, see above.

	product (or surrogate), it should be considered as higher risk."	
104-105 (BIA)	The issue of relevant animal species is predominant in the development of therapeutic antibodies. The emergence (and acceptability) of surrogate molecules and/or transgenic animals should be appropriate to generate safety data. It is suggested that the sponsor discusses which potential additional ex vivo methodologies can be applied to better understand the risk, e.g. testing of cytokine release after drug administration in ex vivo blood container systems (model of cytokine storm). The sponsor should also outline biomarker plans for early safety and efficacy monitoring. If available animal models are **perceived to be** of limited relevance to study properly the pharmacological and toxicological effects of the medicinal product, it should be considered as high-risk. **Previous exposure of humans and animals to compounds that have related biological mechanisms should be discussed. If animal models are of limited relevance due to the high species-specificity of a medicinal product, then the use of homologous proteins (i.e. surrogate antibodies) or relevant transgenic animals expressing the human protein should be considered.**	Redundant, see above. In part considered for the revised draft.
104-105 (BMS)	The relevance of any animal model to assess toxicology and pharmacology will vary for each investigational medicinal product. Animal models may in some cases have very limited relevance to humans thereby placing the burden of the human risk assessment onto the other criteria. Thus, the criteria based on the "limited relevance" of the animal model should be linked to other, perhaps more important considerations, such as the mode of action and/or nature of target. Propose adding the following: "If available animal models are of limited relevance to study properly the pharmacological and toxicological effects of the medicinal product, it should be considered as high-risk, <u>if in addition the mode of action and/or nature of target also place it in the high-risk category</u>."	True, this is now covered by the risk mitigation approach.
105 (AGAH)	In addition to the criteria "Mode of action", "Nature of the target" and "Relevance of animal models", there are more criteria that should be	In part considered for the revised guideline text (in part already covered).

	considered in the overall risk assessment of an investigational compound. Add: "Clinical implications of effect characteristics If during a first-in-man trial physiologic effects need to be monitored that cannot be adequately measured within a reasonable time frame, or if possible adverse reactions might occur with delay, the design of the phase-I study should be adapted accordingly. Special consideration should be given to the timely distance between two subsequent administrations and the number of subjects treated on a particular study day. High safety precautions should also be taken in a first-in-man study when adverse reactions are being monitored for which no causal therapy is available. In any case, a symptomatic treatment must be available."	
105 (PDA)	The use of the term "medicinal product" is not consistent. Rationale: Clarity. The guideline should be consistent with the wording used in the existing ICH guidelines. Suggestion: "medicinal product" is replaced by "drug product"	Redundant, see above.
105 (PDA)	Add "potential" before "high risk" Rationale: Clarity	Not relevant anymore.
105 (Drusafe)	It could be useful to provide some clarity on how to define whether a compound is not of high-risk.	Redundant, see above.
4.1 (Eucrof)	The guideline suggests, that there is a clear distinction between "high risk" medicinal products and others. It also suggests that these high risks are only applicable for first-in-man trials. This means that at the beginning the decision has to be taken, whether a drug is "high risk" or not. This absolute yes or no decision has to be taken by the agency. In reality all medicinal products may have specific risks which have to be considered in the preclinical evaluations, in the selection of subjects, in the study design and in the availability of general and specific medication and equipment to treat any emergency.	Redundant, see above.

	The focus of the guideline should be to minimize the risk of any phase 1 clinical trial. In principle so called “high-risk” medicinal products should be investigated in a manner that all resulting trials are “low risk”. For any medicinal product a specific assessment of any risk should be performed. The in vitro and in vivo pharmacologic investigations and the toxicology studies should be designed to define specific risks for any developmental compound. For instance in drugs acting on the cardiovascular system the focus should be on cardiovascular effects, compounds acting on the immune system effects in this system are most important. This also means that specific measures to avoid risk and to treat possible reactions have to be taken. The most important risk is probably, that the mode of action and/or the nature of the target are different in all animals investigated as compared to humans. In these cases the preclinical investigations have to include studies on human cell lines and transgenic models. In addition really minidoses have to be applied, based on MABEL and data on Exposure as assessed in the toxicokinetic studies. Different types of risks should be discussed and taken into account in the planning of clinical studies: - Immediately apparent risks versus delayed risks, - Reversible versus irreversible reactions, duration of possible reaction - Risks which can be easily identified and diagnosed versus risks which are difficult to identify and diagnose - Possible reactions easily treatable versus reactions difficult to treat - Reactions with (severe) discomfort versus reactions changing vital functions of organs. The points in chapter 4.1 should be considered in any development, not only in “high risk” products. The term “high risk” should not suggest white and black. The aim should not only be to generally define “high Risk” or “low Risk” but to identify specifically risks and provide measures to limit these.	(not entirely agreed, since adverse events are in many cases not restricted to the target organ system) Considered for the revised guideline text.

	Other comments: Definition of potential high-risk investigational medicinal products. Is there an overlap between "Mode of action" (line 78) and "Nature of the target" (line 92) ? Maybe this can be rewritten as one bullet.	
4.2 Quality Aspects		
106 (ICO)	It is not clear to me what should not be considered a high risk new drug Add examples of new drugs considered non high risk	No longer relevant with change to guideline scope.
106-142 4.2 (AGAH)	This section may be too comprehensive. Some of the "usual" quality requirements are also mentioned therein. That section should be streamlined. Focus on the special requirements that have to be observed for high-risk medicinal products. See comment to line 15.	Not accepted – attention is given to particular aspects important for a risk assessment.
107-108 (EFPIA)	We agree with the statement "*The requirements for high-risk medicinal products regarding the physico-chemical characterisation and, additionally biological characterisation of biological products, are not different from any medicinal products.*" Therefore the quality section that follows should not imply that a higher standard of characterisation and method development should be applied to qualify a so called 'high-risk medicinal product' for a first- in- man clinical trial than what is performed for "non-high risk" drugs. Apply this to the quality sections by inserting this statement at line 109. "***The guidance provided in the Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigation Medicinal Products in Clinical Trials (CHMP/QWP/185401/2004) should be appropriate for assuring the quality of all IMPs for first -in -human clinical trials."***	Section modified and clear reference to guidance on investigational products is added.
107-108 (ABPI)	"*The requirements for high-risk medicinal products regarding the physico-chemical characterization and, additionally biological*	See above.

	characterization of biological products, are not different from any medicinal products." We agree with this statement, and therefore the quality section that follows should not imply that a higher standard of characterization and method development should be applied to qualify a high risk drug for an FIH study than what is performed for "non-high risk" drugs. Apply this to the quality sections by inserting this statement at line 109. "The guidance provided in the Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigation Medicinal Products in Clinical Trials (CHMP/QWP/185401/2004) should be appropriate for assuring quality of high-risk IMPs."	
107-108 (BIA)	We agree with the statement that the requirements for high-risk medicinal products regarding the physico-chemical and biological characterisation of biological products are not different from any medicinal products. Therefore it is of importance that this section should not imply that a higher standard of characterisation and method development should be applied to qualify a high-risk drug product for an FIM study than what is performed for non-high risk drug products. Add at line 109: **Whilst it applies principally to chemically defined substances, the general principles set out in the Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigation Medicinal Products in Clinical Trials (CHMP/QWP/185401/2004) are nevertheless appropriate for assuring quality of high-risk IMPs irrespective of their mode of manufacture. For biological products intended for clinical investigation, regard should be given to the established principles, where appropriate, set out in the various guidelines adopted by ICH and the CHMP.**	See above
107-142	**Quality Aspects**	See above

(Takeda)	Regulatory requirements with regard to quality and characterisation of the medicinal product should be aligned with – but not exceed – ICH S3.	
107-142 (BIO)	We agree with the statement "*The requirements for high-risk medicinal products regarding the physico-chemical characterization and, additionally biological characterization of biological products, are not different from any medicinal products.*" Therefore the quality section that follows should not imply that a higher standard of characterization and method development should be applied to qualify a high risk drug for an FIH study than that applied to "non-high risk" drugs. There may be some confusion about whether the guideline is suggesting that the exact clinical formulation, and not just the active pharmaceutical ingredient (API), be required for the "pivotal" animal studies to support FIH. It should be made clear that use of a comparable API is still acceptable.	See above
109 (IPOPI)	Quality of a medicinal product should never be allowed to be a high risk and if there is concern for its quality, one should not go ahead.	Agreed. This was not the intention and has now been reworded.
111 (EFGCP)	…insufficient knowledge for entirely novel types… Again, the Guideline lacks clear-cut standards for decision-making in an environment where many stakeholders have to make joint decisions. The word "insufficient" is used here without any reference point. There needs to be a judge of what is sufficient and what is insufficient. If this is not done, the Guideline will spread among stakeholders a fear of taking responsibilities, which will lead to Phase I being transferred outside the EU territory of applicability of the Guideline. The word "entirely" novel is equally misleading, as no reference point is offered on which all parties can agree.	Deleted.
111 (AMGEN)	The example uses insufficient knowledge of a novel product or process as a possible rationale for a product being "higher risk". The term insufficient knowledge lends itself to inconsistent interpretation. Furthermore, the example does not give direction regarding "sufficient" knowledge.	See above

	Delete line 111 from “e.g.” to the end of the sentence, including line 112	
111 (EBE)	The example uses insufficient knowledge of a novel product or process as a possible rationale for a product being “higher risk”. The term insufficient knowledge lends itself to inconsistent interpretation. Furthermore, the example does not give direction regarding “sufficient” knowledge. Delete line 111 from “e.g.” to the end of the sentence, including line 112	See above
111 (EFPIA)	The example uses insufficient knowledge of a novel product or process as a possible rationale for a product being “higher risk”. The term ‘insufficient knowledge’ lends itself to inconsistent interpretation. In particular it is not clear what is intended by ‘novel types of manufacturing processes (Does this refer specifically to the use of transgenic animals and crops to manufacture the medicinal product?). Furthermore, the example does not give direction of what “sufficient” knowledge is. Delete line 111 from “e.g.” to the end of the sentence, including line 112.	See above
111 (Drusafe)	The example uses insufficient knowledge of a novel product or process as a possible rationale for a product being “high risk”. The term insufficient knowledge lends itself to inconsistent interpretation. Furthermore, the example does not give direction of what “sufficient” knowledge is. Delete line 111 from “e.g.” to the end of the sentence, including line 112.	See above
111	…insufficient knowledge for entirely novel types…	See above

(ECRIN)	Again, the Guideline lacks clear-cut standards for decision-making in an environment where many stakeholders have to make joint decisions. The word "insufficient" is used here without any reference point. There needs to be a judge of what is sufficient and what is insufficient. If this is not done, the Guideline will spread among stakeholders a fear of taking responsibilities, which will lead to Phase I being transferred outside the EU territory of applicability of the Guideline. The word "entirely" novel is equally misleading, as no reference point is offered on which all parties can agree. However, it may be hard to provide in such a general guideline; a suggestion of guideline modules covering specific interventions plus a generic guideline could be eventually a solution.	
111 (EuropaBio)	The example uses insufficient knowledge of a novel product or process as a possible rationale for a product being "higher risk". The term insufficient knowledge lends itself to inconsistent interpretation. Furthermore, the example does not give direction regarding "sufficient" knowledge. Delete line 111 from "e.g." to the end of the sentence, including line 112.	See above
111-112 (BIA)	"Insufficient knowledge" lends itself to inconsistent interpretation. Furthermore, it is unclear of what is intended by novel types of manufacturing processes.	See above
112 (PDA)	Delete "or for entirely novel types of manufacturing processes". Rationale: the novelty of the manufacturing process is not necessarily causing a potentially high-risk product	See above
114 (EBE)	One may add a statement related to the argument on the reliability of very small doses (cf. line 137 ff): High-quality characterization may be difficult in cases where highly diluted formulations have to be applied as a consequence of adhering to the MABEL rule.	Text on characterisation has been modified.
114-119	One may add a statement related to the argument on the reliability of very small doses (cf. line 137 - 142): High-quality characterization may	See above

(Roche)	be difficult in cases where highly diluted formulations have to be applied as a consequence of adhering to the MABEL rule.	
115 (MSD)	"It is important to have reached a high degree of quality characterisation" Merck agrees that it is important to characterise the medicinal product, however it should be noted that in the early stages of development only a limited number of batches will have been generated thus the characterization assays will be very product specific and rely only on a small data set and thus the range in specifications may be wide. In addition, manufacturing changes will most likely occur and possible changes such as clone selection and cell line changes in the production of biological medicinal products may affect the product characterisation. The "high degree" of quality may be difficult to define in the early stage of a FIM product and must be put in the appropriate perspective.	See above
115 (EFPIA)	We agree that it is important to characterise the medicinal product, however it should be noted that in the early stages of development only a limited number of batches will have been generated thus the characterisation assays will be very product specific and rely only on a small data set and thus the range in specifications may be wide. The "high degree" of quality may be difficult to define in the early stage of a FIM product and must be put in the appropriate perspective.	See above
115 (PDA)	Change: “high degree” Rationale: Clarity – original wording is amorphous and open. An adequate level	See above
115-116 (EFPIA)	The amount of detailed information on breakdown products and heterogeneity may be limited at this stage of development. A full characterization of product related variants is usually performed only in phase 2/3 and often rather difficult because of missing data on long-term degradation products and stability. Furthermore, it is extremely difficult to characterise product-related variants, including heterogeneity and degradation products that may	See above

	have an impact on the pharmacological profile of the molecule and it may not be possible prior to MAA filing. It would be impractical to generate enough of a variant to try to characterize whether there is an effect on PD (and with the variability seen in animal models, it is unlikely to show an effect) The degree of detail required on these aspects should not be such that progress is unreasonably slowed. *"To have reached an **appropriate** degree of quality… .An initial search for and characterisation of …"* *"A characterisation of product-related ~~variants~~ **impurities**, including heterogeneity and degradation products ~~that may have an impact on the pharmacological profile~~ of the molecule should be performed **as far as reasonable and practical at this stage of development**."*	
115-119 (ABPI)	It is extremely difficult to characterise product-related variants, including heterogeneity and degradation products that may have an impact on the pharmacological profile of the molecule; especially at this stage of development and it may not be possible prior to BLA filing. It would be impractical to generate enough of a variant to try to characterize whether there is an effect on PD (and with the variability seen in animal models, it is unlikely to show an effect). "A characterisation of product-related variants, including heterogeneity and degradation products of the molecule should be performed."	See above
116-117 (AMGEN)	It is extremely difficult to characterise product-related variants, including heterogeneity and degradation products that may have an impact on the pharmacological profile of the molecule; especially at this stage of development and it may not be possible prior to Marketing Authorization Application (MAA) filing. It would be impractical to generate enough of a variant to try to characterize whether there is an effect on PD (and with the variability seen in animal models, it is unlikely to show an effect).	See above

	Add the words: *"A characterisation of product-related variants, including heterogeneity and degradation products of the molecule should be performed."*	
116-117 (EBE)	It is extremely difficult to characterise product-related variants, including heterogeneity and degradation products that may have an impact on the pharmacological profile of the molecule; especially at this stage of development and it may not be possible prior to Marketing Authorization Application (MAA) filing. It would be impractical to generate enough of a variant to try to characterize whether there is an effect on PD (and with the variability seen in animal models, it is unlikely to show an effect). Add the words: *"A characterisation of product-related variants, including heterogeneity and degradation products of the molecule should be performed."*	See above
116-117 (MP)	Regarding Section 4.2 Quality Aspects – Characterization, the guidelines states: *"A characterization of product-related variants, including heterogeneity and degradation products that may have an impact on pharmacological profile of the molecule should be performed."* The amount of chemical and physical characterization that would be required to adhere to this request does not typically occur in early development. We consider this to be an onerous task for a compound that has not yet been dosed in humans. Please consider early development situations with regard to characterization.	See above

116-117 (PDA)	Delete: A characterisation of product-related variants, including heterogeneity and degradation products, that may have an impact on the pharmacological profile of the molecule should be performed. Rationale: This is requiring a knowledge that the ICH Quality guidances Q1 and Q4 are only expecting for a drug product that is fully developed. This characterisation might not be possible at this early stage of development. It is suggested to encourage the use of a risk management approach instead.	See above
116-117 (Drusafe)	We recommend clarification regarding product variants. *We recommend revising: "A characterisation of product-related variants, including heterogeneity and degradation products of the molecule should be performed."*	See above
116-117 (BIO)	It is very difficult to characterise all major product-related variants, including heterogeneity and degradation products that "may have an impact on the pharmacological profile of the molecule", especially at this early stage of development. It would not be practical and there would be limited value to manufacture these variants for pharmacodynamic (PD) and toxicity characterization. We suggest the alternate wording "A characterisation of product-related variants, including heterogeneity and degradation products of the molecule, should be performed."	See above
116-117 (EuropaBio)	It is extremely difficult to characterise product-related variants, including heterogeneity and degradation products that may have an impact on the pharmacological profile of the molecule; especially at this stage of development and it may not be possible prior to Marketing Authorization Application (MAA) filing. It would be impractical to generate enough of a variant to try to characterize whether there is an effect on PD (and with the variability seen in animal models, it is unlikely to show an effect).	See above

	Add the words: *"A characterisation of product-related variants, including heterogeneity* *and degradation products of the molecule should be performed."*	
116-118 (BIA)	Information on the relationship of product-related impurities to the pharmacological effects of the product is only obtained when greater experience of the characteristics of the product and its effects in man has been gained than could be available at the time of proceeding into first-in-man clinical trials. We propose that the sentence at line 116 is revised: **A characterisation of the product including its heterogeneity and degradation profile should be performed.**	See above
117 (EBE)	*"…product-related variants… that may have an impact on…"* It should be clarified by examples which process- or product-related variants are considered to have a potential impact on the pharmacological profile.	This would be case-by-case and this proposal was not followed.
117 (Roche)	*"…product-related variants… that may have an impact on…"* It should be clarified by examples which process- or product-related variants are considered to have a potential impact on the pharmacological profile.	See above
118 (AMGEN)	Clarification is requested regarding the statement "Special consideration should be given to the suitability and qualification of methods to sufficiently characterize the active substance and drug product." Change sentence to: *"It is expected that analytical methods are demonstrated to be suitable for their intended purpose."*	Proposal not accepted as it is less comprehensive.

118 (EBE)	Clarification is requested regarding the statement *"Special consideration should be given to the suitability and qualification of methods to sufficiently characterize the active substance and drug product."* Change sentence to: *"It is expected that analytical methods are demonstrated to be suitable for their intended purpose."*	See above
118 (PDA)	Add "analytical" before "methods." Rationale: Clarity "analytical methods"	Not needed.
118 (Drusafe)	Clarification is requested regarding the statement "Special consideration should be given to the suitability and qualification of methods to sufficiently characterize the active substance and drug product." Change sentence to: It is expected that analytical methods are demonstrated to be suitable for their intended purpose.	See above
118 (BIO)	Clarification is requested regarding the statement "Special consideration should be given to the suitability and qualification of methods to sufficiently characterize the active substance and drug product." We suggest the alternate wording "It is expected that analytical methods are demonstrated to be suitable for their intended purpose."	See above
118 (EuropaBio)	Clarification is requested regarding the statement "Special consideration should be given to the suitability and qualification of methods to sufficiently characterize the active substance and drug product."	See above

	Change sentence to: *"It is expected that analytical methods are demonstrated to be suitable for their intended purpose."*	
118-119 (PDA)	Change: "sufficiently" Change: "active" After: "……drug product add text as shown Rationale: Clarity and consistency; the term "drug product" is used here correctly and should stay in the ICH terminology, hence use drug product thereafter. Adequately characterise the……. Drug substance…… Add: "at this stage of development."	Text is consistent with European terminology and was not changed.
118-119 & 123 (EFPIA)	It is not clear whether the expectations for "qualification of methods" and "potency of the product needs to be relevant, reliable and **qualified**" are higher for so called 'high -risk IMP' than for non-high-risk IMPs. The guidance provided in the Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigation Medicinal Products in Clinical Trials (CHMP/QWP/185401/2004) should be appropriate for assuring quality of high-risk IMPs. (In this guidance, 2.2.1.S.4.3. states that the suitability of analytical methods acceptance limits and parameters (specificity, linearity, range, accuracy, precision, quantification and detection limit) should be presented). Drug product is typically not evaluated under Characterisation (Section 3.1 Elucidation of Structure).	Text has been revised to clarify further.

	Replace lines 118-119 with the following: "***Consideration should be given to the suitability of analytical methods to sufficiently characterise the active substance, in line with guidance provided in the "Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigation Medicinal Products in Clinical Trials (CHMP/QWP/185401/2004)."*** Suggest deleting drug product.	
118-119 (BIA)	Please clarify what is meant by "special consideration" for assessment of suitability of methods to characterise the product. The methods should be suitable for their intended use.	See above
118-119&123 (ABPI)	It is not clear whether the expectations for "qualification of methods" and "potency of the product needs to be relevant, reliable and **qualified**" are higher than for non-high-risk IMPs. The guidance provided in the Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigation Medicinal Products in Clinical Trials (CHMP/QWP/185401/2004) should be appropriate for assuring quality of high-risk IMPs. (In this guidance, 2.2.1.S.4.3. states that the suitability of analytical methods acceptance limits and parameters (specificity, linearity, range, accuracy, precision, quantification and detection limit) should be presented) Drug product is typically is not evaluated under Characterization (Section 3.1 Elucidation of Structure). Replace lines 118-119 with the following: "Consideration should be given to the suitability of analytical methods to sufficiently characterise the active substance, in line with guidance provided in the "Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigation Medicinal Products in Clinical Trials (CHMP/QWP/185401/2004)." Suggest deleting drug product.	See above

120 (MSD)	It should be noted that in the early stages of development of a biological medicinal product the mode of action is not always known**.** We propose that the potency assay be a biologically relevant assay and not required to address specifically the mode of action unless it is known.	In the majority of cases the mode of action is known or postulated.
121-123 Cancer Research	What does strength mean in this context if not potency?	Strength is used for chemical assays, potency for biological assays.
121-123 (ICAPI)	*4.2 Quality aspects: Determination of strength and potency* Where animal tests are used to determine strength or potency, they should have undergone a formal validation and regulatory approval process. This process is required for new tests for chemicals (OECD Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment, 2005, ENV/JM/MONO(2005)14); and a similar process has long been recommended by ECVAM and followed during the development of non-animal assays (see e.g. Alt Lab Anim 1995, 23:129-147). Animal tests for potency or strength that have not undergone a successful validation study cannot and should not be relied upon.	There is a misunderstanding that the text is recommending whole animal tests. The text has been reworded.
121-123 (RS-LTD)	The sentence implies that potency is not always required. Since majority of high-risk products is expected being of biological nature, NDA suggests to change the wording in order to make clear that potency is a required test parameter. For any exceptions which are expected occurring rather rarely, the applicant can justify the omission of the potency assay. In order to determine a safe starting dose of a high-risk medicinal product, the methods used for determination of the strength and ~~(where appropriate and possible)~~ the potency of the product need to be relevant, reliable and qualified.	Guidance also covers chemicals and in this case it will normally be strength rather than potency.

121-124 (PDA)	Change text as shown and delete "and/or validated" Rationale: Clarity and consistency: the term "drug product" is used here correctly and should stay in the ICH terminology, hence use drug product thereafter. ……..the methods used for determination of the strength and (where appropriate and possible) the potency of the drug substance / drug product need to be appropriately qualified bearing in mind the stage of development.	European terminology has been retained.
122 (WP)	The determination of "strength" is typically attributed to small molecules. It is expected that the majority of high-risk medical products will be biologics where potency is determined. To better clarify that the determination of both strength (small molecules) and potency (biologicals) are not required for each high-risk medicinal product, we recommend that that text be revised to prevent ambiguity (i.e., revise "and" to "or"). We recommend that the statement, *"In order to determine a safe starting dose of a high-risk medicinal product, the methods used for determination of the strength and (where appropriate and possible) the potency of the product…."* be revised to: *"In order to determine a safe starting dose of a high-risk medicinal product, the methods used for determination of the strength ~~and~~ or (where appropriate and possible) the potency of the product…."*	And/or has been used in the revised text.
122 (EFPIA)	The determination of "strength" is typically attributed to small molecules. It is expected that the majority of high-risk medical products will be biologics where potency is determined. To better clarify that the determination of both strength (small molecules) and potency (biologicals) are not required for each high-risk medicinal product, we recommend that that text be revised to prevent ambiguity	See above

	Recommend change '*and*' to '*and**/or'***	
122 (EuropaBio)	For potency of the molecule, this is typically assessed in a cell-based potency assay. The wording implies that the potency assay should be an in vivo assay which is not practical or relevant, reliable or qualified. In addition, a potency range for a bioassay of 50% to 150% has been accepted by regulatory agencies. This is a very reasonable range for these types of assays that may have CVs of 20%. Add the words: *"..the methods used for determination of strength and (where appropriate and possible) the potency of the product need to be relevant, reliable and qualified. For a cell-based potency assay, a range of 50% to 150% is generally acceptable."* *"For a biological medicinal product, the lack of a cell-based potency assay should be fully justified."*	Text has been reworded to clarify this.
122-127 (AMGEN)	For potency of the molecule, this is typically assessed in a cell-based potency assay. The wording implies that the potency assay should be an in vivo assay which is not practical or relevant, reliable or qualified. In addition, a potency range for a bioassay of 50% to 150% has been accepted by regulatory agencies. This is a very reasonable range for these types of assays that may have CVs of 20%. Add the words: *"..the methods used for determination of strength and (where appropriate and possible) the potency of the product need to be relevant, reliable and qualified. For a cell-based potency assay, a range of 50% to 150% is generally acceptable."* *"For a biological medicinal product, the lack of a cell-based potency assay should be fully justified."*	See above. The definition of a range is unnecessary as it is already covered by the guidance that the assays should be appropriate and qualified.
122-127	For potency of the molecule, this is typically assessed in a cell-based potency assay. The wording implies that the potency assay should be	See above

(EBE)	an in vivo assay which is not practical or relevant, reliable or qualified. In addition, a potency range for a bioassay of 50% to 150% has been accepted by regulatory agencies. This is a very reasonable range for these types of assays that may have CVs of 20%. Add the words: *"..the methods used for determination of strength and (where appropriate and possible) the potency of the product need to be relevant, reliable and qualified. For a cell-based potency assay, a range of 50% to 150% is generally acceptable."* *"For a biological medicinal product, the lack of a cell-based potency assay should be fully justified."*	
122-127 (Drusafe)	Methods for assessing potency of the molecule should be clarified. *We recommend revising to"..the methods used for determination of strength and (where appropriate and possible) the potency of the product need to be relevant, reliable and qualified."* *"The lack of a cell-based potency assay should be fully justified."*	See above
122-127 (ABPI)	Strength can be confused with potency and concentration. For potency of the molecule, this is typically assessed in a cell-based potency assay. The wording implies that the potency assay should be an in vivo assay which is not practical or relevant, reliable or qualified. In addition, a potency range for a bioassay of 50% to 150% has been accepted by regulatory agencies. This is a very reasonable range for these types of assays that may have CVs of 20%. "..the methods used for determination of concentration and (where appropriate and possible) the potency of the product need to be relevant, reliable and qualified. For a cell-based potency assay, a range of 50% to 150% is generally acceptable." "For a biological medicinal product, the lack of a cell-based potency assay should be fully justified."	See above

122-127 (BIO)	Potency of the molecule is typically assessed in a cell-based potency assay. The wording here implies that the potency assay should be an *in vivo* assay, which is not always practical or relevant, reliable or qualified. A potency range based on pharmacological and statistical fundamentals should be justified for each bioassay. We suggest the additional text "A potency range based on pharmacological and statistical fundamentals should be justified for each bioassay." We also suggest the alternate wording "For a biological medicinal product, the lack of a cell-based potency assay should be fully justified."	See above
125-127 (EFPIA)	**It is not always possible to have an adequate potency assay prior to phase I, since the mode of action in humans may not be sufficiently known. Therefore, full justification is difficult.** The expected mechanism of action typically drives the development of the bioassay versus in-vivo activity. Edit sentence with: *"For a **biologically-derived** medicinal product, **the need for a relevant bioassay based on the mechanism of action is typically expected. The lack of a relevant bioassay should be appropriately justified."***	See above
126-127 (Drusafe)	Why are 'biological medicinal products' singled out? Justification of the lack of a potency assay should be provided regardless of the type of compound. Remove the phrase '*For a biological medicinal product.*	Chemical substances typically do not require a bioassay as a chemical assay is sufficient.
126-127 (ABPI)	The expected mechanism of action typically drives the development of the bioassay versus in-vivo activity. Edit sentence with: "For a biologically-derived medicinal product, the	See above

	need for a relevant bioassay based on the mechanism of action is typically expected."	
126-127 (BIA)	The wording implies that the potency assay should be an in vivo assay which is not practical or relevant, reliable or qualified. The recommendation made here should be consistent with that provided in ICH Q6B. We suggest rewording as follows: **For a biological medicinal product, the lack of a bioassay measuring the functional or biological activity should be justified.**	See above
128-236 (BMS)	Reference is made to subtle changes which may not be detectable and a possible need for "some further non-clinical studies". Flexible access to scientific advice would be useful. Suggest adding a cross-reference to an appropriate source of scientific advice on these sorts of Quality issues.	Scientific advice is possible for all aspects of development and a specific reference here is not, therefore, needed.
130 (CAG)	Please add "and/or living materials" to underscore the particular concerns in the quality replication of biotech materials	The majority of biologicals covered by this guidance will not be living materials.
130 (Anapharm)	with respect to subtle changes to the molecular structure that can be generated by modifications in the manufacturing process, we believe that the single emphasis on complex molecules alone may introduce a deceitful insurance towards small molecules, as the later may just as well be affected by these changes although with different manifestations (e.g. new impurities may occur or the purity profile may be altered).	Text modified to take this into account.
131 (EFPIA)	Sentence should include the type of **characterisation** studies. Add: "***physico-chemical, biochemical or potency*****"** before *"characterisation studies"*	Not needed.
132 (EFPIA)	The statement about binding characteristics is not clear as characterisation studies usually include *in vitro* binding studies	Reworded.
131-132	"Subtle" changes to the primary sequence or posttranslational	Reworded.

(WP)	modifications of a biological medicinal product are easily detectable with the modern analytical technologies. However, "subtle" (i.e., local) changes to protein folding cannot be currently ascertained through product characterization, short of x-ray crystallography (which may also miss mobile regions), nor have subtle changes been demonstrated to result from a manufacturing process change. We recommend that the statement, *"…result in subtle changes to the molecular structure that may not be detectable from characterisation studies but can affect binding…"* be revised to *"…result in ~~subtle~~ changes to the molecular structure that can affect binding…"*	
131-132 (EFPIA)	**"Subtle" changes to the primary sequence or posttranslational modifications of a biological medicinal product are easily detectable with the modern analytical technologies.** However, "subtle" (i.e., local) changes to protein folding cannot be currently ascertained through product characterization, short of x-ray crystallography (which may also miss mobile regions), nor have subtle changes been demonstrated to result from a manufacturing process change.	See above
133-134 (EMPT)	It is impossible to know whether non-clinical data are valid until the medicinal product goes into humans. "One of the major challenges facing the drug discovery community is the limitation and poor predictability of animal-based strategies." Dr M. G. Palfreyman, Dr V. Charles and J. Blander, The importance of using human-based models in gene and drug discovery, *Drug Discovery World*, Autumn 2002, p.33-40. "It is impossible to give reliable general rules for the validity of extrapolation from one species to another. [This] can often only be verified after the first trials in the target species [humans]. Extrapolation from animal models. . . will always remain a matter of hindsight." The *Handbook of Laboratory Animal Science* Vol. II, p6, 1994. Given this fact, which has been known for many years (see quotes above), the most appropriate & relevant pre-clinical tests should be	This is a general comment on the guideline.

	used, making use of human tissues, computer models, toxicogenomics & pharmacogenomics, and culminating in microdosing trials.	
133-134 (PDA)	Change: "valid" Rationale: clarity. At this stage of development a true and valid result cannot be obtained. Relevant	
133-136 Cancer Research	Does this apply to all non-clinical studies or just GLP safety studies? Efficacy studies in early research are often performed using small quantities of poorly characterised material and showing comparability to GMP material may be impractical. Given the fact that major clinical decisions are based on the non-clinical data, it is important to show that the pivotal non-clinical safety data are still valid.	Not accepted. The context of the guideline is that all relevant non-clinical data needs to be considered in the risk-assessment.
134-135 (ABPI)	Bioassay can provide verification that the binding characteristics and other biological properties are not affected. In some cases, the nonclinical material may have a higher level of impurities than the clinical material, and is therefore not always comparable to clinical material in the strictest sense. However, the nonclinical material does qualify the safety of the clinical material. Edit sentence with "Where there are differences and product characterisation and bioassay cannot fully assure that the clinical product is safe, some…."	Text has been edited to take account of this comment.
134-135 (BIA)	Bioassays would be expected to detect differences in binding characteristics and other biological properties. Such assays would typically be included in the package of characterisation performed to assess comparability of non-clinical and clinical material.	See above

	We suggest editing as follows: Where there are differences and product characterisation **including those based on a bioassay** cannot fully assure that the product is comparable, some further …	
134-136 (EBE)	*"Where there are differences and product characterisation cannot fully assure that the product is comparable, some further non-clinical studies may be needed with the product intended for use in the first in-man trial."* Where the non-clinical programme is primarily based on the use of homologous proteins such requirement cannot be fulfilled. We therefore recommend to delete the sentence. Delete the sentence: *"Where there are differences and product characterisation cannot fully assure that the product is comparable, some further non-clinical studies may be needed with the product intended for use in the first-in-man trial." may be needed with the product intended for use in the first-in-man trial."*	Not accepted.
134-136 (EBE)	The first half of the very last sentence starting " *Where there are differences and product characterisation cannot ensure*…" may be misleading and should be reworded. The emphasis at this stage of development is not to ensure comparability of product characteristics but to provide sufficient assurance that product differences, should they occur, do not have an impact on clinical characteristics of the product, especially safety. Suggest to reword, e.g., as follows: "*Where there are differences in the product quality attributes and the sponsor cannot exclude clinical consequences resulting from such differences*, some further non-clinical studies may be needed with the product intended for use in the first-in-man trial."	Text has been reworded to take account of this comment.
134-136	We especially agree with the recommendation in this sentence.	No action needed.

(J&J)	None	
134-136 (EFPIA)	The first half of the very last sentence starting " Where there are differences and product characterisation cannot ensure…" may be misleading and should be reworded. In some cases, the non-clinical material may have a higher level of impurities than the clinical material, and is therefore not always comparable to clinical material in the strictest sense. However, the non-clinical material does qualify the safety of the clinical material. The emphasis at this stage of development is not to ensure comparability of product characteristics but to provide sufficient assurance that product differences, should they occur, do not have an impact on clinical characteristics of the product, especially safety. Bioassay can provide verification that the binding characteristics and other biological properties are not affected. Also please delete the word "some" Suggest to reword, e.g., as follows*: "Where there are differences* ***in the product quality attributes*** *and product characterisation* ***and bioassay*** *cannot fully assure that the product is comparable* ***clinical consequences may result from*** *such differences,* ~~*some*~~ *further non-clinical studies may be needed with the product intended for use in the first-in-man trial."*	Text has been reworded to take account of this comment.
134-136 (Roche)	The first half of the very last sentence starting " Where there are differences and product characterisation cannot ensure…" may be misleading and should be reworded. The emphasis at this stage of development is not to ensure comparability of product characteristics but to provide sufficient assurance that product differences, should they occur, do not have an impact on clinical characteristics of the product, especially safety. Suggest to reword, e.g., as follows: "*Where there are differences in the product quality attributes and the sponsor cannot exclude clinical consequences resulting from such differences,* some further non-clinical studies may be needed with the product intended for use in the first-in-	See above

	man trial."	
137-142 FRAME	Adsorption can be prevented. The CHMP should define very small doses and indicate whether they are referring to sub-micro-dose levels. With regards micro-dose-based Exploratory Investigational New Drug early phase 1 trials, the CHMP should consider FDA/CDER documentation and provide comments on whether micro-dose studies, at say $1/00^{th}$ of the calculated safe starting dose, would be useful with regards reducing the risk posed by IMPs. The possibility that very small doses may lead to hormesis effects. For example, biological effects that are higher or different from those elicited by higher doses such as those in the pharmacologically active range and that result in either J or U-shaped dose-response curves. Such effects can be equally important to assess during preclinical studies in animals (e.g. to monitor endocrine disruption). Methods to limit adsorption are available and the concentration of a preparation should be confirmed where possible using analytical techniques. [A definition of very low dose should be included] The possibility of hormesis effects should be considered during preclinical studies in animals. In the absence of these effects, early phase 1 trials in healthy volunteers may involve administration of micro-doses.	The guidance is not referring to sub-micro-dose levels and the comment has not been accepted.
137-142 (ABPI)	This section seems to be seeking confirmatory analysis of the actual dosing solution concentration without actually stating that. If that is what is intended, it should be stated clearly. Add “Dosing solution concentration should be accurately documented.”	Text considered to be clear.
138-140 (PDA)	Change: “provides correct dosing”	Text modified.

	Rationale: Clarity Provides the intended dose	
139 (EBE)	"Correct dosing" *should be more appropriately defined. It also needs to be taken into account that –given the outlined low doses- the physico-chemical stability can no longer be determined properly, only potential losses due to adsorption.*	Partly modified, see above.
139 (Roche)	Correct dosing should be more appropriately defined. It also needs to be taken into account that –given the outlined low doses- the physico-chemical stability can no longer be determined properly, only potential losses due to adsorption.	See above
4.2 (FCP)	Comparability with the material used in non-clinical studies, and Reliability of very small dose. Although we have no major disagreement with these 2 last chapters, we considered that they apply not only to potentially high-risk compounds but also to any medicinal products We wonder if it is necessary to keep these chapters that also apply for medicinal products without high risk.	Not accepted.
141-142 (EFPIA)	Clarify intent. Recommended changes to this sentence from *". . . over-estimation of the safety of the initial clinical doses and non-clinical data" to ".* ***. . over-estimation of the safety of the initial clinical doses and low doses and NOAELs in the non-clinical safety studies****."*	Not accepted.
4.2 (Eucrof)	The requirements regarding quality should be the same for all products. Also there specifications should be considered with regard to the possible risk.	Clarified in the introduction to the Quality section.
141-142 (ABPI)	Clarify intent.	Not accepted.

	Recommended changes to this sentence from ". . . over-estimation of the safety of the initial clinical doses and non-clinical data" to ". . . over-estimation of the safety of the initial clinical doses and low doses and NOAELs in the nonclincal safety studies."	
141-142 (BMS)	Over-estimation of actual dose given in animal studies is certainly possible, and should be considered carefully, but could also apply to actual dosing in man. Suggest adding a request to consider the comparability of the container and infusion systems (as well as the route of dosing) and discuss the implications of any differences on the expected delivered dose.	Text modified to take this into account.
4.3 Non-clinical requirements		
143 (MSD)	Merck proposes that the discussion of non-clinical requirements should be changed to two sections - one for drugs and one for biologics. As currently written, the document combines both in one section and attempts to point out the differences for biological products. As the non-clinical testing for therapeutic biological products is different from drugs, each should have its own non-clinical section to avoid confusion. Reference to S6 was made in the introduction but should also be referenced in the 'new' biotech section, as appropriate (to provide alignment with the ICH guidance).	Not accepted

143 (EFPIA)	Rename in line with quality section We propose that the discussion of non-clinical requirements should be changed to two sections - one for small molecule drugs and one for biologics. As currently written, the document combines both in one section and attempts to point out the differences for biological products. As the non-clinical testing for therapeutic biological products is different from small molecule drugs, each should have its own non-clinical section to avoid confusion. Reference to S6 was made in the introduction but should also be referenced in the 'new' biotech section, as appropriate (to provide alignment with the ICH guidance). *'4.3 Non-clinical ~~requirements~~* ***Aspects'***	Accepted
4.3 (Drusafe)	The discussion of non-clinical requirements should be changed to two sections – one for drugs and one for biologics. As currently written, the document combines both in one section and attempts to point out the differences for biological products. As the non-clinical testing for therapeutic biological products is different from drugs, each should have its own non-clinical section to avoid confusion. Reference to S6 was made in the introduction but should also be referenced in the 'new' biotech section, as appropriate (to provide alignment with the ICH guidance).	Not accepted
4.3 (Eucrof)	The investigations described are necessary to identify the risks of a developmental compound. It is certainly difficult to determine whether a compound is "high-risk" before these investigations are performed. The pre-clinical prove may be difficult due to unavailability of sufficient animal models. Most important is the demonstration of relevance of the animal models. In particular in biologics and specific human proteins preclinical investigations should include the use of transgenic animals and/or homologous proteins.	Text reformulated.

4.3.1 Pharmacodynamics		
(AREC)	Sponsors should be required to demonstrate clearly that pharmacodynamic and pharmacokinetic studies are consistent with the principles of GLP.	Not accepted
145 (MSD)	As stated above in regards to novel products there is sometimes limited knowledge of the mode of action. Suggest adding the word "potential" "Pharmacodyamics should address the **potential** mode of action"	Not accepted
145 (EFPIA)	Clarify intent. Recommended changes: substitute the word "***characterise***" for the word "*address*", or improve the sentence to "*Pharmacodynamic studies should* ***characterise the potential*** *mode of action and* ~~*provide evidence on the biology*~~ ***the biological responses of the target****."*	Not changed
145 (ABPI)	Clarify intent. Recommended changes: substitute the word "characterise" for the word "address", or improve the sentence to "Pharmacodynamic studies should characterize the mode of action and the biological responses of the target."	
145-158 4.3.1 (AGAH)	It is important to evaluate the variability of the response and to apply adequate models that allow an estimate of the effect size in humans.	See comments above (line 88)

	Refer to comments line 83 and 88	
145-147 (J&J)	Suggestion to rephrase: Pharmacodynamic studies should address the mode of action, and provide knowledge on the biology of the target. These data will help to characterise the pharmacological effects and to assess relevance of applied animal models.	Accepted
147 (MSD, EFPIA)	After Line 147, we propose to add a reference to conduct tissue cross reactivity studies to help select the relevant animal species. It is recommended that for a biological medicinal product, tissues cross reactivity studies are conducted to identify the most relevant animal species.	Considered in section 4.3.1
147 (RS-LTD)	Suggestion to insert The test conditions of these studies should be as physiologic as possible for the human situation.	Not included
148 (EACPT)	It seems appropriate to require full pharmacodynamic characterization of “high risk medicinal products” in more than one animal species. For high-risk medicinal products, it is particularly important to fully characterise the primary and secondary pharmacodynamics, in *in vitro* animal and human systems and *in vivo* in at least two chosen animal models.	Sentence reworded (not relevant)
148 (BIA)	The need for *in vivo* data in one or more animal models ought to be assessed on a case-by-case basis.	

148 (PDA)	Change “fully” Rationale: avoid absolutes, as they are impossible to achieve at this stage of development “adequately”	
148–150 (EBE)	*“For high risk medicinal products, it is particularly important to fully characterise the primary and secondary pharmacodynamics, in in vitro animal systems and in vivo in one or more chosen animal models”*. A “full” characterisation is dependent on the complexity of the mode of action and therefore not always possible. Even for authorised medicinal products, particularly for biological or biotechnological products, there is no “full” characterisation of the mode of action available. The systems and models clearly depend on their availability. This is particularly true for animals. The text of the guideline should reflect this appropriately. Change as follows: *“For high risk “medicinal products requiring special attention”, it is particularly important to fully characterise the primary and secondary pharmacodynamics, in in vitro animal systems and in vivo in one or more chosen appropriate animal models, where such models are available”*.	

148-150 (EFPIA)	With biologic agents, the in vivo pharmacology work is often done in rodents with a surrogate agent and not the human drug candidate. This is due to 1) the animal models are often in rodent and the human candidate does not cross react with the rodent molecular target and 2) the lack of established pharmacologic models in a cross reactive species. The draft implies that the establishment of in vivo pharmacodynamic models will be mandated which may not be possible. The use of well characterized surrogate biologic agents for the evaluation of biological response should be considered for biologic agents and thus criteria for comparison of the surrogate agent to the human drug candidate should be included in the document e.g. potency for the molecular target. Change "… it is particularly important to fully characterise the primary and secondary pharmacodynamics…" to *"… it is particularly important to **appropriately** characterise the primary and secondary pharmacodynamics…"*	
148-151 FRAME	The CHMP should consider, with worked examples, suitable strategies for resolving the following problems without increasing the demand for using animals: 1) only one species is of relevance to human safety and pharmacology studies, but only a limited number of animals can be feasibly used during preclinical studies (as is the case when non-human primates are used) 2) Studies in more than one species might be relevant but give equivocal results or unexplained inconsistencies and a decision has to be made as to which species is most relevant (e.g. testing of TGN1412 in rhesus and cynomolgus macaques and the preference for data from the latter and for TGN1412 than TGN1112). 3) The safe starting dose estimates from studies in different species are substantially different (rat and macaque values for	The guideline does not include examples. See above.

	TGN1412) Insert after line 151: The definition of a high risk medicinal product should be extended to include products where a) there is only one species suited to the preclinical evaluation of the product b) tests in two or more species give rise to inconsistencies in the data that cannot be resolved by weight of evidence approaches c) for practical or ethical reasons, only a small number of animals can be used in preclinical studies such that the statistical quality of the data is questionable and/or d) There is reliance on information for a species-equivalent product of the medicinal product .	Definition of high-risk removed
148-151 (Drusafe)	With biologic agents, the in vivo pharmacology work is often done in rodents with a surrogate agent and not the human drug candidate. This is due to 1) the animal models are often in rodent and the human candidate does not cross react with the rodent molecular target and 2) the lack of established pharmacologic models in a cross reactive species. The draft implies that the establishment of in vivo pharmacodynamic models will be mandated which may not be possible. The use of well characterized surrogate biologic agents for the evaluation of biological response should be considered for biologic agents and thus criteria for comparison of the surrogate agent to the human drug candidate should be included in the document e.g. potency for the molecular target.	Use of surrogate molecules are considered in the guideline

149-150 (BIO)	There should be clear guidance that *in vivo* data should only be generated in species that display relevant cross-reactivity. For example, misleading data will be generated in non-primate animal models when the only cross-reacting species is the non-human primate. For some products relevant pharmacodynamic parameters may only be available if a surrogate molecule is manufactured or from *in vitro* studies with human cells/tissues. The sponsor should justify the approach taken. We suggest that "chosen" be replaced with "relevant" (to read: "…in one or more relevant animal models…").	These principles are reflected in the text
149-150 (Centocor)	There should not be an insistence on producing in vivo data in animal models when the only cross-reacting species is the non-human primate. Relevant pharmacodynamic parameters may only be available for a surrogate molecule.	
150 (EFPIA)	If an IMP is defined as high-risk due to its human specificity (i.e. lack of relevant animal models) then by definition the PD profiling in an animal species is not relevant. The document seems a little inconsistent in this effect as it suggests in line 149 PD profiling in non-clinical species, and yet (in line 204) use of non-relevant species for toxicology is discouraged. The PD requirements for human-specific molecules should be clarified. For example, more emphasis could be given to human ex vivo / in vitro data than non-clinical data, especially when determining the starting dose in man. Many investigational compounds that fit into the 'high risk' category are likely to be monoclonal antibodies or other biologics that bind to soluble ligands and therefore this statement is not relevant for all compounds. Add a statement to address evaluation of the quantitative interaction of investigational compounds with soluble ligands. **Recommend change: *"These studies should include*** intended target interactions preferably linked to functional response (e.g***. receptor binding and occupancy*** *noting whether binding is to soluble ligand or receptor using in vitro, and where feasible ex or in vivo*)***, duration of effect, and dose response."***	Partially accepted. Sentence rephrased

150 (Drusafe)	Receptors are not primary targets of some pharmaceuticals. The wording implies that receptor occupancy data should always be included. Calculations of receptor occupancy in vivo are highly theoretical, and are sensitive to assumptions regarding total receptor concentration in tissue, receptor turnover, internalization and catabolism of drug by the receptor, and partitioning of drug to tissue. Receptor occupancy can usually only be calculated with reasonable accuracy for drugs targeting receptors on circulating blood cells. If an IMP is defined as high-risk due to its human specificity (i.e. lack of relevant animal models) then by definition the PD profiling in an animal species is not relevant. The document seems a little inconsistent in this effect as it suggests in line 149 PD profiling in preclinical species, and yet (in line 204) use of non-relevant species for toxicology is discouraged. The PD requirements for human-specific molecules should be clarified. For example, more emphasis could be given to human ex vivo / in vitro data than preclinical data, especially when determining the starting dose in man. Recommend change: “These studies should include intended target interactions (e.g. receptor binding and occupancy - in vitro, and where feasible ex or in vivo), duration of effect, and dose response."Add a statement to address evaluation of the quantitative **interaction of investigational compounds with soluble ligands.**	Partially accepted and reworded

150 (ABPI)	It should be indicated that receptor occupancy is not necessarily relevant for all targets (e.g. some enzymes and kinase inhibitors). If an IMP is defined as high-risk due to its human specificity (i.e. lack of relevant animal models) then by definition the PD profiling in an animal species is not relevant. The document seems a little inconsistent in this effect as it suggests in line 149 PD profiling in preclinical species, and yet (in line 204) use of non-relevant species for toxicology is discouraged. The PD requirements for human-specific molecules should be clarified. For example, more emphasis could be given to human ex vivo / in vitro data than preclinical data, especially when determining the starting dose in man. Where preclinical models do provide information with conserved target sequences, the effects of immunogenicity must be considered when evaluating experimental results. Recommend change: "These studies should include intended target interactions (e.g. receptor binding and occupancy – in vitro, and where feasible ex or in vivo) preferably linked to a functional response, duration of effect, and dose response." In cases where species specificity precludes assessments of in vivo pharmacodynamics, use of a homologous proteins (species specific surrogates of the product) may provide additional information. Immunogenicity to the medicinal product can impact the maximal effect and duration of effect observed in animals and this aspect should be considered.	
150 (BIO)	Receptor occupancy and binding should ideally be linked to a functional response. We suggest an expanded sentence to read: 'These studies should include receptor binding and occupancy (preferably linked to a functional response), duration of action of effect and dose response.'	

150-151 Cancer Research	This is written assuming all targets are reversibly bound receptors. The target may not be a receptor; the drug may bind terminally or it could be an enzyme substrate. These studies should include pharmacological characterisation of the medicinal product, including the duration of effect and dose-response.	
150-151 (BIO)	The statement 'should include receptor binding and occupancy' applies only to compounds that bind to cell receptors. Many investigational compounds that fit into the proposed 'high risk' category are likely to be monoclonal antibodies or other biologics that bind to soluble ligands and therefore this statement is not relevant for all compounds. Add a statement to address evaluation of the quantitative interaction of investigational compounds with soluble ligands. We suggest the alternate wording: 'These studies should include binding and occupancy (whether soluble ligand or receptor) duration of effect and dose-response'.	
150-151 (BIA)	It should be indicated that receptor occupancy is not necessarily relevant for all targets (e.g. monoclonals that bind to soluble ligands, some enzymes and kinase inhibitors). If an IMP is defined as high-risk due to its human specificity (i.e. a lack of relevant animal models) then by definition the PD profiling in an animal species will not be relevant. The PD requirements for human-specific molecules should be clarified. For example, more emphasis could be given to human ex vivo / in vitro data than preclinical animal data, especially when determining the starting dose in man. Also the effects of immunogenicity must be considered when evaluating experimental results. We suggest revising this paragraph as follows: **These studies should include the duration of the effect and dose-response with receptor occupancy or cell signalling as readouts for downstream effect. As immunogenicity to the medicinal product**	Not accepted

	can impact the maximal effect and duration of effect observed in animals, the immunogenic response to the product in pharmacodynamic studies should be assessed and considered when evaluating experimental results.	
151 (MSD)	After Line 151, it should be noted that evaluation of findings from non relevant animal species may be difficult to interpret and justification to conduct such studies needs to be supported. This is noted as a concern in section 4.3.3. Demonstration of relevance of the animal model.	Implicit in section 4.3.1 and partially reworded.
151 (AMGEN, EBE, Drusafe, EuropaBio)	Correlation of receptor occupancy and pharmacodynamic effect are both markers of downstream effect. It should be indicated that receptor occupancy is not necessarily relevant for all targets (e.g. some enzymes and kinase inhibitors). Also, species specificity may entirely preclude in vivo PD information from preclinical models. And where preclinical models do provide information with conserved target sequences, the effects of immunogenicity must be considered when evaluating experimental results. Change as follows: "*These studies should include the duration of the effect and dose-response with receptor occupancy or cell signalling as readouts for downstream effect.*" In cases where species specificity precludes assessments of in vivo pharmacodynamics, use of a homologous proteins (species specific surrogates of the product) may provide additional information. In all cases, immunogenicity to the medicinal product can impact the maximal effect and duration of effect observed in animals. Therefore, the immunogenic response to the product in pharmacodynamic studies should be assessed and considered when evaluating experimental results.	

151 (EFPIA)	It should be indicated that receptor occupancy is not necessarily relevant for all targets (e.g. some enzymes and kinase inhibitors). Also, species specificity may entirely preclude in vivo PD information from non-clinical models. And where non-clinical models do provide information with conserved target sequences, the effects of immunogenicity must be considered when evaluating experimental results. In cases where species specificity precludes assessments of in vivo pharmacodynamics, use of a homologous proteins (species specific surrogates of the product) may provide additional information. Suggest: "***As immunogenicity to the medicinal product can impact the maximal effect and duration of effect observed in animals (either directly or indirectly, by alteration of pharmacokinetic properties), the immunogenic response to the product in pharmacodynamic studies should be assessed*".**	

151 (BIO)	Receptor occupancy and pharmacodynamic effect are both markers of downstream effect. It should also be recognized that receptor occupancy is not necessarily relevant for all targets (e.g. some enzymes and kinase inhibitors). Species specificity may entirely preclude *in vivo* PD information from preclinical models. Where preclinical models do provide information with conserved target sequences, the effects of immunogenicity must be considered when evaluating experimental results. We suggest the alternate wording: "These studies should include the duration of the effect and dose-response, with receptor occupancy or cell signalling as markers of downstream effect." "In cases where species specificity precludes assessments of *in vivo* pharmacodynamics, use of a homologous protein (species specific surrogates of the product) may provide additional information." "In some cases, immunogenicity to the medicinal product can impact the maximal effect and duration of effect observed in animals. The immunogenic response to the product in definitive pharmacodynamic studies may add value to the interpretation of the experimental results, particularly if repeated dose administration is employed in these studies."	
151-152 (EFPIA)	The concentration effect relationship should be established and not just dose/effect. If these lines referred to concentration effect this would be very clear and section 4.3.2 could be deleted. Replace 'dose' with '**concentration'.**	Changed to dose/concentration

151-152 (Drusafe)	The concentration effect relationship should be established and not just dose/effect. If these lines referred to concentration effect this would be very clear and section 4.3.2 could be deleted. Replace '*dose*' with '*concentration*'.	
151-152 (BIO)	The concentration effect relationship should be established, not just dose/effect. These lines should refer to concentration effect (and then section 4.3.2 could be deleted). We suggest that 'dose' be replaced with 'concentration'.	
152 (ABPI)	We would prefer that the discussion focuses on dose/concentration/effect relationships with a clear statement up front that understanding dose/exposure/effect relationships and their potential difference between species is critical.	
154 (AGAH)	Put this in a more general way. Examples may be given. Replace "… *with U-shaped or bell-shaped dose-response*" by "… *which do not follow a clear and predictable dose-response relationship*".	Not changed
154 (EFPIA)	These shaped dose response curves are seen with small molecules. Delete sentence: 'Such distinct or even contrary effects have been reported with biologicals.'	Rephrased

154 (Drusafe)	We agree that U-shape dose-response may be of concern, but we do not believe that a bell-shaped dose-response, though of relevance to efficacy assessment, is of safety concern. Suggest delete '*bell-shaped*' in this sentence.	
154 (ABPI)	These shaped dose response curves are seen with small molecules Delete sentence: 'Such distinct or even contrary effects have been reported with biologicals.'	
154 (BIA)	Shaped dose response curves are seen with small molecules. Delete this sentence: Such distinct or even contrary effects have been reported with biologicals.	
154 & 82 (EFPIA)	Certain products can have paradoxical responses depending on the concentration. There is more than one reference to the U and bell shaped dose-responses, and whilst this is important to understand the dose range, it is also important to focus on the steepness of the dose-response. We agree that U-shape dose-response may be of concern, but we do not believe that a bell-shaped dose-response, though of relevance to efficacy assessment, is of safety concern. Add "***paradoxical dose responses, steepness of curve***"" after "U-shaped". Suggest delete 'bell-shaped' in this sentence	

154 & 82	Certain products can have paradoxical responses depending on the concentration. There is more than one reference to the U and bell shaped dose-responses, and whilst this is important to understand the dose range, it is also important to focus on the steepness of the dose-response. Add “paradoxical dose responses, steepness of curve”” after “bell shaped”.	
156 (EFPIA)	Clarify Suggested Change from *“Since a low dose is to be administered to humans in the First in man trial, this is of high importance” to “It is of high importance to study the pharmacological effects over the full dose range that is to be studied in the first in man trial, with a particular emphasis **on** studying the low dose that **is** to be i**nitially** administered to humans.”*	
157-158 (AMS)	This statement on GLP could be restrictive for academic studies.	Sentence clearly says the GLP compliance is not mandatory, but GLP principles should be followed
157-158 (EBE)	*“Although GLP compliance is not mandatory for pharmacodynamic and pharmacokinetic studies, they should be of high quality and consistent with the principles of GLP.”* This is felt to be contradictory. Change as follows: *“Although GLP compliance is not mandatory for pharmacodynamic and pharmacokinetic studies, they should be of high quality and consistent with the principles of GLP.”*	

157-158 (EBE)	Recommend rewording of sentence to remove reference to GLP. Add the words: *"The pharmacodynamic and pharmacokinetic studies should be of high quality."*	
157-158 (EFPIA)	The requirements of GLP are not applicable for pharmacological studies, since such flexible models are generally not validated according to GLP rules. Experiments should be performed according to good scientific practice. Remove second part of the sentence from *"… and consistent with …"* Replace "consistent with the principles of GLP" by *"consistent with good scientific practice"*. Alternatively wording in S7A – *' to the greatest extent feasible'* could be used.	
157-8 (IFAPP)	Compliance of PK/PD studies to GLP may establish more reliable background for planning human studies Suggest requesting GLP compliant studies for high-risk IMPs	
157-158 (MRC)	The MRC is of the view that the final sentence does not provide clear guidance as to the need for GLP in areas where it is not already mandatory. For academic units an assumption that GLP must be implemented for all pharmacodynamic and pharmacokinetic studies would be problematic and difficult to comply with. While the MRC accepts the importance of good practice in all areas of such studies the strict and specific requirements of GLP may not be proportionate for all research described in this section. The sentence is reworded to make clear what standards are applicable for research studies and inspection.	

157-158 (SPC)	4.3.1 Non-clinical requirements: pharmacodynamics The requirements for GLP-like studies in the drug discovery could potentially lower the amount of information available. The largest uncertainty in pharmacodynamic responses is tied to the translation of information across species and applicability of the measured unity to the human biology and target associated risk. Good scientific practices should be adhered to for those involved in drug discovery and development. GLP-like approach is unlikely to substantively reduce the overall uncertainties while consuming resource might be devoted to better delineating the animal and human biology.	
157-158 (EuropaBio)	Recommend rewording of sentence to remove reference to GLP. Add the words: *"The pharmacodynamic and pharmacokinetic studies should be of high quality."*	
158 (AGAH)	This is another interesting aspect. Add: "Special consideration will be given to pharmacodynamic effects or safety results in non-clinical studies that cannot be explained by the postulated mechanisms of action."	
158 (PDA)	Change text: …..they should be of high quality and consistent with the principles of GLP. Rationale: clarity, the intent is to focus on sound science. "……they should be in accordance with sound scientific principles. Elements of GLP could be incorporated into the conduct and documentation of these studies."	

158 (BIO)	It is important that pharmacokinetic (PK) and PD studies in these early stages of drug development are designed, conducted and analysed consistent with principles of Good Laboratory Practice(GLP). The term "high quality" is vague and impractical to define in these early stages of development and may be prone to misinterpretation, leading to impractical resource intensive studies that may not be informative or useful for the design of FIH studies. We suggest deletion of "of high quality and" because compliance with principles of GLP will sufficiently assure appropriate 'quality control' of the study.	
4.3.2 Pharmacokinetics		
159-162 (JPMA)	**Does "ICH S3" include not only S3A (Toxicokinetics) but also S3B (Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies)? If it does, and S3B applies to the profile of the medicinal product, do the sponsors need to conduct repeated dose tissue distribution study before first-in-man (not required by ICH-M3)? Since the title of this draft guideline is "requirements for first-in-man", this 4.3.2 section may be potentially confusing.** **According to ICH M3, the completion of all A, D, M and E studies is usually by the end of Ph 1 study, while this document for FIM requires earlier completion of the studies. In addition, ADME studies are not always conducted in all species used for *in vivo* studies.**	Sentence amended in line with cited guidelines

159-162 (EFPIA, Drusafe)	ICH S3, M3 and S6 Guidance documents do NOT require ADME studies in all species for first in man clinical trials. This is an incorrect reference. Typically, PK and TK data are available for each of the animal species employed in the safety assessment program, together with information on routes of metabolism in in vitro liver preparations from these species, as well as humans, to support the selection of the safety species. In addition, most sponsors typically provide preliminary data on the routes of elimination of the test compound in one animal species (normally the rat) to assess the primary mechanism of drug clearance in vivo, and also would have determined whether the compound had inductive or inhibitory effects on human cytochrome P450 isoforms. Finally, data from human cytochrome P450 phenotyping studies and plasma protein binding (human and safety species) make up the DMPK component of IND / IMPD packages. This data set would seem adequate to qualify both "high-risk" and "normal" new chemical entities prior to FIM studies. Requiring full ADME packages in all species used non-clinically would be extremely resource- intensive (including increased use of large animal species) and have an adverse impact on both ability and willingness to develop such therapies. In addition, by definition, data derived from non-clinical species for high-risk products would be less likely to have human relevance than similar data for "normal risk" products and likely would not improve the design of FIM studies. Distribution studies are seldom done in non-rodents at all during development and this will significantly increase non-rodent use with no value added to the safety profile. For many biotechnology-derived pharmaceuticals, classical ADME studies are not applicable and are considered irrelevant. Thus, such studies should not be recommended and the text should restrict a requirement for ADME studies only for species that are relevant and applicable and only at doses that are feasible for evaluation. Suggest the reference is corrected.	

159-162 (MP)	Regarding Section 4.3.2 – Pharmacokinetics, the guideline states: "*In addition to standard absorption, distribution, metabolism and elimination (ADME) requirements (see ICH S3, S6), which should be available in all species used for in vivo studies, exposures at pharmacological doses in the relevant animal models should be determined."* We believe that the pharmacokinetics and ADME requirements in this guideline are not consistent with ICH S6. According to UCH S6, pharmacokinetics and metabolism are mainly used to support preclinical safety for biotechnology-derived pharmaceuticals. The CHMP guideline specifically mentions "*comparison of pharmacokinetics", "ADME….in all species used for in vivo studies"*. Considering the nature of biologics, are these requirements necessary? We recommend the inclusion of additional information to clarify and provide a rationale for the differences between this guideline and ICH S6. In addition, we recommend the inclusion of a definition for comparable or relevant pharmacokinetics for biologics.	
160-162 Cancer Research	Are such studies really needed for all species used for *in vivo* studies or just the species used for the toxicology studies? In addition to standard absorption, distribution, metabolism and elimination (ADME) requirements (see ICH S3, S6), which should be available in all species used for in vivo safety studies, exposures at pharmacological doses in the relevant animal models should be determined	

160-162 (EBE)	With species-specific biologics, exposure in the animal model of disease with the clinical candidate may not be attained and thus exposure information comes from a surrogate molecule. The wording was changed to 'relevant animal species' to better determine exposure of the clinical candidate. In addition, the assay sensitivity for biologics (ELISA vs HPLC for small molecules) may not be sufficient to detect drug at the low end of the dose-response curve. Add the words: *"In addition to standard absorption, distribution, metabolism and elimination (ADME) requirements (see ICH S3, S6) which should be available in all species used for in vivo studies, exposures at pharmacological doses in the relevant animal species should be determined. Consideration should be given to the sensitivity of the assay for biologics, where a pharmacologic effect may be seen even in the absence of detectable drug. In these cases, exposure in the nonclinical studies may not be accurately assessed at the lowest end of the dose-response curve."*	

160-162 (EFPIA)	It should to be clarified that a complete ADME package, as implied by the use of the descriptive phrase in the draft guideline, is not required at this stage of development, but rather PK or TK data. ADME is not generally required for large proteins with limited distribution volumes. With species specific biologics, you may not be able to get exposure in the animal model of disease with the clinical candidate and thus the exposure information comes from a surrogate molecule. In addition, the assay sensitivity for biologics (ELISA vs HPLC for small molecules) may not be sufficient to detect drug at the low end of the dose-response curve. Change "standard absorption, distribution, metabolism and elimination (ADME)" to "***pharmacokinetic or toxicokinetic***". Suggest add sentence to end of paragraph: **'ADME is not generally required for large proteins with limited distribution volumes.** "Exposures at pharmacological doses in the relevant animal species should be determined **where possible**. ***Consideration should be given to the sensitivity of the assay for biologics, where a pharmacologic effect may be seen even in the absence of detectable drug. In these cases, exposure in the non-clinical studies may not be accurately assessed at the lowest end of the dose-response curve."***	
160-162 (ICAPI)	*4.3.2 Pharmacokinetics* A note should be provided regarding the usefulness of microdosing (phase 0 tests) in humans as a tool in determining pharmacokinetics in humans (See FDA Guidance for Industry, Investigators and Reviewers on IND studies, 2006).	

160-162 (ABPI)	It should to be clarified that a complete ADME package, as implied by the use of the descriptive phrase in the draft guideline, is not required at this stage of development, but rather PK or TK data. Also, ADME is not generally required for large proteins with limited distribution volumes. Change "standard absorption, distribution, metabolism and elimination (ADME)" to "pharmacokinetic or toxicokinetic". Suggest add sentence to end of paragraph: 'ADME is not generally required for large proteins with limited distribution volumes.'	
160-162 (BIO)	With species specific biologics, you may not be able to get exposure in the animal model of disease with the clinical candidate and thus the exposure information comes from a surrogate molecule. The wording should be changed to 'relevant animal species'. In addition, the assay sensitivity for biologics (ELISA vs. HPLC for small molecules) may not be sufficient to detect drug at the low end of the dose-response curve. We suggest the alternate wording "… exposures at pharmacological doses in the relevant animal species should be determined. Consideration should be given to the sensitivity of the assay for biologics, where a pharmacologic effect may be seen even in the absence of detectable drug. In these cases, exposure in the nonclinical studies may not be accurately assessed at the lowest end of the dose-response curve."	
160-162 (BIO)	It should to be clarified that a complete absorption, distribution, metabolism and elimination (ADME) package, as implied by the use of the descriptive phrase in the draft guideline, is not required at this stage of development, but rather PK or toxicokinetic (TK) data. We suggest the alternate wording "standard absorption, distribution, metabolism and elimination (ADME)" to "pharmacokinetic or toxicokinetic".	

160-162 (BIO)	ADME does not generally add value and is not generally required for large proteins with limited distribution volumes. We suggest the addition of this sentence to the end of the paragraph: "Traditional ADME evaluations do not generally add value for large proteins with limited distribution volumes".	
160-162 (Centocor)	If the pharmacology studies are conducted with a surrogate molecule and the toxicology studies are conducted with the clinical product in most cases, it will not be possible to make the relative exposure or dosage comparisons or extrapolations.	
160-162 (EuropaBio)	With species specific biologics, exposure in the animal model of disease with the clinical candidate may not be attained and thus exposure information comes from a surrogate molecule. The wording was changed to 'relevant animal species' to better determine exposure of the clinical candidate. In addition, the assay sensitivity for biologics (ELISA vs HPLC for small molecules) may not be sufficient to detect drug at the low end of the dose-response curve. Add the words: *"In addition to standard absorption, distribution, metabolism and elimination (ADME) requirements (see ICH S3, S6) which should be available in all species used for in vivo studies, exposures at pharmacological doses in the relevant animal species should be determined. Consideration should be given to the sensitivity of the assay for biologics, where a pharmacologic effect may be seen even in the absence of detectable drug. In these cases, exposure in the nonclinical studies may not be accurately assessed at the lowest end of the doseresponse curve."*	

160-162 (BIA)	Standard absorption, distribution, metabolism and elimination requirements are not relevant for biological products (ICH S6). Generally, a complete ADME package in accordance with ICH would not be available at this stage of development. Modify as follows: In addition to **the applicable** standard absorption, distribution, metabolism and elimination (ADME) requirements (see ICH S3 **for small molecules and ICH S6 for biological products**), which … should be determined. **ADME is not generally required for large proteins with limited distribution volumes.**	
161 (AGAH)	It may be useful to put this more precisely. Add: "… *target receptor* exposures …"	
161 (EBE)	"In addition to standard absorption, distribution, metabolism, and elimination (ADME) requirements (see ICH S3, S6), which should be available in all species used for in vivo studies, exposures at pharmacological doses in the relevant animal models should be determined." This requirement clearly depends on the availability of animal models. Change as follows: "*In addition to standard absorption, distribution, metabolism, and elimination (ADME) requirements (see ICH S3, S6), which should be available in ~~all~~ representative/relevant species used for in vivo studies, exposures at pharmacological doses in the relevant animal models should be determined, where such models are available."*	
161 (Roche)	Conducting ADME studies on "all species used for in vivo studies" may be unnecessary. Such studies may be more appropriately conducted on a single relevant species, particularly a model of drug safety.	

4.3 (EuropaBio)	The expectations described in this section are not readily applicable to small molecules and not all biologicals would meet all of the expectations as presented.	
159-162 (MSD)	ICH S3, M3 and S6 Guidances do NOT require ADME studies in all species for first in man clinical trials. This is an incorrect reference. Typically, PK and TK data are available for each of the animal species employed in the safety assessment program, together with information on routes of metabolism in *in vitro* liver preparations from these species, as well as humans, to support the selection of the safety species. In addition, most sponsors typically provide preliminary data on the routes of elimination of the test compound in one animal species (normally the rat) to assess the primary mechanism of drug clearance *in vivo*, and also would have determined whether the compound had inductive or inhibitory effects on human cytochrome P450 isoforms. Finally, data from human cytochrome P450 phenotyping studies and plasma protein binding (human and safety species) make up the DMPK component of IND / IMPD packages. This data set would seem adequate to qualify both "high-risk" and "normal" new chemical entities prior to FIM studies. Requiring full ADME packages in all species used preclinically would be extremely resource-intensive (including increased use of large animal species) and have an adverse impact on both ability and willingness to develop such therapies. In addition, by definition, data derived from preclinical species for high risk products would be less likely to have human relevance than similar data for "normal risk" products and likely would not improve the design of FIM studies. Distribution studies are seldom done in non-rodents at all during development and this will significantly increase non-rodent use with no value added to the safety profile. For many biotechnology-derived pharmaceuticals, classical ADME studies are not applicable and are considered irrelevant. Thus, such studies should not be recommended.	

160-163 4.3.2 (FCP)	4.3.2 Pharmacokinetics We think it may be appropriate to specify that ADME requirements applies to all species used for in vivo toxicological studies We suggest: " should be available in species used for in vivo **toxicological** studies, exposures at the pharmacological doses in the **most** relevant model should be determined" rather than "should be available in all species used for in vivo studies exposures at the pharmacological doses in the relevant models should be determined,"	
162 4.3.2 (BEBO)	Change into: pharmacological and toxicological doses in relevant…..	
162 4.3.2 (EANM)	Nuclear imaging techniques can give insight of pharmacokinetics profile into humans and provide validation of animal models Add sentence: **Human clinical trials based on a single micro-dose may result into important information.**	Not included as too specific for this general chapter
162 (EFPIA)	For specific high-risk medicinal products such as therapeutic vaccines (if not exempt from the guideline), PK data are not applicable. Therefore please add a sentence. Add "***The lack of such investigations because of the specific nature of the high-risk medicinal product should be justified."***	See modified text
4.3.3 Demonstration of relevance of the animal model		
163-194 (EFPIA, EBE, ABPI, Drusafe)	The expectations described in this section are not readily applicable to small molecules and not all biologicals would meet all of the expectations as presented. Whole section 4.3.3 deals with and refers to biologicals. If this is the intention, the header should be specified.	Not agreed, small molecules may be also involved.

164-194 (BIO)	The list of potential tests for relevance is extensive and many are not practical or feasible for all molecules. There must continue to be flexibility in the requirements for testing species relevance. It needs to be clarified and stated that this is not an inclusive "check-list" requirement for all molecules, but a set of points to consider case by case based on scientific rationale and feasibility. Cross-reactivity studies using human and animal tissues must be interpreted in the context of the available pharmacodynamic and toxicity data. Until human *in vivo* data are generated, there is a potentially high level of uncertainty in the value of the nonhuman data.	Text has been revised.
164-194 (Centocor)	The list of potential tests for relevance is extensive and many are not practical or feasible for all molecules. There needs to be some flexibility in the requirements for testing species relevance. Tissue cross-reactivity studies are only relevant for monoclonal antibodies and not produce definite evidence of species relevance or target organs of toxicity. Overall, it needs to be clarified and stated that this is not to be used as a "check list" requirement for all molecules, but as a guideline based on scientific rationale, case by case and feasibility. In the sentence on Line 178, it should be re-worded based on current experience to " It should be noted that human specific proteins can be immunogenic in animal species." Low and infrequent doses are likely to be immunogenic, but experience has shown that higher and frequent doses minimize an immunogenic response.	See above
169 4.3.3 (EANM)	Alternative in vivo testing might be used by researcher to prove species-specificity Change: ...with cells from a test species, the value of the in vivo ...Into: with cells from a test species **or comparative in vivo imaging of human and animal behaviour of the active molecule**, the value of the in vivo ...	This sentence recommends caution when extrapolating from *in vitro* to *in vivo* and do not discuss specific *in vivo* models (which can be of value)
170-172 FRAME	Similarities, or indeed differences, in responses between animal and human cells do not always translate to similarities between the responses of live animals and of humans. This type of extrapolation	Agreed, sentence has been (partially) added.

	seems only possible for genotoxicity testing at present. However, this does not prevent integration of information from *ex vivo* and *in vitro* studies into the decision-making process. Insert after line 172: Nevertheless, a weight-of-evidence approach should involve integration of information from *ex vivo* and *in vitro* studies into the decision-making process.	
170-172 (Drusafe, BIO)	In most cases, the only comparative data across humans and test species is in vitro. Thus, the sentence indicating that similar in vitro data may not predict in vivo data could be applied to almost all development programs. The key statement that would question the translation of the nonclinical to the clinic is contained in the previous sentence (lines 168-170) and adequately frames the remainder of this section. Suggest eliminating the sentence, '*It should be noted……response will be similar*'.	Agreed that the sentence may apply to all products, but is particularly critical for species-specific ones. Therefore the sentence has been kept.
173 (ECRIN)	…that non-clinical animal studies… The neologism "non-clinical animal" should be changed.	Agreed and revised.
173 (ECRIN)	Toxicity studies in non-relevant species… How are non-relevant species defined?	Criteria of relevance to consider are explained later in the section.
176 (EFPIA)	Highly species-specific medicinal products may also lead to different pharmacodynamic effects, thus add Suggest the following change*: "… to misinterpretation of pharmacokinetic **and pharmacodynamic** results*"	Agreed and revised.
176-177 (EMPT)	92% of all potential new drugs fail in clinical trials despite years of animal tests (US FDA white paper, *Innovation or* Stagnation, 2004). This abysmal failure rate strongly implies that, irrespective of the anticipated species-specificity of the drug candidate, there are serious flaws with the current mandatory testing regime. It is estimated that	This general statement is not a comment to the guideline.

	40% fail because of unfavourable pharmacokinetics in Phase I ((EUMAPP Background Paper, January 2006; Nature Reviews Drug Discovery 2003; 2:233-40), while the vast majority of the remaining drugs fail because of unforeseen toxicity or inefficacy.	
178 (BIO)	Low and infrequent doses are likely to be immunogenic, but experience has shown that higher and frequent doses minimise immunogenic response. We suggest the alternate wording: "It should be noted that human specific proteins can be immunogenic in animal species".	Agreed but the sentence remains true as the quantitative aspect of the immunogenicity is not mentioned. (sentence moved into toxicology section)
178-182 (AMGEN, EBE, EFPIA, ABPI, EuropaBio)	Is unclear if the endpoint being discussed is pharmacodynamic or toxicity. Further, immunogenicity in animal species does not mean that useful information will not be collected. Binding anti-drug antibodies alone do not a priori interfere with pharmacodynamics or toxicity. Delete lines 178-182.	Partially deleted and rephrased.
178-182 (Drusafe)	This section should clarify if the endpoint (effect) being discussed is pharmacodynamic or toxicity. *We recommend revising Line 179: "Therefore, repeat dosing studies in animals may not predict the effects of such substances in humans when neutralizing antibodies are present."*	Has been deleted.
178-182 (BIO)	This section is unclear as to whether the endpoint being discussed is pharmacodynamic or toxicity. Further, immunogenicity in animal species does not mean that useful information will not be collected. Binding anti-drug antibodies alone do not *a priori* interfere with pharmacodynamics or toxicity. We suggest that lines 178-182 be deleted.	
182 (PDA)	Change "highly": Rationale: avoid absolute statements	Sentence deleted

	"particularly"	
183 (EFPIA)	This wording seems too strict, since some of the requirements may be difficult or unnecessary to fulfil. Replace by: "*The demonstration of relevance **<u>should</u>** include **<u>the following aspects, if applicable:"</u>***	Rephrased
183-194 (BIO)	This section should indicate that the extent to which the relevant species is relevant should be discussed, i.e. a discussion of the limitations of the available species and models to predict human safety.	
185-186 (MSD)	Merck requests clarification regarding "receptor structure" The primary structure such as DNA sequence and/or amino acid sequence would most likely be available. Other protein structure (secondary, tertiary, quaternary) and post-translational changes may not always be available or feasible in the early stages of development.	
185-187 (EMPT)	The recent TGN1412 clinical trial demonstrated that point as clearly as possible: the CD28 receptor sequence in cynomolgous monkeys is identical to that in humans (*The Lancet* 2006; 368:1387-1391).	Statement
185-187 Cancer Research	This statement assumes that all targets are receptors. Target structure, pharmacology and pharmacodynamics, including cell signalling if relevant.	Rephrased

185-187 (BIA)	This bullet point suggests that all pharmaceuticals are specific receptor antagonists. While that accounts for a large portion of drugs in development, it does not take into account the variety of approaches (siRNA, enzyme inhibitors, etc). We suggest rewording the first sentence as follows: **Consideration of distribution and homology of target, functional consequences and pathways, including cell signaling, if relevant, and receptor structure, binding and occupancy, if relevant**. A high degree of homology…..	
185-189 (AMGEN, EBE, BIO, EuropaBio)	The 'functional consequences' in the relevant animal model may not be understood. A surrogate may need to be used. May need to add an example after functional consequences. There needs to be some recognition this information may not be obtained in the relevant species as these assays may be extremely difficult (or impossible) to adapt to the animal species being used. In addition, Fcs regions are very different in nonhuman primates and rodents compared to humans, so data on functionality of the Fc regions in animals is unlikely to add value. Add the words: *"Receptor structure, binding, occupancy and functional consequences, including cell signalling, if relevant. In cases where it is not possible to get these data from the relevant animal species, data from a homologous protein may be used to understand these PD effects."* *"Data on the functionality of additional functional domains in an in vitro assay with human cells, if applicable e.g. Fc receptor system for monoclonal antibodies."*	Agreed and revised
185-189 (EFPIA, ABPI)	This part is written to suggest that all pharmaceuticals are specific receptor antagonists. While that accounts for a large portion of drugs in development, it does not take into account the variety of approaches (siRNA, enzyme inhibitors, etc). We may not be able to understand the 'functional consequences' in the	Rephrased. See above

	relevant animal model. Again, we might need to use a surrogate. May need to add an example after functional consequences. There needs to be some recognition that we can't always get this information in the relevant species as these assays may be extremely difficult (or impossible) to adapt to the animal species being used. In addition, Fc regions are very different in nonhuman primates and rodents compared to humans, so data on functionality of the Fc regions in animals is unlikely to add value. We request clarification regarding "receptor structure" The primary structure such as DNA sequence and/or amino acid sequence would most likely be available. Other protein structure (secondary, tertiary, quaternary) and post-translational changes may not always be available or feasible in the early stages of development. Recommended changes, reword line 185-187 as follows: *"Comparison of pharmacodynamics* • ***Consideration of distribution and homology of target,*** *functional consequences* ***and pathways****, including cell signaling, if relevant****, and*** *receptor structure, binding and occupancy, if relevant* ***and available. In cases where it is not possible to get these data from the relevant animal species, data from a homologous protein may be used to understand these PD effects.*** *A high degree of homology …"*	
185-189 (Drusafe)	The methods that can be applied for comparison of pharmacodynamics should be clarified. *We recommend the following revision:"Receptor structure, binding, occupancy and functional consequences, including cell signalling, if*	See above

	relevant. In cases where it is not possible to get these data from the relevant animal species, data from a homologous protein may be used to understand these PD effects." *"Data on the functionality of additional functional domains in an in vitro assay with human cells, if applicable e.g. Fc receptor system for monoclonal antibodies."*	
188-189 (BIA)	The functionality of additional functional domains e.g. Fc regions may be very different in non-human primate and rodent compared to humans so the relevance of these data is questionable.	See above
190 (EBE)	*"- comparison of pharmacokinetics"* In the context of an assessment for a first-in-man trial this requirement cannot be fulfilled. Human pharmacokinetic data would need to be available for the demonstration of relevance. Delete: *"- comparison of pharmacokinetics"*	Rephrased
190 Cancer Research	At this stage human data will not be available so what should be compared? Does this mean a comparison between the toxicological species?	
190 (EFPIA)	Too general phrase Comparison of pharmacokinetics should be further explained since human data are not available. Most often only one relevant animal model is available. Therefore kinetics in this model is most likely the only meaningful data, which can be generated. Replace: "Comparison of *relevant and available* pharmacokinetic *and drug metabolism data with particular reference to known species differences"*	

190 (Drusafe)	Pharmacokinetic differences across species do not necessarily invalidate the relevance of animal models. Species differences in PK are expected, interspecies scaling is often applicable and acceptable to bridge PK differences to man, with the exception of major metabolic profile differences. Suggest modification: 'Comparison of pharmacokinetic and metabolism profiles (interspecies scaling of pharmacokinetics may be applied prior to the comparison)."	
190 (EuropaBio)	This states that "comparison of pharmacokinetics" which is difficult as this is prior to FHD. Hence, this should be clarified.	
191 Cancer Research	This bullet point is most pertinent to antibodies and may not be appropriate for other agents. Cross-reactivity studies using human and animal tissues, if appropriate.	Reworded
191 (AMGEN)	Cross-reactivity studies using human and animal tissues must be interpreted in the context of the available pharmacodynamic and toxicity data. Further, these assays are of limited predictive value for potential effects in humans due to variability and limitations of the immunohistochemistry systems utilized in the assay. Lastly, this assay is only applicable to monoclonal antibodies. Delete line 191.	
191 (EBE)	Cross-reactivity studies using human and animal tissues must be interpreted in the context of the available pharmacodynamic and toxicity data. Further, these assays are of limited predictive value for potential effects in humans due to variability and limitations of the immunohistochemistry systems utilized in the assay. Lastly, this assay is only applicable to monoclonal antibodies. Delete line 191.	

191 (EFPIA)	Cross reactivity as described is relevant for Mabs, but not for all potentially high-risk drugs. If this is not exclusively for antibodies, a more general description of the requirement is needed. Recommended change: "Cross reactivity studies using human and animal tissues." To *"Cross reactivity studies using human and animal tissues,* ***if possible and appropriate."***	
191 (Drusafe)	The document should note that this assay is only applicable to monoclonal antibodies We recommend revising Line 191 to reflect the assay is only applicable to monoclonal antibodies.	
191 (ABPI)	Cross reactivity as described is relevant for Mabs, but not for all potentially high risk drugs. Recommended change: "Cross reactivity studies using human and animal tissues." To "Cross reactivity studies using human and animal tissues, if possible and appropriate."	
191 (EuropaBio)	Cross-reactivity studies using human and animal tissues must be interpreted in the context of the available pharmacodynamic and toxicity data. Further, these assays are of limited predictive value for potential effects in humans due to variability and limitations of the immunohistochemistry systems utilized in the assay. Lastly, this assay is only applicable to monoclonal antibodies. Delete line 191.	

191 (BIA)	Cross reactivity as described is relevant for monoclonal antibodies, but not for all potentially high risk drugs. Modify as follows: Cross reactivity studies using human and animal tissues**, if possible and appropriate.**	
192-193 (EBE)	*"Where no relevant species exists, the use of relevant transgenic animals expressing the human receptor or the use of homologous proteins is strongly recommended."* It should be acknowledged that such models are not always available. A human target may not necessarily be a receptor. Change as follows: *"Where no relevant species exists, the use of relevant transgenic animals expressing the human receptor target or the use of homologous proteins is strongly recommended, where such models are available."*	Wording has been revised
192-193 (EMPT)	We would question the relevance of using even transgenic animals as adequate models for humans. Our concern is shared by Dr. Francesco M. Marincola, Editor-in-Chief of the Journal of Translational Medicine, amongst others: "These models do not represent the basic essence of human diseases. Prestigious journals, however, appear more fascinated with the modern mythology of transgenic and knock-out mice than the humble reality of human disease." *Journal of Translational Medicine*, 2003; 1:8. "One might expect that these animals would mimic human symptoms, not just the genetic mutations. In fact, that is usually the exception, not the rule." Dr Tyler Jacks, regarding genetically modified mice in cancer research. *Science* (1997) 287: 1041.	

192-193 (EBE)	It should be acknowledged that transgenic animal models are not always available. Clarification should also be provided that a human target may not necessarily be a receptor. For transgenic animals the need for applying the same qualifying criteria should probably be stated. Change as follows: "*Where no relevant species exists, the use of relevant transgenic animals expressing the human ~~receptor~~ target or the use of homologous proteins is strongly recommended, where such models are available*." Include a statement that adequate comparisons of the transgenic models to the human condition should be performed consistent as if transgenics were not required.	

192-193 (EFPIA)	Feasibility of the use of transgenic animals should be evaluated by the applicant. There may be situations, were there are technical issues with the generation of appropriate transgenic animal models, e.g. when more than just one human receptor is involved. Limitations of the data generated in these models, e.g.: • There may insufficient data to confirm that the pharmacological response between human and animals is comparable particularly with novel targets. • There may be limited historical data for use as reference when evaluating study results in these genetically modified animals. • The stability of the transgene needs to be continually confirmed. The use of homologues may not be the ideal solution either as a different molecule to the IMP is being tested. Suggest revise this paragraph to read: '*Where no relevant species exists, the use of relevant transgenic animals expressing the human receptor or the use of homologous proteins* ~~*is strongly r*~~*ecommended* ***may be the only way to conduct a non-clinical assessment. However, the relevance and limitations of such models should be carefully considered and discussed fully in the supporting documentation.'***	

192-193 (ABPI)	There may be some reservations about the use of transgenic animals and the data generated in these models, e.g.: • There may insufficient data to confirm that the pharmacological response between human and animals is comparable particularly with novel targets. • There may be limited historical data for use as reference when evaluating study results in these genetically modified animals. • The stability of the transgene needs to be continually confirmed. The use of homologues may not be the ideal solution either as a different molecule to the IMP is being tested. Suggest revise this paragraph to read: 'Where no relevant species exists, the use of relevant transgenic animals expressing the human receptor or the use of homologous proteins ~~is strongly recommended~~ may be the only way to conduct a preclinical assessment. However, the relevance and limitations of such models should be carefully considered and discussed fully in the supporting documentation.'	

192-193 (BIO)	There may be some reservations about the use of transgenic animals and the data generated in these models, e.g.: • There may insufficient data to confirm that the pharmacological response between human and animals is comparable particularly with novel targets. • There may be limited historical data for use as reference when evaluating study results in these genetically modified animals. • The stability of the transgene needs to be continually confirmed. The use of homologues may not be the ideal solution either as a different molecule to the IMP is being tested. A definition of relevant species might be needed. Is it only pharmacologically responsive animal models carrying the target which are considered relevant or should a model without the target but with similar non-specific staining in cross reactivity be considered relevant? In that case studies in a species not carrying the target could be considered relevant. It would be preferable to have a combination of a relevant non-specific toxicity study and a study in a transgenic or homologous model then to just have the transgenic or homologous study alone. Transgenic or homologous models are supplements for assessing pharmacological effects but require a number of compromises that disqualify them from being stand-alone safety models. We suggest revising this paragraph to read: ”Where no relevant species exists, the use of transgenic animals or the use of homologous proteins may be the only way to conduct a preclinical assessment. However, the relevance and limitations of such models should be carefully considered and discussed fully in the supporting documentation.”	

192-193 (BIA)	There are significant caveats associated with the data generated using transgenic animals expressing the human receptor and with homologous proteins. Modify as follows: Where no relevant species exists, the use of relevant transgenic animals expressing the human receptor or the use of homologous proteins **could be considered**.	
192-194 (AMS)	This statement is rather optimistic: transgenic animals may or may not be more or less predictive, depending on whether the downstream signalling is similar across species.	
193 FRAME	In the case of TGN1412, the surrogate (or homologous protein) was a mouse-anti-rat CD28. It was not CDR engrafted to afford it more rat-like qualities whereas TGN1412 was humanised and thus was, in my opinion, not a true homolog. The guideline should set out the criteria that a homologous protein must satisfy in order to be considered a true homolog to an IMP. Homologous proteins must demonstrate target, functional and structural equivalence and be derived by the same methods and produced to the same standards as the test material. Where true homology cannot be established, the decision to rely on preclinical information about the mechanism of action, pharmacology or toxicology of a homologous protein should be assessed on a case-by-case basis.	Not accepted. It seems self-evident that the principles described in the guideline for the medicinal product (mode of action, knowledge of the target, quality etc...) would apply (as much as possible) similarly to homologous products. The demonstration of homology needs to be addressed on a case-by-case basis.
193 (AMGEN, Drusafe, EuropaBio)	For transgenic animals the need for applying the same qualifying criteria should probably be stated. Include a statement that adequate comparisons of the transgenic models to the human condition should be performed consistent as if transgenics were not required	See above comment on homologous proteins.

194 (EBE)	*"The search for a relevant animal model should be documented and justified in detail."* Delete "in detail": *"The search for a relevant animal model should be documented and justified ~~in detail~~."*	Agreed. Sentence has been rephrased.
194 (PDA)	Change text: "The search for a relevant animal model should be documented and justified in detail." Rationale: improved clarity "The selection criteria and options considered in the chosen animal model(s) should be documented with adequate justification."	
4.3.4 Safety Pharmacology		
4.3.4 (EuropaBio)	It would make most sense to refer to both ICHS6 and 7A/B in relation to safety pharmacology - to more clearly cover the cases where the drug candidate falls within ICHS6. This will most likely be a significant number of the cases relevant to this guideline.	Clarified
4.3.4 (MSD, Drusafe)	The request for evaluation of "other organ systems" should be clarified. Additional assessments beyond standard toxicity studies should be scientifically justified.	
200 (PDA)	Change: "material" Rationale: clarity "tissues, cells or other material of human origin"	
195-200 (EFPIA)	Safety pharmacology studies in non-relevant species are meaningless and omission based on lack of test system should be justified. The request for evaluation of "other organ systems" should be clarified. Additional assessments beyond standard toxicity studies should be scientifically justified.	Agreed See above

	Additional guidance on the type of additional immune function testing that would be required for support of a First in human study for a molecule targeting the immune system should be provided. For medicinal products targeting the immune system, potential unintended effects should be investigated, e.g. using in vitro studies, including human material. This is confusing and we're not sure what is being requested here. Per the ICH S8 guidance on Immunotoxicity testing, unintended effects on the immune system are assessed through a 'weight-of-evidence' approach and should be completed prior to Phase III. Furthermore potential unintended effects of medicinal products targeting the immune system are generally not the subject of Safety Pharmacology studies, but rather of, toxicity studies including immunotoxicological parameters,special immune function studies (according to ICH S8 guideline) or in immunopharmacological studies. It would make most sense to refer to both ICHS6 and 7A/B in relation to safety pharmacology - to more clearly cover the cases where the drug candidate falls within ICHS6. This will most likely be a significant number of the cases relevant to this guideline. Suggest delete the sentence A separate paragraph on immunological assessment should be considered.	The need for additional testing of organ systems is case-dependant. Agreed
195-200 (BIO, Centocor)	It needs to be stated that safety pharmacology endpoints can be incorporated into the toxicity studies and that separate safety pharmacology studies are not required when the only relevant species is the non-human primate. Stand alone safety pharmacology studies should only be conducted in non-human primates if there is scientific rationale to do so.	Agreed, but not mentioned to avoid repetition with other guidelines.
196 (EBE)	It would make most sense to refer to both ICHS6 and 7A/B in relation to safety pharmacology - to more clearly cover the cases where the drug candidate falls within ICHS6. This will most likely be a significant number of the cases relevant to this guideline.	See above

	In addition to the core battery outlined in the CHMP/ICH guidelines ICH S6, S7A and S7B…….	
196 (ECRIN)	In addition to core battery…CHMP/ICH… Not based alone on ICH.	These are ICH guidelines adopted as such by CHMP for implementation in Europe.
196-200 4.3.4 (BEBO)	It would be beneficial if some concrete examples of "additional studies" could be included. Same for the *in vitro* studies for products targeting the immune system	Would go beyond the intention of this guideline.
196-200 (ICAPI)	*4.3.4 Safety Pharmacology* We welcome the heavier emphasis placed on *in vitro* human data, particularly for immune reactions. Subsequent *in vitro* tests of TGN1412, using human blood cells, showed that when the drug was immobilised by drying onto plates, it stimulated cytokine release and a profound proliferation of human CD4+ lymphocytes. Results using macaque cells were highly dissimilar. The *in vitro* test revealed that the dose of TGN1412 given to volunteers in the Northwick Park trial was close to the maximum immunostimulatory dose. These results were summarised in Section 5 of the Duff Report, above. It would have been entirely possible to demonstrate these activities prior to the clinical trial, as the *in vitro* assay used was not novel. This suggests that not all the relevant *in vitro* tests were conducted during pre-clinical development of TGN1412, and it emphasises the need to use human cells and tissues. We therefore suggest this section of the draft guideline should emphasise these factors more strongly. This is not only important for providing greater evidence of safety and pharmacological activity, but in the long-term will encourage the increasing sophistication of these tests and obviate the need for less predictive animal models."	Agreed that *in vitro* methods, when available should be used to refine the safety profile as much as possible.
196-200 (SPS)	Provision of a basic process which identifies which "other organ system" would reduce/aid understanding of risk would be beneficial. We would suggest this be driven through what categorised the compound as high risk i.e. what organ systems or physiological processes are at risk from this medicinal product by implication or uncertainty. Justification for the method of in vitro or in vitro organ	Not relevant with the deletion of high-risk MP classification.

	system assessment may also be of use. Additionally a step to review the pharmacological relevance of any animal model/tissue to the human system should be considered assessing e.g. the relevant receptor/effector numbers and their involvement in the physiological process in the test system vs human. It is recognised that this is, and will continue to be, an area in which our experience will grow and evolve rapidly and reference to this should be given. *Proposed changes:* In addition to the core battery outlined in the CHMP/ICH guidelines S7A and S7B, for high risk medicinal products, additional studies to investigate effects in other organ systems should be carried out on a case by case basis. These organ systems should be identified based on the organ systems or physiological processes which are at risk due to 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. The selected in vitro or in vivo assessment should be justified as new technologies/methods will emerge to address these concerns. In particular, for medicinal products targeting the immune system, potential unintended effects should be investigated, e.g. using *in vitro* studies, including human material.	
198 (EFPIA)	On a case-by-case basis it is sometime possible (but should not be mandatory) to identify appropriate counterstrategies. *"... on a case -by -case basis* ***including the search for relevant counterstrategies".***	This is implicit.
198 (Roche)	The statement on *"…medicinal products targeting the immune system…"* should be deleted and integrated at the end of the toxicology paragraph in an amended version.	Not agreed. Both are correct as it concerns safety.

	Add after line 213: "*For medicinal products targeting the immune system, potential unintended effects should be investigated, e.g. using in vitro studies, including human material, such as whole blood or human tissue."*	
198-200 (JPMA)	The *in vitro* studies using human material would be very helpful to predict adverse events in humans. Especially, cytokine release testing should be conducted for potential high risk medical products targeting the immune system. Add some examples and/or references for the *in vitro* studies, especially for *in vitro* cytokine release test.	Agreed See above
198-200 (AMGEN, EBE, Drusafe ABPI, EuropaBio)	The word "unintended" should be better defined to state which agents that target the immune system that are of most concern (exaggerated stimulation of the immune system). Suggest replacing "unintended" with "*immunostimulatory*":. Line 198-200 state: *"In particular, for medicinal products targeting the immune system, potential immunostimulatory effects should be investigated., e.g., in vitro studies."*	Not changed

198-200 (EFPIA , BIO)	Delete sentence “In particular, for medicinal products targeting the immune system, potential unintended effects should be investigated, e.g. using in vitro studies, including human material.” This is confusing and we’re not sure what is being requested here. If what is being requested is information about the potential for cytokine release using human PBMC in vitro, then it is worth being more specific. However, it should be recognised that whilst an in vitro assay for cytokine release using human PBMCs may be relevant for certain products with agonistic activity or antibodies directed against certain cell surface targets on immune cells, such a test may not be relevant for all medicinal products targeting the immune system.	
200 (Drusafe)	Safety pharmacology studies in non relevant species are meaningless and omission based on lack of test system should be justified.	See above
4.3.5 Toxicology		
201 (EFPIA)	This section is concerned with toxicological requirements for standard FIM studies but does not mention FIM studies with microdosing or other exploratory approaches. We suggest the addition of the statement like “<u>If microdosing approaches are intended the appropriate guidance on non-clinical data (CPMP/SWP/2599/02/rev 1) is applicable, but the relevance of the animal models should still be justified</u>”.	Done.
202 (EFPIA)	What is meant with „appropriate“. Species are defined in the respective guidelines. Replace “appropriate” with “relevant”	
202 (RS-LTD)	Many high-risk IMPs do not induce serious adverse reactions due to inherent toxicity but due to its primary or secondary pharmacology. It is therefore suggested to add a sentence referring to the need to carefully planning the preclinical program taking into account the molecular attributes of the compound. Furthermore, safety and toxicity investigations are often combined, for example when only non-human	Not relevant anymore

	primates are left as relevant animal model.	
202-213 Also 192-4 (CAG)	It may be useful to advise the use of more than one animal species when appropriate models exist or when different species may provide indicators of different potential toxicological effects; when no relevant species exists, the lack of a model should be explained especially with regard to concerns of predicting human risk and biological significance.	Already in other guidelines
202-123 (EFPIA)	This section needs to be clear about the use of pharmacological/disease models to assess toxicity. Transgenic and human disease models are very specialized and expensive to use. Scientific justification of these models will be needed, as will agreement between the authorities and the sponsor on the appropriate model for a specific product.	Agreed that these models are used when scientifically justified as reflected in the text.
202-203 Cancer Research	Toxicokinetics may not be relevant or even possible for some agents, i.e. viruses. The toxicology programme should be performed in appropriate animal species and include toxicokinetics, if appropriate.	Gene-therapy products are excluded from the scope
203 (EFPIA)	Clarify Suggested additional text: ***"The route and frequency of administration should be as close as possible to that proposed for clinical usage."***	Stated in other guidelines
204 (EMPT)	As evidenced from the small sample of quotes used in the above points, it is clear that one cannot know until the drug goes into humans which species of animal used will prove to have been relevant, if any.	Criteria for relevance are complex and can include studies with human material (e.g. metabolism, pharmacology)
204 (J&J)	This line is not appropriate it suggest that toxicology in pharmacologically non-responsive species would not be required. In the case of highly human specific products this would suggest that no toxicological evaluation is required? When toxicity studies can only be performed in species that are considered not or minimally pharmacological responsive the risks due to exaggerated pharmacology should either be assessed on the basis of the pharmacological data available or, if inadequate, additional safety	Search for relevant models is required. In their absence, *in vitro* models with human materials might be more useful.

	measures should be taken when progressing to first-into-man trials.	
204 (AMGEN)	We agree with the statement that toxicity studies in non-relevant species may give rise to misinterpretation and are discouraged. The document should clarify that using a surrogate molecule for the toxicology studies is acceptable and that evaluation for potential off-target toxicity in a non-relevant species with the clinical candidate would not be required. Add the wording: *"When using a surrogate molecule for the toxicology program, evaluation for potential off-target toxicity in a non-relevant animal species with the clinical candidate would not be required"*	See above
204 (EBE)	We agree with the statement that, *"Toxicity studies in non-relevant species may give rise to misinterpretation and are discouraged."* The document should clarify that using a surrogate molecule for the toxicology studies is acceptable and that evaluation for potential off-target toxicity in a non-relevant species with the clinical candidate would not be required. Add the wording: *"When using a surrogate molecule for the toxicology program, evaluation for potential off-target toxicity in a non-relevant animal species with the clinical candidate would not be required"*.	Agreed
204 (EFPIA)	The sentence 'Toxicity studies in non-relevant species may give rise to misinterpretation and are discouraged' should be reconsidered. 'Discouraged' may be too strong a word if the guideline applies to NCEs as well as biologicals. For NCEs, in the absence of pharmacologically responsive species, the sponsor is usually required to conduct toxicology studies in non-responsive species to detect off-target effects or chemically-mediated toxicity. Can you clarify the acceptability of using a surrogate molecule and not evaluate for potential off-target toxicity in a non-relevant species with the clinical candidate?	Does not apply exclusively to biological products.

	Suggest revise the sentence to read: '***<u>For biological products</u>***, *toxicity studies in non-relevant species may give rise to misinterpretation …..*	
204 (ICAPI)	*4.3.5 Toxicology* 'Non-relevant species' should never be used, for reasons of scientific validity and patient safety, and due to the requirements of Directive 86/609/EEC. The wording of the draft guideline at this point must be strengthened.	Agreed. See above.
204 (MP)	Regarding Section 4.3.5 Toxicology, the guideline states: *"Toxicity studies in non-relevant species may give rise to misinterpretation and are discouraged."* For small molecules it is not clear how one would establish chemical structure and impurity based on toxicologic liability, if studies are not conducted in rats, dogs or cynomolgus monkeys, or in the event that these three species are not pharmacologically responsive. In addition, it is not clear how human dosing could ever occur for a pharmacologic target with no non-human primate or lower species cross reactivity, if this statement were to stand. Does this statement mean that all toxicity testing could be restricted to a single species, if only a single laboratory animal species were pharmacologically responsive (specifically in the case of small molecules)? For example: could all small molecule toxicologic testing be limited to the nude mouse if only the nude mouse was pharmacologically responsive? Might this statement be antibody specific? We recommend inclusion of additional specific information to clarify this statement.	These studies are not recommended. The use of a single species needs to be justified on a case-by-case basis.

204 (PDA)	Delete "Toxicity studies in non-relevant species may give rise to misinterpretation and are discouraged." Rationale: sentence does not add to clarity nor does it give additional information.	See above.
204 (Drusafe)	The document should clarify when use of a surrogate molecule for the toxicology studies is acceptable. *We recommend the following wording is added: "When using a surrogate molecule for the toxicology program, evaluation for potential off-target toxicity in a no relevant animal species with the clinical candidate would not be required."*	
204 (ABPI)	The sentence 'Toxicity studies in non-relevant species may give rise to misinterpretation and are discouraged' should be reconsidered. 'Discouraged' may be too strong a word if the guideline applies to NCEs as well as biologicals. For NCEs, in the absence of pharmacologically responsive species, the sponsor is usually required to conduct toxicology studies in non-responsive species to detect off-target effects or chemically-mediated toxicity. Suggest revise the sentence to read: 'For biological products, toxicity studies in non-relevant species may give rise to misinterpretation …..'	
204 (BIO)	The sentence 'Toxicity studies in non-relevant species may give rise to misinterpretation and are discouraged' should be reconsidered. 'Discouraged' may be too strong a word if the guideline applies to new chemical entities (NCEs) as well as biologicals. For NCEs, in the absence of pharmacologically responsive species, the sponsor is usually required to conduct toxicology studies in non-responsive species to detect off-target effects or chemically-mediated toxicity. We suggest revising the sentence to read: "For biological products, toxicity studies in non-relevant species may give rise to misinterpretation …"	

204 (EuropaBio)	We agree with the statement that toxicity studies in non-relevant species may give rise to misinterpretation and are discouraged. The document should clarify that using a surrogate molecule for the toxicology studies is acceptable and that evaluation for potential off target toxicity in a non-relevant species with the clinical candidate would not be required. Add the wording: *"When using a surrogate molecule for the toxicology program, evaluation for potential off-target toxicity in a non-relevant animal species with the clinical candidate would not be required"*	
204-205 (BIA)	The statement that "toxicity studies in non-relevant species may give rise to misinterpretation and are discouraged" is specific to biologicals. Specify where the guidance is only relevant to biological products or to small molecules as appropriate.	
204-207 (EBE)	These expectations are directly applicable to only biologics. Reference needs to be made throughout section 4.3 on applicability of each section to the pertinent medicinal product types and not a generic approach Reference needs to be made throughout section 4.3 on applicability of each section to the pertinent medicinal product types and not a generic approach	May apply also to NCE (depending on the target)
204-207 (EFPIA)	These expectations are directly applicable to only biologics. Reference needs to be made throughout section 4.3 on applicability of each section to the pertinent medicinal product types and not a generic approach	
204-207 (Drusafe)	This section should be clarified that it is directly applicable to only biologics.	

204-207 (ABPI)	These expectations are directly applicable to only biologics. Reference needs to be made throughout section 4.3 on applicability of each section to the pertinent medicinal product types and not a generic approach.	
204-207 (EuropaBio)	These expectations are directly applicable to only biologics. Reference needs to be made throughout section 4.3 on applicability of each section to the pertinent medicinal product types and not a generic approach.	
208 (J&J)	Suggestion to rephrase: <u>Pharmacological animal</u> models that are thought to be similar to the human disease may provide further…	May apply also to safety as mentioned.
208 (PDA)	Replace “thought to be” Rationale: stresses scientific intent “expected to be”	Implicit
208-213 (BIO)	The guideline should state that if toxicology studies are conducted in animal disease models rather than in normal animals then these studies may be conducted non-GLP if GLP is not feasible.	Could be accepted with a suitable justification.
208-213 (Centocor)	Needs to state that if toxicology studies are conducted in animal disease models rather than in normal animals then these studies may be conducted non-GLP if GLP is not feasible.	
209 (Drusafe, EFPIA, BIO)	Animal models of disease often exhibit different pharmacokinetic characteristics than normal animals (e.g. absorption, distribution, protein binding, metabolism and elimination), introducing complexity in the prediction of human pharmacokinetics (typically performed using normal/non-diseased animals). Normal animals should be used to predict human PK. However, a comparison of exposure differences	Agreed, but text do not need to be modified.

	between normal and disease animals may be helpful in the interpretation of data. Suggest delete the word '*pharmacokinetics*'. Perhaps additional clarification can be added in a separate statement that pharmacokinetics in diseased animals may be different from normal animals.	
210-212 Cancer Research	Does this statement mean that studies with tumour xenografts and/or transgenic animals may be used to support non-clinical safety? If normal animals are considered of limited relevance would non-clinical safety studies in normal animals also be required?	Yes, if the model is relevant for safety evaluation.
211 (PDA)	After "alternative" add text Rationale: these are not necessarily mutually exclusive "or in addition to."	Agreed, but implicit as there would normally be other toxicity studies.
213 (AGAH)	Some findings from animal studies may give reason for concern which should have an impact on the clinical development programme. Other guidelines may be concerned in this respect. Sometimes, adverse reactions found in animal studies are being considered as "species-specific" by researchers. It may be useful to address this issue in this guideline because the relevance of animal models is concerned which, in turn, may give hints for the classification of an investigational compound as high-risk medicinal product. By the way, the conclusion that a particular adverse reaction observed in an animal study was species-specific may not be correct, and that is why such an assessment does already bear an implicit risk. Add: "If a severe adverse reaction was observed in an animal toxicity study at a low dose, and if that reaction is considered to be related to a high species-specific sensitivity for that effect, the sponsor should justify that conclusion in detail. It may be appropriate to classify an investigational compound as a high-risk medicinal product because of alarming findings observed during the toxicology programme. Adequate measures should be taken to monitor questionable findings from animal studies in human safety trials. Human experimentation is generally not justified if there are any doubts that a fatal or otherwise severe adverse	Principles agreed. This is reflected in the overall guideline

	reaction observed in an animal toxicity study at a low dose is a species-specific phenomenon (e.g. cardiotoxic findings). An additional animal toxicity study in a species close to humans may be appropriate, or even mandatory, to obtain further information on the relevance for humans."	
4.3.6 Calculation of the first dose in man		
4.3.6 line 214 (EFPIA)	This section should be numbered 4.4 as it is not a subchapter of section "4.3 Non- clinical requirements". It may not be possible to get receptor binding and receptor occupancy in vivo in the relevant animal species and model for instance the absence of disease models in NHPs will make this impossible. The same goes for concentration response curves *in vivo* molecule. The size of appropriate safety factors could be open to greatly divergent opinions between Competent Authorities. It should be acknowledged that the MABEL is only one method to determine the starting dose for FTIM studies and that no single method of calculation is appropriate in all circumstances. MABEL is an approach that is typically used for starting dose in certain cases; therefore it is not quite correct that in general NOAEL is the only factor used to set the starting dose for FIH. The text should differentiate MABEL from the anticipated lowest efficacious level (as the MABEL is lower when referring to the effect level). The section is somewhat vague on what safety factors should be applied to the calculated MABEL. Considerations are included, but not how to adjust the MABEL to the starting dose. Example of MABEL calculations would be helpful for different types of molecules (this could be an appendix to the guidance). [e.g. when would a factor of 10 vs 100 be applied? Could the MABEL be defined as the dose that is expected to achieve 10% of the maximal effect (or 5% or 1% depending on where the lowest efficacious level is expected to be); or could there be a general rule that the starting dose should be 10-fold lower than the likely minimum	Principles agreed. The text has been modified.

	efficacious level. Should first dose be based on mg/kg or normalized to "typical" subject, or case-by-case?]. For a compound with unexpected pharmacology, a small dose administered first may give information on an allergic-like response prior to escalating the dose to potentially efficacious levels. The guidance does not cover multi-dose administration and the potential situation in which significant toxicity may not be predicted after a single dose. Usually, the NOAEL is determined after repeat dose administration in animals. However, we are concerned with acute single dose effects in humans. This disparity may be more relevant where neutralizing antibodies are formed non-clinically. Some consideration of this issue may be helpful May need to acknowledge that this information can be gathered using a surrogate "*For high-risk medicinal products, an additional approach to dose calculation should be taken. The use of 'Minimal Anticipated biological Effect Level' (MABEL) approach is recommended.* ***This is different from the minimum anticipated efficacious level****. The MABEL is the anticipated dose level leading to a minimal biological effect level in humans."* It would be very helpful if the guideline could include some examples on calculation of starting dose. Ideally these could be "anonymised" real life examples. Suggest an appendix to provide examples of MABEL calculations for different types of molecules.	It was decided not to add examples. Some have been discussed at the workshop (see presentations on the EMEA website- "post-conferences")
4.3.6 (BIO, EuropaBio)	It should be acknowledged that the MABEL is only one method to determine the starting dose for FIH studies	See above

4.3.6 (Drusafe)	We agree that the MABEL is an appropriate consideration in addition to the NOAEL for basing the FIM starting dose. The guidance, however, would benefit from specifics on how this is to be determined particularly where the range of pharmacodynamic response is broad (e.g., is the EC10 or another parameter to be used as the basis?). It should be acknowledged that the MABEL is only one method to determine the starting dose for FTIM studies.	
(AREC)	The Association strongly supports the use of MABEL in such studies. Subjects should be made aware of the dose it is proposed to administer to them.	
214 (EBE)	It should be acknowledged that the MABEL is only one method to determine the starting dose for FTIM studies.	
214-241 (ABPI, Amgen)	i) may not be able to get receptor binding and receptor occupancy in vivo in the relevant animal species. Again, with biologics, since no disease models in NHPs, you may not be able to get these data. The same goes for ii) concentration response curves in vivo. May need to acknowledge that this information can be gathered using a surrogate molecule.	Agreed. This would be a case-by-case approach.
215 (IPOPI)	Is there a timescale between administering the medicine and any adverse reactions?	Any range is possible (from seconds to weeks), although this guideline focuses on acute events, i.e. less than a day (but not only)
215-219 (EFPIA, WP)	The July 2005 FDA Guidance for Industry entitled, "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" is generally accepted by Industry as the standard approach to calculate the first dose in man ("traditional" approach). This FDA guidance was also referenced in the 30 November 2006 Final Report from the UK/MHRA Expert Safety Group. Please note, that it is good practice when establishing the first-in-man dose to consider different methods of calculation irrespective of the nature of the compound; this includes typically a consideration of the potentially pharmacologically active dosage which has been introduce in this guidance as the MABEL. Therefore, beginning this chapter with "in general" may be misleading.	Agreed. The reference has been added.

	We recommend that the guideline include a reference to the FDA Guidance for Industry entitled, "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers." http://www.fda.gov/cder/guidance/5541fnl.pdf Suggested rewording for this section *The calculation of the first dose in man is an important element to safeguard the safety of subjects participating in first in man studies. Typically, all available information has to be taken in consideration for the dose selection and this has to be made on a case-by-case basis. Typically, the No Observed Adverse Effect Level (NOAEL) determined in non-clinical safety studies performed in the most sensitive and relevant animal species, adjusted with allometric factors or on the basis of pharmacokinetics gives the most important information. The relevant dose is then reduced/adjusted by appropriate safety factors according to the particular aspects of the molecule and the design of the clinical trials.* *In addition and particularly important for high-risk medicinal products, an additional approach to dose calculation should be taken. Information about pharmacodynamcis can give further guidance for dose selection. The 'Minimal Anticipated Biological Effect Level' (MABEL) approach is recommended. The MABEL is the anticipated dose level leading to a minimal biological effect level in humans. Regarding this approach potential differences between humans and animals regarding the sensitivity toward the agent respective the mode of action need to be taken into consideration e.g. derived from in-vitro. Safety factors are usually applied for the calculation of the first dose in man from MABEL.*	
215-234 (MRC)	The MRC restates the view above that dose calculation is important in all first in man studies and investigators should be able to justify the approach chosen in relation to the potential risk of the product.	Agreed

215-234	**Calculation of first dose in man** An 'integrated PK/PD modelling approach' represents only one method for calculating the first dose for man. Guideline should allow calculation of this parameter using methodology of choice, provided the methodology can be justified.	See above
216 (EFPIA)	For calculation of the starting dose the most relevant species should be selected. Most sensitive could lead to confusion in cases where effects in a very sensitive species but not relevant species could lead to very low dose levels which would lead to an unreasonable low starting dose. To apply this one should have data to explain, otherwise the most sensitive species is also relevant. Please, omit the words '*sensitive and'*	Sensitive have been kept as criteria of relevance are complex. If the species is too sensitive, and therefore not relevant, it would have to be justified.
216-217 (EFGCP)	…in the most sensitive and relevant animal species The most sensitive animal species is either the most sensitive of a number of species tested, taking into consideration the actual species tested, or it is the most sensitive of all species which can be tested today. In other words the Guideline should recommend a relative approach or an absolute approach to rank species sensitivities. If this is not carefully worded, it will lead to animal overkill in the search for the most sensitive species in absolute terms.	
216-271 (ECRIN)	…in the most sensitive and relevant animal species… The most sensitive animal species is either the most sensitive of a number of species tested, taking into consideration the actual species tested, or it is the most sensitive of all species which can be tested today. In other words the Guideline should recommend a relative approach or an absolute approach to rank species sensitivities. If this is not carefully worded, it will lead to animal overkill in the search for the most sensitive species in absolute terms.	
217 4.3.6	Molecular imaging can contribute to the determination of the starting	Agreed. Already mentioned in the "micro-dose guideline" the reference of

(EANM)	dosage Add sentence after "... pharmacokinetics.": **Nuclear imaging, used as micro-dosing early assessment of pharmacokinetics and dose-escalade monitoring, tool may contribute to the determination of starting dose and tentative dosage interval**	which has been added.
218 (Roche)	Roche agree that "safety factors" should and usually are applied to determine the initial dose (and dosing schedule). However, can some advice be given in what is "appropriate"?	Safety factors are case specific, based on a "weight of evidence". Text has been modified.
218 (EuropaBio)	We would welcome clarification on how appropriate and justified safety factors are to be selected, for example, further guidance based on current industry standards and some examples.	
218-219 FRAME	The issue of applying allometric scaling, body surface area and other safety factors to MABEL/NOAEL values from preclinical studies should be more fully considered. The issue of whether an additional safety factor should be applied for potential high risk IMPs where a) some preclinical studies involved studies on a species homolog b) there is over reliance on data from a single species c) there is a high probability that individual trials subjects may be subject to different levels of risk because of inherent differences in susceptibility should be clarified. Insert after text: Safety factors should take into account: a) the reliability of allometric scaling b) whether preclinical data is composed (partly) of data from studies on a species surrogate c) whether there is a likelihood different patient groups of subpopulations of human volunteers are likely to display differences	Agreed. Reflected in the guideline

	with regards the efficacy or safety of a product	
220 (EACPT)	The introduction of MABEL (minimal anticipated biological effect level) could be beneficial, but might cause analytical problems and unrealistic scenarios. How can any biologic effect in humans be excluded?	Agreed that absence of any effects in humans cannot be excluded. MABEL is only the *anticipated* effect level.
220 (MSD)	We agree that the MABEL is an appropriate consideration in addition to the NOAEL for basing the FIM starting dose. The guidance, however, would benefit from specifics on how this is to be determined particularly where the range of pharmacodynamic response is broad (e.g., is the EC10 or another parameter to be used as the basis?).	See above.
220 (AMGEN, EBE)	Biologic compounds which are not higher risk may not have toxic effects identified (sometimes small molecules too) Change as follows: *"For drugs <u>where a toxic effect is not established</u> (which may include higher risk molecules), an additional approach to dose calculation should be taken."*	Text modified as high-risk MP classification removed.
220 (Drusafe)	Recommend clarification on applicability of MABEL. *We recommend revising: "For drugs where a toxic effect is not established (which may include high risk compounds)…."*	
220 (EuropaBio)	Biologic compounds which are not higher risk may not have toxic effects identified (sometimes small molecules too) For drugs where a toxic effect is not established (which may include higher risk molecules)….	
220-222 (BIA)	Calculation of the first in man dose can be based on NOAEL or MABEL (whichever is lower). Greater guidance should be provided on situations where a MABEL approach may be most appropriate. How	Text has been modified.

	would a MABEL approach help predict potential for allergencity/immunogenicity? The guideline should differentiate MABEL from the anticipated lowest efficacious level (as the MABEL is lower when referring to the effect level). The section is somewhat vague on what safety factors should be applied to the calculated MABEL. Considerations are included, but not how to adjust the MABEL to the starting dose. It would be helpful to include examples of MABEL calculations for different types of molecules in an annex to the guidance. The FDA guidance on first-in-human dosing recommends a minimum 10-fold safety margin, with a higher multiple when certain criteria are met such as evidence of irreversible effects, difficulty in monitoring in the clinic, etc. Modify as follows: For high-risk medicinal products, an additional approach to dose calculation should be taken. The use of 'Minimal Anticipated Biological Effect Level' (MABEL) approach is recommended. **This is different from the minimum anticipated *efficacious* level.** The MABEL is the anticipated dose level leading to a minimal biological effect level as a guide for determining the safe starting dose in *humans*.	
220-239 (SPC)	MABEL in general describes the previous process that has been used in estimating PD effects and translating these effects into humans. The goal of most drug development is to start at a minimal biologically effective dose in all but life threatening indications. For most compounds if the projected human PD/beneficial effect is not clearly below NME concentrations anticipated for undesirable effects, further work on the NME is stopped. The process has not been formally given an acronym. This information may have been included in the pharmacology, pharmacokinetic and other sections of the dossier. Providing a single section integrating this information may be useful. As MABEL represents a departure from previous presentation, examples would be useful in providing guidance on computational approaches and information presentation. The difficulties in the estimating the MABEL dose is most evident in NME challenging human translational capacities. There needs to further exploration of the MABEL approach in translating preclinical	See modified text.

	pharmacology into human starting doses. Directly human-applicable information will be limited in most cases and the use of a conservative approach to series of translational estimates could lead to very low initial starting doses. For short half-lived molecules, the additional time required to dose escalate to a truly pharmacologically active human doses would delay the project by several months -- an inconvenience and deterrent to innovative small drug developers. For large molecules, which may be markedly over represented in those classified high risk, a very low starting could extended initial dose escalation for years in patients complicated by difficulties in reliably delivering the small stating doses. A lower bound of large molecule molar mass should be established for a starting dosing when uncertainties of estimates are numerous.	
221 (Drusafe)	Additional information regarding the calculation of dose using MABEL, including worked examples, would be helpful,	See above
222-223 (EFPIA, AMGEN, EBE, Drusafe, ABPI, Europabio, BIO)	Reference to "safety factors are usually applied for the calculation of the first dose in man from MABEL" Depending on the risk profile of the IMP and clinical population, the starting dose may be set above the MABEL, at the MABEL or at some fraction of the MABEL. Recommendations should take account of the frequent circumstance with biologicals where a PK assay may not be adequately sensitive to return reliable data at exposure levels which provoke a biological effect. Often there is not a true PD assay other than estimates of ex-vivo occupancy at the cellular level. Thus if the MABEL approach is taken (i.e. the minimal detectable dose predicted to give a reliable estimate of biological effect) and a fraction of this is used for the first in human dose, the resulting exposure for the subject will effectively be a placebo and not a test of safety and tolerability. In particular, for an antagonist with no evidence of any agonistic activity, a case may be made for starting dose to be set at a level predicted to result in high (e.g. 90%) receptor occupancy. A more conservative approach would be appropriate for an agonist.	
4.3.6 (EuropaBio)	Line 226: "receptor" should be replaced with "target" to make the approach also cover non-receptor targeting drug candidates (e.g.	Text has been modified.

	soluble targets). Line 226+229: reference to "target cells" should be omitted for same reasons. In general: this section could be misunderstood in what defines a MABEL, i.e. it should be clear that target occupancy (although a pre-requisite) does not in itself constitute a biological effect. Rather a MABEL relates to the level at which a pharmacological activity is anticipated.	
222-239 (MP)	Regarding Section 4.3.6 – Calculation of the First Dose in Man, the guideline states: *"For high-risk medicinal products, an additional approach to dose calculation should be taken, the use of Minimal Anticipated Biological Effect Level" (MABEL) approach is recommended. The MABEL is the anticipated dose level leading to a minimal biological effect level in humans. Safety factors are usually applied for the calculation of the first dose in man form MABEL. The calculation of MABEL should utilise all relevant in vitro and in vivo available information from pharmacodynamic/pharmacokinetic data such as….The above data should be integrated in a PK/PD modelling approach for the determination of MABEL…."* The statement is made that safety factors should be applied based on MABEL rather than only considering the NOAEL. Is there any data to support this as relevant for small molecules, if the toxicology species are pharmacology relevant? If not, then MABEL should be excluded from use when the toxicology species are pharmacologically relevant. This will significantly increase costs and time requisite in clinical development for study of molecules that are of low toxicity potential but potent pharmacologically in circumstances where the toxicology species are pharmacologically relevant. We also consider that a reliable PK/PD modelling to understand the PK parameter that drives in vivo effect is nice to have, but perhaps should not be required. The use of MABEL is not necessary for determining a safe starting dose for first-in-ma, if the toxicology test species is pharmacologically relevant.	See above

222-223 (BIO)	Regarding the sentence "safety factors are usually applied for the calculation of the first dose in man from MABEL," we note that depending on the risk profile of the IMP and clinical population, the starting dose may be set above the MABEL, at the MABEL or at some fraction of the MABEL. Also, the wish to provide flexibility and to cover all applications in a guideline often renders it more or less useless due to vague or broad statements that can be understood and interpreted freely and differently. In that respect some guiding safety factors to apply when calculating FIH dose would be a useful addition to this guideline. Statements on recommended minimum safety factors to be used in e.g. life-threatening diseases vs. non-life threatening diseases, with "high-risk compounds" would be helpful, perhaps with an example of how different levels of risks and uncertainties can be visualized. It should be noted that a different safety factor may be used if it is justified. Recommendations should take account of the frequent circumstance with biologicals where a PK assay may not be adequately sensitive to return reliable data at exposure levels which provoke a biological effect. Often there is not a true PD assay other than estimates of *ex-vivo* occupancy at the cellular level. Thus if the MABEL approach is taken (i.e. the minimal anticipated dose predicted to give a reliable estimate of biological effect) and a fraction of this MABEL is used for the FIH dose, the resulting exposure for the subject will effectively be a placebo and not a test of safety and tolerability. This may be appropriate when a steep dose- response is anticipated and unacceptable toxicity is predicted to be coincident with maximal pharmacologic activity.	
224 (EBE, Roche)	The list of factors that should be considered for the calculation of MABEL should be extended, since it does not take into account binding of therapeutic mAb to target-unrelated cells, e.g. to FcR bearing cells via the Fc portion. This consideration may impact the calculation of MABEL as the increased number of target cells changes the actual receptor occupancy *in vivo.* Add after line 232 a further bullet point:	Text has been modified

	" iv) binding studies in vitro involving human immune cells to study capture of the medicinal product by target-unrelated molecules, e.g. binding of antibodies via the Fc portion to Fc receptor bearing immune cells."	
224-225 (JPMA)	The methods for calculation of MABEL have not yet been common in Japan. In addition, it is not very clear to make a decision on how much safety factor should be adopted. Add examples and/or references on the methods for calculation of MABEL and safety factor.	See above
226-185 (ABPI)	See recommended considerations above for line 185. This part is written to suggest that all pharmaceuticals are specific receptor antagonists. While that accounts for a large portion of drugs in development, it does not take into account the variety of approaches (siRNA, enzyme inhibitors, etc). Comment: See recommended considerations above for Line 185. **"**Consideration of distribution and homology of target, functional consequences and pathways, including cell signaling, if relevant, and receptor structure, binding and occupancy, if relevant. A high degree of homology …"	See modified text.

226 (EFPIA)	Line 226: "receptor" should be replaced with ***"target"*** to make the approach also cover non-receptor targeting drug candidates (e.g. soluble targets). Line 226+229: reference to "target cells" should be omitted for same reasons. **In general: this section could be misunderstood in what defines a MABEL, i.e. it should be clear that target occupancy (although a pre-requisite) does not in itself constitute a biological effect. Rather a MABEL relates to the level at which a pharmacological activity is anticipated.** This part is written to suggest that all pharmaceuticals are specific receptor antagonists. While that accounts for a large portion of drugs in development, it does not take into account the variety of approaches (siRNA, enzyme inhibitors, etc). Suggested additional text: "***To define, when appropriate, the degree of receptor occupancy required to achieve a minimum anticipated biological effect."***	
226-232 (EBE, EuropaBio)	With regard to point, i) it may not be possible to get "*receptor binding and receptor occupancy in vivo in the relevant animal species*", with biologics, since no disease models in Non-human Primates (NHPs), you may not be able to get these data. The same is true for, *'ii) concentration response curves in vitro"*. May need to acknowledge that this information can be gathered using a surrogate molecule.	
226-232 (ABPI)	For some biological products the non-human primate is the only relevant species. NHP animal models do not exist for some diseases hence it is not possible to obtain the data in bullets i to iii	
226-232 (BIA)	For some biological products the non-human primate is the only relevant species. However, it should be noted that NHP animal models do not exist for some diseases in assessing the in vivo PD properties.	

220-234 4.3.6 (BEBO)	Some suitable examples on how to calculate the MABEL and how to use suitable PK/PD modelling would be helpful.	Examples have not been added. See above comment at the beginning of the section.
220-241 (J&J)	Could the MABEL approach in general and in particular the safety factors to be applied be more specified. Consider adding some further explanation and detail about the suggested PK/PD modelling approach to the determination of the MABEL.	
224-232 (WP)	While the calculation of NOAEL ("traditional" approach where typically in vitro data are not taken into account) may be familiar to most Sponsors, the concept of MABEL may be less familiar. Inclusion of specific examples would assist Sponsors in how to calculate the MABEL. We recommend that, similar to the 30 November 2006 Final Report from the Expert Safety Group (e.g., page 25+), specific examples on how to calculate the MABEL be included in the guideline.	
224-232 (Drusafe)	This section should clarify if any of these data are deemed to be critical to the MABEL calculation.	See modified text

226 (EBE)	"*receptor*" should be replaced with "*target"* to make the approach also cover non-receptor targeting drug candidates (e.g. soluble targets). In general: this section could be misunderstood in what defines a MABEL, i.e. it should be clear that target occupancy (although a pre-requisite) does not in itself constitute a biological effect. Rather a MABEL relates to the level at which a pharmacological activity is anticipated. *i) ~~receptor~~ target binding and ~~receptor~~ target occupancy studies in vitro in target cells from human and the relevant animal (s) species and in vivo in the relevant animal species.*	
227 4.3.6 (EANM)	In vivo receptor binding should not be limited to animal species Add at the end of existing sentence: **or whatever possible in humans at micro-dose concentration**.	
227 (AMGEN, EBE, Drusafe, EuropaBio)	Receptor occupancy and receptor binding are not usually conducted *in vivo* Delete the use of *in vivo* on this line	
229 (EBE)	Reference to "target cells" should be omitted for same reasons as outlined for line 226. *ii) concentration-response curves in vitro ~~in target cells from~~ human and the relevant animal(s) species and dose response in vivo in the relevant animal species;*	

230 (EFPIA)	There needs to be an additional point here – knowledge of potential species differences in biological pathways or effects of drug action. These need to be taken into account in any extrapolation of dose/concentration/effect between species and provide a potential mechanistic basis for in vivo species differences in exposure/effect. This should be described as dose/exposure/response and not just dose/exposure	
230 (ABPI)	On the same theme this should be described as dose/exposure/response and not just dose/exposure There needs to be an additional point here – knowledge of potential species differences in biological pathways or effects of drug action. These need to be taken into account in any extrapolation of dose/conc/effect between species and provide a potential mechanistic basis for in vivo species differences in exposure/effect.	
232 (EFPIA)	Dose calculation advice based on exposure needs to take account of protein binding differences between animal species and human. The MABEL may also be influenced by the half-life of the product and its interaction with the receptor/ligand in the animal model vs. humans. This may be especially true with biological products. Suggested additional point: **“ <u>iv) Half-life in the animal model vs. expected half-life in humans</u>**	Not added as too restrictive. It is already mentioned that all PK/PD information should be used.

232 (RS-LTD)	Following this line, it is suggested to provide an example for MABEL. For example, MABEL could be the dose which causes induction of certain cytokines in an *in vitro* whole blood assay using human lymphocytes and monocytes. As soon as this assay delivers the lowest dose with a pharmacological, in this case immunological, effect, this would be declared the MABEL= starting dose for the first clinical investigation.	See above
232 (Drusafe)	The MABEL may also be influenced by differences in pharmacokinetics of the product in the animal model vs. humans. Add: iv) pharmacokinetics in the animal model vs. expected pharmacokinetics in humans	
233 (RS-LTD)	Suggestion to insert prior to the sentence of line 233 The use of the MABEL requires a particularly critical choice of a variety of relevant assay systems since otherwise the MABEL determined using irrelevant assays provides an irrelevant estimate for the safe starting dose.	
233 (Drusafe)	Rephrase for clarity. If the IMP is high-risk in terms of being human specific, then it may not be possible to construct a formal PK-PD model to determine MABEL. 'Whenever possible, the above data should be integrated using a PK/PD modelling and simulation approach, for the determination of the first dose in man.'	
233 (EuropaBio)	we would welcome further guidance on the use of a PK/PD modelling approach. We suggests highlighting the possibility of using the microdosing approach for a more precise understanding of the product profile before the initiation of phase I clinical trials.	

232-234 (EFPIA)	PK/PD modelling per se is not essential and no mention is made of target density and target turnover. Replace this sentence with: '***All available non-clinical concentration-response (PK/PD) data should be extrapolated to humans with relevant adjustments for potency, pharmacokinetics, target density and target turnover, where known.'***	Agreed. See modified text.
Line 233 (Eurocrof)	The calculation of the first dose and subsequent doses should in any case be based on the consideration of NOAEL, MABEL and Exposure as assessed in the toxicokinetic studies. Line 233: "The above data should be integrated in a PK/PD modeling.." : could be replaced by "The above data should be done using a PK/PD model".	Sentence rephrased
233-234 (ABPI, BIO)	PK/PD modelling per se is not essential and no mention is made of target density and target turnover. Replace this sentence with: 'All available preclinical concentration-response (PK/PD) data should be extrapolated to humans with relevant adjustments for potency, pharmacokinetics, target density and target turnover, where known.'	Agreed but not modified here. Potency mentioned later and overall section has been modified.
233-234 (BIA)	If the IMP is high-risk in terms of being human specific, then it may not be possible to construct a formal and accurate PK/PD model to determine MABEL. Modify as follows: **Wherever possible**, the above data should be integrated in a PK/PD modeling approach…..	See above. Text modified.

234 (ICO)	The MABEL concept is a new one and reads well but the description is too non-specific, which is understandable because the concept is drug-target specific but difficult to work out Add one simple example of how to calculate MABEL, clarifying that the calculation is drug-target specific	
235 (BIA)	It is unclear how safety factors would overcome another TGN1412. Concrete examples should be given. The use of microdosing techniques should be considered if there are serious concerns.	
237 (ACRO)	Line 237 reads "risks such as the novelty of the active substance" – we suggest that novelty per se is not a risk criterion, rather this should read: REPLACE: "**first use of a compound with a novel mechanism of action**"	
235-239 4.3.6 (BEBO)	This paragraph is rather vague. Recommendations or examples of safety factors and/or guidance on how safety factors can be justified should be included	
235-239 (ABPI)	There may be valid scientific reasons to be able to rely more on one estimate than another. The sponsor should have the option to justify using a different model than that which results in the lowest value, to estimate the starting dose When the methods of calculation (e.g. NOAEL, MABEL) give different estimations of the first dose in man, the lowest value should be used, unless otherwise justified	Text modified and more flexible approach adopted.

240 (EFPIA)	Knowledge of mode of action would not be fully understood, if at all, for most small molecular entities. Indeed the exact mechanism of action is still unknown for many long-time marketed small molecules. We agree that more than one method for calculating FIH dose should be employed, and that the use of MABEL should be considered. We do not agree with the mandate that the lowest value obtained with these methods of FIH dose should be employed. We recommend that the most scientifically appropriate method be used, with appropriate justification, and that a carefully considered safety factor be applied to provide a greater margin of protection to human subjects. There may be some instances e.g. oncology entry into human (EIH) studies where a MABEL dose is considered inappropriate and maybe even unethical. Furthermore, calculation of MABEL may be difficult for some high-risk products simply by definition (e.g. uncertainty of non-clinical predictability). Insert a statement to recognise that if MABEL is not used, a justification must be provided. In line 240 - 241, change the statement "When the methods of calculation (e.g. NOAEL, MABEL) give different estimations of the first dose in man, the lowest value should be used" to "*When the methods of calculation (e.g. NOAEL, MABEL) give different estimations of the first dose in man, the lowest value should be used* ***unless scientific and medical justification indicate otherwise***"	
240-241 (AMGEN)	Knowledge of mode of action would not be fully understood, if at all, for most small molecular entities. Indeed the exact mechanism of action is still unknown for many long-time marketed small molecules.	
240 (IPOPI)	What if the effect of the medicine is slow and cumulative?	This is part of the PK parameters to take into account.

240-241 (Roche)	We agree that more than one method for calculating FIH dose should be employed, and that the use of MABEL should be considered. We do not agree with the mandate that the lowest value obtained with these methods of FIH dose should be employed. We recommend that the most scientifically appropriate method be used, with appropriate justification, and that a carefully considered safety factor be applied to provide a greater margin of protection to human subjects. There may be some instances e.g. oncology entry into human (EIH) studies where a MABEL dose is considered inappropriate and maybe even unethical. Furthermore, calculation of MABEL may be difficult for some high risk products simply by definition (e.g. uncertainty of preclinical predictability). Insert a statement to recognise that if MABEL is not used, a justification must be provided . In line 240 - 241, change the statement "When the methods of calculation (e.g. NOAEL, MABEL) give different estimations of the first dose in man, the lowest value should be used" to "When the methods of calculation (e.g. NOAEL, MABEL) give different estimations of the first dose in man, the lowest value **should be considered if feasible**"	Agreed. See above
240-241 (EuropaBio)	Knowledge of mode of action would not be fully understood, if at all, for most small molecular entities. Indeed the exact mechanism of action is still unknown for many long-time marketed small molecules.	
240-241 (BIA)	The sponsor should have the option to justify using a different model than that which results in the lowest value to estimate the starting dose. Modify as follows: When the methods of calculation (e.g. NOAEL, MABEL) give different estimations of the first dose in man, the lowest value should be used**, unless otherwise justified.**	

215-241 (Drusafe)	The section is somewhat vague on what safety factors should be applied to the calculated MABEL. Considerations are included, but not how to adjust the MABEL to the starting dose. Example of MABEL calculations would be helpful for different types of molecules (this could be an appendix to the guidance). Suggest appendix to provide examples of MABEL calculations for different types of molecules.]	See above
4.3.6 (FCP)	Calculation of the starting dose It may be useful to reference the July 2005 FDA guidance for Industry entitled "Estimating the maximum safe starting Dose in initial trials for Therapeutics in adult healthy volunteers "(http:/www.fda.gov/cder/guidance/5541fnl.pdf) as it is currently accepted as an approach of calculating the starting dose in human for traditional non high-risk product. We suggest adding examples of calculation using MABEL in an appendix as in the FDA 2005 guidance . As concept of MABEL is less familiar to sponsors, inclusion of specific examples would assist sponsors in how to calculate the MABEL. We suggest To give reference to the FDA 2005 guidance and to add examples of calculation of MABEL	
4.3.6 (ACRO)	This section recommends calculation of the MABEL, which is useful. However, this is less helpful in the absence of worked examples to illustrate how the MABEL should be calculated, and ACRO recommends that appropriate examples be included in the final Guideline. We note that useful examples of dose calculations are given in the Duff report based on the MABEL (derived from receptor occupancy).	

CLINICAL requirements		
4.4.1. General aspects		
(Rottapharm spa)	Finally, I would suggest adding in the study design a sentence indicating the need for Sponsors to consider collection of urine during FIM trial with high risk product. This will allow on one side the determination of the renal clearance and thus a preliminary assessment of the role of the kidney in the disposition of the new product. This will address other issues such as transporters involvement, target organ for toxicity, and will provide another means for assessing exposure (the amounts excreted in urine were previously in the systemic circulation). This should be done regardless of the results of the preclinical investigations and regardless of the therapeutic/chemical class of the new product as it will provide further data on it safety and will aid in the design of future studies. It should also be considered if determination of the parent drug and of identified metabolites (if any) should be conducted before and after hydrolysis of the urine samples (to release the unchanged drug and/or it metabolites from glucuronides and/or sulfates) to provide an initial indication of Phase II metabolism and thus potential entero-hepatic cycling etc. etc.	Guidance on collecting urine is too detailed to include in this guideline and is expected to be considered in the overall design of the trial based on the information from non-clinical studies.
4.4.1 (Drusafe)	The use of an IDSMB is fairly uncommon in Phase1 studies and its utility might be limited because these studies can be easily conducted in a single blind fashion, are often done at a single site and are closely monitored by Phase 1 unit Ethics Committees. In addition, finding IDSMB members with sufficient Phase 1 experience may cause delay that is unwarranted given the low potential of an IDSMB for meaningful input. The guidance implies that the involvement of an IDSMB would be the norm, since the sponsor would have to provide justification if an IDSMB were not used. Given the practical limitations described above, the guidance should only propose the involvement of an IDSMB for high risk products, where the sponsor has particular cause for concern rather than recommend use of an IDSMB, with justification for its absence. This statement has also been included under section 4.4.2.7	Agreed. The text has been changed to take account of this.
244-255 4.4.1	The IEC could and should play an important role when considering the various aspects in this paragraph, and in the following subparagraphs Not only should they give their initial approval, they also should play a	An IEC with the appropriate experience can take responsibility for decisions relating to changes to the protocol, starting a new cohort or next dose cohort and stopping the trial. Since this may not be available to all sponsors of FIM

(BEBO)	pivotal role in giving approval to changes in the protocol, to start with a new or next dose cohort, etc. Moreover, the IEC should be informed immediately on any serious adverse reactions, and be able to review the situation and take appropriate actions (including stopping of the study) within 24 hrs, seven days a week. Our IEC has been working with these rules for all FIM studies reviewed over the last 5 years and our experience is quite positive. We believe that the responsible IEC is in a much better position to fulfil the tasks associated with stopping rules and decisions with respect to subject dosing and dose escalation than an independent safety monitoring board.	trials needing special attention, the guidance provides for this type of arrangement as well as others.
4.4.1 (AGAH)	These general aspects apply for any Phase I trial. The risk assessment has to be performed for any compound.	Agreed. Many aspects of this guidance also apply to any Phase I trial
246 (GCPA)	'Key aspects of trial design' do not determine risk. Rather, these key aspects should be evaluated and guided by a determination of the nature and degree of the defined risk. As this sentence now stands, it demonstrates a recurrent weakness of this guideline in its ability to provide clear criteria for defining levels of risk in first-in-man studies. The guideline appears to deliberately place the onus and responsibility for defining risk on the shoulders of the sponsor and does not meet the requirements of Directive 2001/20/EC that requires additional public assurance through responsible action by Competent Authorities and ethics committees.	Agreed. The text has been modified to take account of this.
246-247 (EFPIA)	Please rephrase – The design is not used to identify the risks. It is the risks that define the design. A rewording is therefore proposed to replace: "To identify those risks several key aspects of the trial design should be evaluated and guide the choice of:" "***Following identification of those risks several key aspects of the trial design can be chosen****: …"*	Agreed. The text has been modified to take account of this.
248 &/or 271 (BARQA)	Informed consent of subjects is not mentioned. In some places this draft guidance reiterates regulations already in force (e.g. expedited reporting of SUSARs) so it is surprising that there is no section on consent of subjects, given the circumstances from which this has	Agreed: New text added [line 266-268]

	guidance has arisen. It should be re-emphasised that subjects should be informed of:- the basis of the risk benefit analysis; the degree to which factors are unknown; and that subjects should have a prior interview with ample time to consider. These are key requirements and should be added. Regulations & guidelines for fully informing subjects before gaining consent should be adhered to. Special emphasis should be placed upon informing subjects of; the basis of the risk benefit analysis; the degree to which factors are unknown; and that subjects should have a prior interview with ample time to consider participation.	
248-255 (EFPIA)	Although this section omitted that 'First in Man' studies are typically **single-dose**, dose-escalation studies, in some diseases individual patients only receive multiple 'single doses' separated by a suitable washout period. The 'number of doses' is omitted from the list. This is relevant as monitoring requirements may be different between a design that administers only a single dose to each subject and one in which multiple 'single doses' are administered. The following addition to the list is therefore suggested. **"number of doses"**	Agreed. Text added
248-255 (Drusafe)	Although this section omitted that 'First in Man' studies are typically single-dose, dose-escalation studies, in some diseases individual patients only receive multiple 'single doses' separated by a suitable washout period. The 'number of doses' is omitted from the list. This is relevant as monitoring requirements may be different between a design that administers only a single dose to each subject and one in which multiple 'single doses' are administered. Suggest addition of '*number of doses*'.	Agreed. Text added
248-255 (ABPI)	Rate of administration (e.g. slow IV infusion) can also be a key aspect of trial design to manage risk	Agreed. Text added
248-255	Although this section omitted that FIH studies are typically **single-dose**,	Agreed. Text added

(BIO)	dose-escalation studies, in some diseases individual patients only receive multiple 'single doses' separated by a suitable washout period. The 'number of doses' is omitted from the list. This is relevant as monitoring requirements may be different between a design that administers only a single dose to each subject and one in which multiple 'single doses' are administered. We suggest addition of "number of doses".	
255 (BIA)	We suggest adding "Route of administration" Generally, intravenous infusion is considered to be the safest, because it can be interrupted or terminated in case of serious adverse events.	Agreed. Text added
251 and after 304 (CAG)	Please consider elaborating on issues of interval between dosing subjects within the same cohort, especially to consider individual sequence of subjects rather than concurrence of dose administration in first uses.	Agreed. Text added
256-260 (ABPI)	The scope of the guidance is single dose first-in-man and the need for a IDSMB is questionable where there is a well defined strategy for managing risk including a plan for monitoring safety and managing of any adverse reactions and well defined stopping and dose escalation criteria. FIM studies are very closely monitored by the responsible investigator and medical staff assessing safety measures in real time throughout the course of the investigation (with appropriate follow-up) and the sponsor study team including medical contact (e.g. unblinded review of emerging safety data). FIM studies are usually very dynamic and representatives from the sponsor and investigators are usually best placed to analyze the data on time. The protocol should describe the strategy for managing risk including a plan for monitoring safety and managing of any adverse reactions ~~and the use of an independent safety monitoring board~~.	Agreed. Text added

258 (ACRO)	ACRO believes a statement regarding the need for a formalized process for Sponsor review of protocols for any FIM studies with a potential high-risk medicinal product should be inserted following the words "first-in-man study" on line 258. ADD: "**Sponsor should assure and document the review and approval of any first-in-man study protocol for a potential high-risk medicinal product. This would include a review and approval process by preclinical, CMC, and clinical scientific personnel appropriate to make such evaluations**."	Agreed. Text added
258 (EFPIA)	As the scope of the guidance is single dose First In Man clinical trials for high risk, the need for an independent safety monitoring board is questioned where there is a well defined strategy for managing risk including a plan for monitoring safety and managing of any adverse reactions and well defined stopping and dose escalation criteria. This could imply that allFIM studies with high-risk products require an independent safety monitoring board. This is inconsistent with the statement (line 327) "*Sponsors should consider the use of an Independent Drug Safety Monitoring Board (IDSMB) and if this is not considered appropriate, this should be justified*.". The inconsistency should be removed. In addition, managing of 'any' adverse event - wording is too general and should be consistent with the one used in Line 334 and 336. It is therefore suggested to revise the sentence *"The protocol should describe the strategy for managing risk including a plan for monitoring safety and managing of ~~any~~ **likely** adverse reactions **which may include** ~~and~~ the use of an independent safety monitoring board."*	Agreed. Text added Agreed. Text added
258-259 (MSD)	"The protocol should describe the strategy for managing risk including a plan for monitoring safety and managing of any adverse reactions and the use of an independent safety monitoring board."	Agreed. Text modified.

	We propose the suggestion to use an independent safety monitoring board be considered on a case-by case basis, where deemed necessary and supportive	
258-260 (WP)	We believe that use of an independent expert safety monitoring board in a Phase 1 environment is not practical. The lack of resources to fulfil this role is further compounded by the time commitment that would potentially be required to commit to frequent meetings (i.e., weekly/bi-weekly for typical SAD or MAD studies) and short duration of these studies. We recommend that the statement be revised from "*The protocol should describe the strategy for managing risk including a plan for monitoring safety and managing of any adverse reactions and the use of an independent safety monitoring board*." to "*The protocol should describe the strategy for managing risk including a plan for monitoring safety and managing of any adverse reactions and the use of an independent expert, as deemed necessary by the Sponsor ~~safety monitoring board~~*."	Agreed. Text modified
258-260 (ACRO)	We suggest that this read: "The protocol should describe the strategy for managing risk including a plan for monitoring safety and managing of any adverse reactions." DELETE: "**and the use of an independent safety monitoring board**".	Agreed. Text modified
258-260 (Roche)	The sentence does not allow option of **not** having an independent safety monitoring board, whereas in lines 328-329 suggests that there may be occasions where sponsor may consider this not appropriate. The two sections should be more consistent? Consider addition of "where appropriate" to the beginning of the	Agreed. Text modified

	sentence in lines 258 – 260 i.e. Where appropriate, the protocol should describe the strategy for managing risk including a plan for monitoring safety and managing of any adverse reactions and the use of an independent safety monitoring board.	
259 4.4.1 (FCP)	Clinical requirements : General aspects The use of an Independent Drug Safety Monitoring Board (IDSMB) is most of the time not necessary and not doable during First-in-Man studies . These studies are most of the time single centre studies of short duration. There is therefore one investigator who is responsible for the safety of the subjects. Progression to next higher dose occurs every week or every 2 weeks after a meeting involving at least the investigator and the sponsor's medical monitor during which all relevant safety data are reviewed. Both the investigator and the sponsor's medical monitor need to be fully experienced in FIM trials. Another expert may involved in this meeting if specific risks are expected or have been identified. As far as stopping rules and supervision of adverse events is fully described in the protocol, there is no added value of involving a third party safety monitoring board. In addition, it would certainly be difficult to find enough INDEPENDENT EXPERTS IN EARLY DEVELOPMENT that would be available for teleconferences every week 365 days by 365 days for all high-risk products FIM studies. We think an IDSMB should remain the exception and therefore it would be better to justify when it is necessary. We suggest line 259 to state "The protocol should describe the strategy for managing including a plan for monitoring safety and managing of any adverse reactions and **if deemed necessary for specific reasons,** the use of **a specific expert** or even, when a justification exists, an independent drug safety monitoring board.**"**	Agreed. Text modified
259 (J&J)	Use of an independent safety monitoring board appears mandatory here, but is noted to be open to consideration in line 328.	Agreed. Text modified

	Note that consideration should be given to using an independent SMB.	
259 (EuropaBio)	The Guidance does not intend (see line 329) to mandate an IDSMB as is currently written. Delete "an independent", replace with *"a"*	Agreed. Text modified
259-260 (EFGCP)	An independent safety monitoring board It is probably unrealistic to imagine that sponsors will pay for an IDSMB for each protocol. The CT Directive and its Guidance documents recommend an IDSMB in the context of high morbidity or high mortality studies, not Phase I studies.	Agreed. Text modified
259-260 (Drusafe)	The statement seems to imply an independent safety monitoring board is always required. This is not always the case, as has been stated in latter sections of this Guideline. Propose: 'The protocol should describe the strategy for managing risk including a plan for monitoring safety and managing any adverse reactions and the use of an independent safety monitoring board, if deemed necessary by the sponsor.'	Agreed. Text modified
259-260 (BIO)	The statement seems to imply an independent safety monitoring board is always required. This is not always the case, as is been stated in the latter sections of this guideline. We suggest the alternate wording: "The protocol should describe the strategy for managing risk including a plan for monitoring safety and managing ~~of~~ any adverse reactions and	Agreed. Text modified

	the use of an independent safety monitoring board, if deemed necessary by the sponsor."	
259-260 (ECRIN)	An independent safety monitoring board It is probably unrealistic to imagine that sponsors will pay for an IDSMB for each protocol. The CT Directive and its Guidance documents recommend an IDSMB in the context of high morbidity or high mortality studies, not Phase I studies. Better should be to have a unique DSMB for all the phases of drug development preceding phase 3, starting to have a unique DSMB at phase 3.	Agreed. Text modified
259-260 (GCPA)	The terms 'independent data monitoring board' and 'Independent Drug Safety Monitoring Board (IDSMB)' should be replaced with the term 'Data Monitoring Committee' for consistency with CHMP and EMEA usage. Reference should be made to the 2005 CHMP/EMEA Guideline on Data Monitoring Committees and to the 2005 WHO-TDR Operational Guidelines for Data & Safety Monitoring Boards. The latter provides clearer guidance on the determination of the need and role of DMCs in clinical trials.	This helpful comment was noted. Based on other comments, the text has been modified to omit a specific reference to IDSMB.
259-260 (BIA)	This implies that high-risk safety monitoring boards will become mandatory for high-risk drug candidates. There is already oversight by the ethics committee in matters regarding the safety of trial subjects. FIM studies with potential high risk products are very closely monitored by the responsible investigator and medical staff assessing safety measures throughout the course of the investigation as well as by the sponsor study team. The use of an independent safety monitoring board for every potentially high risk product would make it very difficult to run studies in a time effective fashion if required to meet before every dose escalation. We believe that a well thought out and executed risk management strategy may not require an independent safety monitoring board to manage risk. Revise as follows: The protocol should describe the strategy for managing risk including a plan for monitoring safety and managing any adverse reactions **~~and the~~**	Agreed. Text modified

	~~**use of an independent safety monitoring board**~~.	
259 (EuropaBio)	We are concerned regarding the Independent Drug Safety Monitoring Board (IDSMB) - the guideline states that if the IDSMB is not considered appropriate **it should be justified**. It is the responsibility of the sponsor to secure safety for the volunteers participating in the trial and to define stopping rules for the individual subjects, cohorts and trial. The process and responsibilities for making decisions reg. dosing/dose escalation should be clearly described in the protocol. How to organise this process is the sole responsibility of the sponsor, including an IDSMB or not does not have to be justified. We recommend to delete the text on page 8 line 259: ... "and the use of an independent safety monitoring board" and on page 9, line 327: …. "Sponsors should consider the use of an Independent Drug Safety Monitoring Board (IDSMB) and if this is not considered appropriate, this should be justified."	Agreed. Text modified.
259 (AMGEN)	The Guidance does not intend (see line 329) to mandate an IDSMB as is currently written. Delete "an independent", replace with *"a"*	Agreed. Text modified
259 (EBE)	The Guidance does not intend (see line 329) to mandate an IDSMB as is currently written. Delete "*an independent*", replace with "a"	Agreed. Text modified
260 (ICO)	The standard approach to designing oncology cytotoxic trials account for all the issues described in section 4.4 Add one reference to design of traditional oncology phase 1 trials as an example (J. Whitehead, Y. Zhou, N. Stallard, et al. Br. J. Clin Pharmacol, 52,1-7, 2001.)	This reference is noted. However, the guideline will refer only to existing oncology guidelines.
261 (IPOPI)	Why use placebo in these trials? In other less high risk potential it makes sense, but not in a first-in-human	The use of placebo provides appropriate comparative data and can help to evaluate the likelihood of an adverse event being an adverse reaction. Text

		modified.
261-265 (AMS)	The inclusion of subjects receiving a placebo in trials of "high-risk" biologicals may not be desirable. The safety of the active compound should be established before proceeding into a randomised, placebo controlled study.	The use of placebo provides appropriate comparative data and can help to evaluate the likelihood of an adverse event being an adverse reaction. Text modified.
261 to 265 (BARQA)	How do they propose to be able to take account the number of subjects receiving active treatment in blinded trials? As subject safety is paramount, the sponsor should consider ways of being able to monitor the subjects taking active treatment, whilst maintaining the blind. Line 265 additional wording: - In high risk blinded trials consideration should be given to having an on-site unblinded medical oversight role, whilst maintaining measures to preserve the integrity of the blind for those involved in the treatment and/or assessment of subjects.	Agreed. Text added.
261 Cancer Research	Studies in patients rarely include placebos. In general the guidance focuses on normal volunteer studies and does not consider the differing issues found in patient studies.	Agreed. Text modified
261-5 (IFAPP)	True identity of the administered IMP (placebo) should be known by the investigator to avoid any potential delay on encountering a potentially dangerous ADR Using protocol designs with masking higher than single blind randomisation should be avoided if there are no cogent reasons for it	Agreed. Text added.
261-265 (RS-LTD)	The content of this paragraph is not very clear.	Text clarified.
261-265 (ABPI)	As subject safety is paramount, the sponsor should consider ways of being able to monitor the subjects taking active treatment, whilst maintaining the blind. Suggested additional wording A single-blind study design may be appropriate for the rapid interpretation of safety data providing the other study data are not compromised. In blinded trials consideration should be given to having	Agreed. Text modified.

	an on-site unblinded medical oversight role, whilst maintaining measures to preserve the integrity of the blind for those involved in the treatment and/or assessment of subjects.	
263 (Roche)	Can the wording "…*taking into account* the number of subjects that *might* have received the active medicinal product" be clarified?	Agreed. Text modified
263 (BMS)	Is the point being made that block randomization could lead to the first few subjects at any dose level receiving only placebo? This concern seems to be overcome by lines 306-7 which mandate that the complete cohort be dosed before proceeding to the next. Proposal: " ... it will be important that any decisions taken with respect to subsequent dosing at the same dose level and or dose escalation, take into account the number of subjects that might have received the active medicinal product and consider unblinding of first-dosed subjects prior to dosing the remainder of or next cohort."	Text modified to clarify this point
265 (EFGCP)	The Informed Consent process is of utmost relevance at this stage of drug development. This should be reflected in this guideline. Suggested addition: *The Informed Consent process should ensure a detailed communication of all potential risks and documented verification of the participants' comprehensive understanding of the involved risks and the safe-guards, including the indemnity conditions in case of short- and long-term health damages.*	Agreed. Text modified
265 (ACRO)	At the end of line 265, we suggest inserting: ADD: "**FIM studies with potential high-risk products should be single-blinded or unblinded.**"	Agreed. Text modified
4.4.1 (Eucrof)	These general aspects apply for any phase 1 trial. The risk assessment has to be performed for any compound.	Agreed. Many aspects of this guidance also apply to any Phase I trial

4.4.2 Protocol Design **4.4.2.1. Choice of subjects**		
267-284 (MRC)	CR-UK have made a separate submission in relation to the participation of patients in first–in man studies and MRC supports the issues highlighted by that submission, in particular that relating to equating potential toxicity and adverse events to their risk in trials of oncology treatments.	Noted.
268 (EFPIA)	The word tolerance can be confusing, suggested wording instead: ***'tolerability'***	Agreed. Text modified.
268 (ABPI)	Replace "tolerance" with "tolerability" to avoid ambiguity with pharmacological tolerance, which is not the intended meaning One of the main purposes of a first-in-human trial is to assess tolerability and subjects are not generally expected to derive any therapeutic benefit	Agreed. Text modified.
268 (BIA)	Replace "tolerance" with "tolerability" to avoid ambiguity with pharmacological tolerance, which is not the intended meaning. Modify as follows: One of the main purposes of a first-in-man trial is to assess **tolerability** and subjects are not generally expected to derive any therapeutic benefit.	Agreed. Text modified.
268- 269 (EBE)	*"One of the main purposes of a first-in-man trial is to assess tolerance and subjects are not generally expected to derive any therapeutic benefit."* It should be considered that in certain areas, such as oncology or immunotherapy a trial participant may benefit from the treatment. For "medicinal product requiring special attention" it should be considered to enrol patients instead of healthy volunteers in first-in	Agreed. Text modified

	man-trials.see also comment to lines 9 –10 Change as follows: *"One of the main purposes of a first-in-man trial is to assess tolerance. and subjects are not generally expected to derive any therapeutic benefit.* *Depending on the trial design, subjects may derive a therapeutic benefit.* *For "medicinal product requiring special attention" it should be considered to enrol patients instead of healthy volunteers in first-in-man trials."*	
268-269 (EBE)	"One of the main purposes of a first-in-man trial is to assess tolerance and subjects are not generally expected to derive any therapeutic benefit." It should be considered that in life threatening and severely disabling clinical settings a trial participant may benefit from the treatment. For "higher risk" it should be considered to enrol patients instead of healthy volunteers in first-in man-trials. See also comment to lines 9 –10 Change as follows: *"One of the main purposes of a first-in-man trial is to assess tolerance. ~~and subjects are not generally expected to derive any therapeutic benefit.~~ Depending on the trial design, subjects may derive a therapeutic benefit. For "higher risk medicinal products" the enrolment of patients in first-in-man trials instead of healthy volunteers should be considered."*	Agreed. Text modified.
4.4.2.1 (AGAH)	The recommendation should be followed for any development. Healthy subjects should never participate simultaneously in another trial. Also concurrent medication should not be allowed in any first-in-man trial – neither in patients nor in healthy subjects.	Agreed this is the general expectation but there may be a few exceptions such as very rare diseases.

271 (EFPIA)	**An additional criterion in the assessment of the risk for a FIM trial should be the indication, possible benefit and the targeted patient population (e.g. life expectancy), if the trial is carried out in patients, as is often seen in oncology.** It is therefore suggested the following additional statement. "***The indication, possible benefit and the targeted patient population (e.g. in relation to life expectancy), if done in patients, should also be taken into consideration for this assessment. Special consideration should be given to the clinical setting foreseen for the FIM study, e.g. possible benefits for patients, if included in FIM trials, have to be taken into account as often seen in oncology****."*	Agreed. Text modified.
272 (ABPI)	The choice of study population, ….. i.e. healthy subjects or patients… …	Text modified
272 (GCPA)	The term 'healthy subjects' may not be the most appropriate. It might be clearer to use the term 'subjects not expressing the condition the chemical or biological entity is intended to address'. Correct throughout.	Disagree. Healthy subjects is a well understood and accepted term.
272-275 (MP)	Regarding Section 4.4.2.1 Choice of Subjects for First-in-man Trials with High-Risk Medicinal Products, the guideline states: *"….The choice of the study population for high-risk medicinal products, i.e. healthy subjects or patients should be fully justified by the Sponsor on a case-by-case basis. Several factors should be considered, such as (a) the risks inherent in the type of medicinal product, (b) its molecular target (c) immediate and potential long term toxicity (d) the presence of the target in healthy subjects or in patients only and (e) the possible higher variability in patients….."* We do not have a clear understanding of what is expected regarding "potential long term toxicity". In an early stage of development, the compound has only been dosed in animal models for up to 28 days, at most. With this consideration, we feel that it will be difficult to evaluate the potential long term toxicity.	Text clarified. Potential long term toxicity can be based on the pharmacodynamic properties and duration of action of the medicinal product. E.g. immunotherapy.

	We recommend the inclusion of information to clarify the expectation regarding "potential long term toxicity". **Please also consider early development situations where it will be difficult to evaluate "potential long term toxicity".**	
272-276 FRAME	The draft guidelines should consider more fully how doses for first-in-man studies in patients should be estimated for a potentially high risk medicinal product and the circumstances under which the starting dose for such trials should be within the predicted pharmacologically active range. This is particularly significant given that some IMPs may have a narrow therapeutic range, and risk-benefit analysis may make it unacceptable to conduct phase 1 trials in healthy volunteers, but acceptable for trials in patients who do not have alternative treatment options. After point e) insert: f) the ability of a particular patient group to give their consent without coercion especially where patients have few, if any, other treatment options g) the predicted therapeutic window of the IMP. Where this is narrow, risk-benefit analysis may support the case for studies on patient groups rather than on healthy volunteers.	Agreed. Text modified
272-281 (J&J)	In rare cases patients could benefit in an early trial or preclinical toxicities may not be relevant to the patient population (such as genotoxicity for an end stage oncology patient). Include in discussion consideration of any potential benefit to a patient and the relevance in the patient population of preclinical toxicology findings.	Agreed. Text modified
275 (ABPI)	(d) the relative presence of the target in healthy subjects and patients….	Text modified
275 (BIA)	Very little information on long term toxicity data would be available at this stage of development.	The guidance asks sponsors to consider potential long term toxicity e.g. immunotherapy. The text has been clarified.
275 & 276 (FECS)	Items D & E are particularly important in subjects with cancer.	Agreed. Text modified.

	This should be stated.	
275-6 (IFAPP)	The list for consideration may be amended by another item Suggest adding “the potential pharmacogenomic difference between the targeted patient group and the healthy subjects” to the list	Agreed. Text modified.
“	This line discusses potential long term toxicity including reversibility and reproduction toxicity. It should further stress reversibility, e.g. symptoms disappear upon stopping the medication and then reappear when drug administration is started again	Agreed. Text modified.
276 (IPOPI)	It would make the outcome of a first-in-human trial difficult to assess if patients are using other medication. Therefore is it correct to use patients?	Text clarified.
273-278 (CAG)	Please list also as one of the factors to consider “risks that use of the product may adversely affect the participant/patients’ ability to benefit from other products or interventions”.	Agreed. Text modified
274 (Roche)	When deciding on the risk inherent in the type of medicinal product”, it is important that those risks (and uncertainty about them) be quantified and justified	Agreed. Text modified.
275,280-281 (EBE)	This paragraph discusses in several places the potential for long-term toxicity, potential long-term consequences on physiological systems and potential long-term safety problems. Very little information on long-term toxicity is likely to be available at this stage of development. Add the examples of what information you might have on potential long-term toxicity. Delete the last sentence about *“Special considerations should be given to potential long-term consequences on physiological systems and potential long-term safety problems.”*	Agreed. Text modified.

	Add the words: *"Several factors should be considered, such as…c) immediate and potential long term toxicity (e.g., information from transgenic or knock-out mice, data from other molecules with similar pharmacological mechanism, etc.), d)…"*	
275& 280-281	This paragraph discusses in several places the potential for long-term toxicity, potential long-term consequences on physiological systems and potential long-term safety problems. Very little information on long-term toxicity is likely to be available at this stage of development. It is suggested to add the examples of what information one might have on potential long-term toxicity, and to delete the last sentence "Special considerations should be given to potential long-term consequences on physiological systems and potential long-term safety problems." "*Several factors should be considered, such as (a) the risks inherent in the type of medicinal product, (b) its molecular target (c) immediate and potential long term toxicity* ***(e.g., information from transgenic or knock-out mice, data from other molecules with similar pharmacological mechanism, etc.)***. *(d) the presence of the target in healthy subjects or in patients only and (e) the possible higher variability in patients".*	Agreed. Text modified.
275, 208-281 (Drusafe)	The terms "potential long-term consequences on physiological systems and potential long-term safety problems" should be clarified to provide context for assessment.	Text modified.
275,208-281 (ABPI)	This paragraph discusses in several places the potential for long-term toxicity, potential long-term consequences on physiological systems and potential long-term safety problems. Very little information on long term toxicity is likely to be available at this stage of development. It would be helpful to provide more specific guiding principles here. If all theoretical safety aspects were equal (i.e. risks could not be	Agreed. Text modified.

	differentiated a priori), should the new medicine be used in the healthy population or a patient? Suggest add new paragraph: For first-in-man where it is particularly difficult to characterise the risk profile (see above), a confirmatory pharmacodynamic measure is strongly recommended as a means of establishing proof of pharmacology and confirming preclinical experience.	
276 (EFPIA)	For better clarity, it is suggested to amend the sentence. "***The disease state and c****oncurrent medication in patients may give rise to* ***greater variability in response and*** *the potential for interactions with the possibility for adverse reactions and/or difficulties in the interpretation of results".*	Agreed. Text modified.
276 (Drusafe)	Rephrase for clarification. Propose: 'The disease state and concurrent medication in patients may give rise to greater variability in response and the potential for interaction…."	Agreed. Text modified.
276 (BIO)	Rephrase for clarification. We suggest the alternate wording: "The disease state and concurrent medication in patients may give rise to greater variability in response and the potential for interaction…"	Agreed. Text modified.
276 (BMS)	As noted in lines 9-10, no benefit is expected to subjects. In most cases, assessment of first doses will be more safely performed in otherwise healthy, generally younger subjects.	Agreed. Text modified.

	Consider adding to line 276: "... and (f) the ability of healthy volunteers to tolerate any potential side effects..."	
278 (RS-LTD)	Suggestion to insert The sponsor should discuss the potential for on-target and off-target effects and how this will be handled in the clinical trial. Furthermore, the sponsor should also discuss the ability of the subjects of choice to maintain a normal physiological response to challenge in the presence of the high-risk IMP.	See modified text.
278 (EuropaBio)	we would welcome clarification in terms of practical impact of the following recommendation; examples would be welcome: "Sponsor should also consider whether any effects that may be seen in the population of choice are indeed relevant and can be extrapolated to the intended clinical application.". We believe that it is relevant but that "prior to Phase I" might be too early in the development of the product to implement this recommendation.	Agreed. Text modified. Deleted
280-281 (AMGEN)	This paragraph discusses in several places the potential for long-term toxicity, potential long-term consequences on physiological systems and potential long-term safety problems. Very little information on long term toxicity is likely to be available at this stage of development. Add the examples of what information you might have on potential long-term toxicity. Delete the last sentence about "Special considerations should be given to potential long-term consequences on physiological systems and potential long-term safety problems." Add the words: *"Several factors should be considered, such as…c) immediate and potential long term toxicity (e.g., information from transgenic or knock-out mice, data from other molecules with similar pharmacological mechanism, etc.), d)…"*	Agreed. Text modified

280-281 (BIO)	This paragraph discusses in several places the potential for long-term toxicity, potential long-term consequences on physiological systems and potential long-term safety problems. Very little information on long term toxicity is likely to be available at this stage of development. We request addition of examples of what information is available on potential long-term toxicity. We suggest the deletion of the last sentence "Special considerations should be given to potential long-term consequences on physiological systems and potential long-term safety problems." We suggest the alternate wording "Several factors should be considered, such as…c) immediate and potential long term toxicity (e.g., information from transgenic or knock-out mice, data from other molecules with similar pharmacological mechanism, etc.), d)…"	Agreed. Text modified
280-281 (EuropaBio)	This paragraph discusses in several places the potential for long-term toxicity, potential long-term consequences on physiological systems and potential long-term safety problems. Very little information on long term toxicity is likely to be available at this stage of development. Add the examples of what information you might have on potential long-term toxicity. Delete the last sentence about "Special considerations should be given to potential long-term consequences on physiological systems and potential long-term safety problems." Add the words: *"Several factors should be considered, such as…c) immediate and potential long term toxicity (e.g., information from transgenic or knock-out mice, data from other molecules with similar pharmacological mechanism, etc.), d)…"*	Agreed. Text modified
281 (AMGEN)	Adding text to focus considerations on agents likely to require a long-term monitoring plan Add to the end of the sentence: *"for agents anticipated to produce a demonstrable PD effect beyond the*	Agreed. Text modified.

	period required to fully assess PK."	
281 (AMGEN)	Add information on half life (or mean residence time). Drugs with long duration of action may be more appropriate to dose in patients since toxicity may be prolonged	Agreed. Text modified.
281 (EBE)	Adding text to focus considerations on agents likely to require a long-term monitoring plan Add to the end of the sentence: *"for agents anticipated producing a demonstrable PD effect beyond the period required to fully assess PK."*	Agreed. Text modified.
281 (EBE)	Add information on half life (or mean residence time). Drugs with long duration of action may be more appropriate to dose in patients since toxicity may be prolonged	Agreed. Text modified.
281 (EFPIA)	It is suggested to add a statement to focus considerations on agents likely to require a long-term monitoring plan "*Special considerations should be given to potential long-term consequences on physiological systems and potential long-term safety problems* ***for agents anticipated to produce a demonstrable PD effect beyond the period required to fully assess PK.****"*	Agreed. Text modified.
281 (Drusafe)	Adding text to focus considerations on agents likely to require a long-term monitoring plan Add to the end of the sentence: "for agents anticipated to produce a demonstrable PD effect beyond the period required to fully assess PK."	Agreed. Text modified.
281 (Drusafe)	Add information on half life (or mean residence time). Drugs with long duration of action may be more appropriate to dose in patients since toxicity may be prolonged	Agreed. Text modified.
281 (BIO)	Text should be added to focus on agents likely to require a long-term	Agreed. Text modified.

	monitoring plan. We suggest that the following text be added to the end of the sentence: "for agents anticipated to produce a demonstrable PD effect beyond the period required to fully assess PK."	
281 (BIO)	We suggest addition of information on half life (or mean residence time). Drugs with long duration of action may be more appropriate to dose in patients since toxicity may be prolonged.	Agreed. Text modified.
281 (EuropaBio)	Adding text to focus considerations on agents likely to require along-term monitoring plan Add to the end of the sentence: *"for agents anticipated to produce a demonstrable PD effect beyond the period required to fully assess PK."*	Agreed. Text modified.
285 (EuropaBio)	While fully relevant in some instances, the reference to infusion over hours may not be appropriate in cases where the starting dose is very low. Due to potential adsorption problems (as mentioned ln. 137), the higher volume needed to infuse over hours may introduce uncertainty. To ensure consistency this section should reflect the balance. In addition, the limitation of slow infusion in relation to future intended routes of administration should be described.	See modified text.
281 (EuropaBio)	Add information on half life (or mean residence time). Drugs with long duration of action may be more appropriate to dose in patients since toxicity may be prolonged	Agreed. Text modified.
281 (BIA)	This will depend on the <u>duration</u> of PD effects.	Agreed. Text modified.
282 (J&J)	Editorial change: word missing Add underlined text: *Healthy subjects or patients included in first-in-man clinical trials must not be simultaneously <u>participating</u> in another clinical trial.*	Agreed. Text modified.

282 (GCPA)	A blanket exclusion of patients being simultaneously enrolled in another clinical trial may not be in the best interest of the patient in all cases.	Agreed. Text modified.
282-283 (EFGCP)	Must not be simultaneously in another trial A volunteer died in 1985 at a Phase I unit in Dublin because of this issue. It is agreed that this is an absolute exclusion criterion. However, Phase I units depend on the honesty of volunteers in this regard. The Guideline should recommend measures which would create a really objective measure of participation in clinical trials, e.g., volunteers could be given a trial participation card, which must be filled out successively by all Phase I units for all volunteers. Entries could be anonymous regarding the Phase I units visited. A volunteer who “lost” his/her card would be denied access to any trial at any unit. However, this system relies on the honesty of Phase I units actually entering each study in every case. Violations could lead the Phase I unit losing its accreditation or qualification with its IEC.	See modified text.
282-283 (ECRIN)	Must not be simultaneously in another trial A volunteer died in 1985 at a Phase I unit in Dublin because of this issue. It is agreed that this is an absolute exclusion criterion. However, Phase I units depend on the honesty of volunteers in this regard. The Guideline should recommend measures which would create a really objective measure of participation in clinical trials, e.g., volunteers could be given a trial participation card, which must be filled out successively by all Phase I units for all volunteers. Entries could be anonymous regarding the Phase I units visited. A volunteer who “lost” his/her card would be denied access to any trial at any unit. However, this system relies on the honesty of Phase I units actually entering each study in every case. Violations could lead the Phase I unit losing its accreditation or qualification with its IEC. Another solution could rely on 'the French model' for all Europe: one large register for all phase I participants for EU, which could grow into a	See modified text.

	global register.	
282 to 284 (BARQA)	There is a need to protect the volunteers from multiple participation ("over volunteering") in a short period of time. Therefore immediately consecutive trials should be avoided as well as simultaneous ones. Healthy subjects or patients included in first-in-man clinical trials must not be simultaneously, or immediately consecutively, in another clinical trial. It is important to include clear exclusion criteria to prevent concomitant or immediately consecutive, exposure to investigational medicinal products.	Agreed. Text modified.
282-284 (EFPIA)	Although it is normal clinical practice and not specific to high-risk products, the following rewording is suggested. "*Healthy subjects or patients included in first-in-man clinical trials must not be simultaneously* ***or immediately consecutively,*** *in another clinical trial. It is important to include clear exclusion criteria to prevent concomitant* ***or immediately consecutive,*** *exposure to investigational medicinal products"*.	Agreed. Text modified.
282-284 (PDA)	Delete the paragraph Rationale: Adequately covered by existing ICH GCP guidance	This guidance is specific for first in man trials for medicines requiring special consideration.
282-284 (ABPI)	This is standard practice Delete 282-284	This guidance is specific for first in man trials for medicines requiring special consideration.
284 (ABPI)	Subjects should be informed of the risk benefit analysis during the informed consent; the degree to which factors are unknown. Subjects should have a prior interview with ample time to consider. Suggested text after line 284: Patients should be informed of the basis	See modified text.

	of the risk benefit analysis for the study, the degree to which factors are unknown and should have prior interview with time to consider the study before participation.	
4.4.2.1 (Eucrof)	The recommendations should be followed for any development. Healthy subjects should never participate simultaneously in another trial. Also concurrent medication should not be allowed in first-in-man studies. For the patients, the concomitant medication has to be discussed case by case.	See modified text.
4.4.2.2 Route and rate of administration		
4.4.2 (Drusafe)	Lines 301 and 302 speak to the need of the n to vary depending the PK and PD. Allowing for a larger N in a FIM study for a "high-risk" IMP secondary to PD concerns seems dismissive of potential safety concerns. For "high-risk" products, with the exception of indications such as Oncology, PD concerns should be handled in Phase 2 once safety and tolerability have been realized.	The text is intended to refer to the objective of the trial which is likely to be safety and tolerability.
285-290 (ICAPI)	*4.4.2.2 Route and Rate of administration* The same route of administration, and the same or lower rate of administration as are used in the animal trial/s should be used in the clinical trials. It appears that this did not occur in the TGN1412 trial (infusion rate of one hour in monkeys compared to 3-6 minutes in humans, see Duff Report and Investigator's Brochure); and this is therefore is worthy of greater emphasis in the guideline.	See modified text.
4.4.2.2 (ACRO)	In general, intravenous administration of a potential high-risk medicinal product precludes the possibility of observing local effects, with the exception of vessel irritation. Yet, the intensity of an immunological effect, for instance, might well be revealed if a minimal test dose is administered subcutaneously. We suggest that the final Guideline might include a discussion of this issue relative to the route of administration. This discussion might begin with guidance concerning useful distinctions in initial dosing using potential high-risk products	See modified text.

	which are meant ultimately for intravenous/subcutaneous dosing versus potential high-risk products meant for oral administration.	
4.4.2.2 (Eucrof)	The administration mode should be adjusted to the possible risks. A starting dose will always be small. Therefore slow rate infusions starting with short term infusions with exactly defined dose and infusion time should be applied. Depending on the pharmacodynamics and the pharmacokinetics dose increase could be performed by prolongation of infusion time as well as increase of dose.	Agreed. Text modified.
286 (Rottapharm spa)	Careful consideration should be given to the administration route. While I agree with this statement I would suggest considering that, depending on the metabolic profile of the new product, slow intravenous infusion might be more harmful than a bolus injection. This is due to the fact that slow infusion allows the liver to produce higher amounts of potentially toxic metabolites, whereas a bolus injection, due to saturation of the liver enzymes responsible for the formation of the metabolites, might produce lower circulating level of these metabolites. I have witnessed an actual case in the past for an anticancer drug that well tolerated after bolus intravenous injection and produced serious adverse events including one death when the same dose was administered as a slow infusion. Further studies indicated that the toxic effects and death were due to the metabolites that circulated at much higher level after infusion compared with a bolus injection.	See modified text.
286 (ABPI)	Additional text as a guide. The minimum rate of intravenous infusion should be such that the infusion time is not less than 60 minutes.	See modified text.
4.4.2.2 (AGAH)	The administration mode could be adjusted to possible risks. A starting dose will always be very low. Therefore short term infusion could be possible. Depending on PD and PK dose escalation could be performed by prolongation of infusion as well as increase of dose.	See modified text.
287 (EFPIA)	A slow intravenous infusion is clearly to be preferred compared to bolus administration. However, a general recommendation of infusion times	Agreed. Text modified.

	of several hours for any indication/substance may be too restrictive or even not fully justified. For substances with substantially delayed effects (e.g. CNS drugs with slow penetration of blood-brain barrier) or substances with long half-lives there is no additional safety benefit by prolonging infusion times up to several hours. A "slow infusion" bears the risk of not reaching necessary C_{max} concentration for receptor activation and thus a false clinical safety evaluation of the administered dose. This should be considered. Infusion velocity should be chosen depending on pharmacokinetics, mechanism of action etc.. It is thus suggested to amend the statement as proposed. *"In the case of an intravenous administration, a slow infusion ~~over several hours~~ may be more appropriate than a slow bolus over several minutes.* ***The infusion period should be justified*** *"*	
287-289 Cancer Research	The appropriateness of a slow infusion is highly dependent on the chemical stability of the drug in solution. In the case of an intravenous administration, a slow infusion over several hours, if possible, may be more appropriate than a slow bolus over several minutes.	Agreed. Text modified.
288 (IPOPI)	Intravenous administration of the medicine appears ideal, but not all trial medicinal products can be given that way	See modified text.
288 4.4.2.2 (FCP)	We suggest to remove references to vague timing for comparing slow infusion (over several hours) and bolus (several minutes) We recommend "In the case of an intravenous administration, a slow infusion may be	See modified text.

	more appropriate than a bolus"	
288 (EBE)	An infusion over hours will maximize the administered volume and subsequently lowers significantly the drug concentration in the solution to be infused. The limit of dilution would be considered as the lowest concentration being measurable reliably, however, without measuring stability endpoints in the dilution. *"…a slow infusion over several hours may be more appropriate than a slow bolus over several minutes. This would allow monitoring for an adverse reaction and if clinically indicated, timely discontinuation of the infusion in order to prevent a serious outcome. The method of administration should be justified."*	Agreed. Text modified.
288 (Roche)	"…a slow infusion over several hours may be more appropriate than a slow bolus over several minutes…" An infusion over hours will maximize the administered volume and subsequently lowers significantly the drug concentration in the solution to be infused. The limit of dilution would be considered as the lowest concentration being measurable reliably, however, without measuring stability endpoints in the dilution. Furthermore, can "slow" and "several" be quantified?	See modified text.
288 (ABPI)	Another possible strategy to minimise risk could be to administer a small fraction (e.g. 10%) of the intended starting dose on day 1.30% of the dose on a day 2 and the remaining 60% of the dose on day 3. This would give the opportunity to terminate doing should an unexpected adverse event occur. Doses and timing of administration should ideally be defined with an appropriate PK/PD model and may be adapted within pre-defined criteria as data emerges during the clinical trial	See modified text.
288-9 (IFAPP)	Altering the method of administration may give rise to concerns the paper itself warns of (lines 137-142/§4.2) Suggest reconsidering this recommendation (e.g. use of syringe pump instead of infusion)	See modified text.

286-290 (AMS)	For intravenously administered drugs, a metered device should be used so that the dose can be titrated. The protocol should include details of the rate and duration of titration.	See modified text.
4.4.2.3 Choice of the first dose in humans		
291 (PDA)	Replace “choice” Rationale: stresses need of science-based decision “determination”	Agreed. Text modified.
292 (Roche)	The guidance should explicitly require that the uncertainty in the estimated first dose be quantified and that uncertainty clearly explained (whether by including statistical confidence intervals or by some other means)	Agreed. Text modified.
4.4.2.4 Precautions to apply between doses within a cohort		
293-300 (AGAH)	This section is very general. It would be helpful to give some specific recommendations on design issues therein depending on the risk category. This would be of particular interest for the highest risk category. It would be helpful to define certain risk categories, and to give specific requirements especially for the highest risk category, *i.e.*, a recommendation should be given regarding the maximum number of subjects to be treated on the first study day and the minimum period of time between two subsequent administrations. But there are more design issues that may be concerned. Example: For the highest risk category, it may be useful to conduct a single-blind study with the second subject on placebo. Consider to add a binding statement that compounds which do have the potential to initiate a cascade of reactions, e.g. in the immune system, and/or bypass physiologic feedback mechanisms belong to the highest risk category as a rule of thumb. We understand that a universal and generally applicable definition of different risk categories is not easy because such a classification depends on many factors that are difficult to assess. However, we propose that the guideline should be more specific and more obliging in	See modified text.

	terms of giving recommendations and instructions to sponsors and investigators. That may also include the definition of 'stopping criteria'.	
294 (EFGCP)	Precautions between doses This sentence should be modified as follows: For first-in-man trials with high-risk medicinal products, a sequential enrollment and dosage administration should be employed etc.	Agreed. Text modified.
294 (ECRIN)	Precautions between doses This sentence should be modified as follows: "For first-in-man trials with high-risk medicinal products, a sequential enrolment and dosage administration should be employed" etc.	Agreed. Text modified.
294-295 (WP)	We believe the statement, "For trials with high-risk medicinal products, an initial sequential dose administration design should be employed within each cohort in order to minimise any risks." is unclear (i.e., intended to imply that dosing should be limited to one participant at a time) and can therefore lead to misinterpretation. The July 2006 Early Stage Clinical Trial Taskforce – Joint ABPI/BIA Report [3] includes specific recommendations on drug dosing and numbers of subjects per study cohort and intervals between cohorts. We believe these recommendations present a reasonable approach and should be included in the guideline. Recommendations provided by the ABPI/BIA that may be incorporated into the guideline "For the first dose of a novel molecule against a known target then it may be reasonable to dose two subjects and if the target is very precedented with significant human experience from several related molecules then three or four subjects could be dosed on the first day. In all cases it is recommended that at least one subject be dosed with placebo on the same day. Two or more subjects should only be dosed on	Agreed. Text modified.

[3] http://www.abpi.org.uk/information/pdfs/BIAABPI_taskforce2.pdf

	the same day if there is no reason to expect significant adverse effects with delayed onset." We recommend that the statement *"For trials with high-risk medicinal products, an initial sequential dose administration design should be employed within each cohort in order to minimise any risks."* be revised for clarity as recommended.	
294 (BIA)	Please clarify what kind of justification is expected for non-sequential dose administration.	Justification should be case specific.
294-300 (ABPI)	The guidance on the sequential dose administration is not entirely clear. Suggest revise this paragraph to read: An initial sequential dose administration design should be employed within each cohort in order to minimize the number of individuals exposed to unanticipated adverse effects. Any non-sequential dose administration within each cohort should be justified. There must be an adequate period of observation between the administration of the medicinal product to the first, second and subsequent subjects in a cohort to allow any significant adverse events to be captured. Fractional within-subject dose escalation may also be considered (see comment above). The duration of the interval of observation should be fully justified and will depend on the properties of the product and the data available, including non-clinical PK and PD if available. Already existing experience with comparable medicinal products and identified risk factors should also be considered.	Agreed. Text modified.
296 (EFGCP)	"..adequate period of observation". This is too imprecise. The text should define the criteria, for example: There must be *sufficient time between the* periods of observation of the first, second, and subsequent administrations *to observe and interpret reactions and adverse events,* depending on…….	Agreed. Text modified.
296-299	This sentence currently does not read very well. It is too long and becomes very hard to follow towards the end.	See modified text.

(UCLH)	Suggest splitting it in two as follows: ‘’There must be an adequate period of observation between the first, second and subsequent administrations. Factors that should be taken into account when deciding the length of this period include the properties of the product; available data including non-clinical PK and PD data and where available, data from comparable existing products.’’	
296-300	This paragraph requires clarification. We suggest revising as follows: There must be an adequate period of observation between the administration of the medicinal product to the first, second and subsequent subjects in a cohort to detect acute adverse events. The duration of the interval of observation should be fully justified taking into account the properties of the product, the data available including nonclinical PK and PD data, already existing experience with comparable medicinal products and identified risks.	See modified text.
297 (J&J)	We understand the “sequential dose administration design” to mean that the subjects in the study will be dosed in a sequential manner rather than simultaneously. In agreement with this interpretation, we propose to replace “administrations” in line 297 with “subjects”. Revise as follows: *There must be an adequate period of observation between first, second, and subsequent ~~administrations~~ subjects, depending on […]*	See modified text.
300 4.4.2.4 (FCP)	Last sentence : We recommend removing the word “fully” “The duration of the interval of observation should be justified”	Agreed. Text modified.
4.4.2.3 (Eucrof)	The calculation of the first dose in man should follow the MABEL approach.	See text.

294-295 (EFPIA)	With this imprecise wording, wide definition and the amount of subjective influence on what substances will be defined as “high-risk” it will be very difficult to predict timelines for first time into man studies if all cohorts are to be dosed sequentially.	See modified text.
294-296 (MSD)	Sequential enrolment in cohorts Would propose that beyond the first cohort that the need for continued sequential enrolment, as opposed to simultaneous enrolment, be considered on a case-by-case basis depending on the evaluation of results from the first cohort.	See modified text. 4.4.2.5
294-296 FRAME	The interval between administrations of a first dose to individual subjects within a cohort should reflect the longest time of onset of clinical or biochemical changes in any preclinical species. The adjustment factor applied to this interval must take into account differences between the plasma half lives in humans and the test species. This information must be available to and understood by the clinicians in charge of the clinical trial. Insert after second sentence: The interval between administrations of a starting dose to individual volunteers within a cohort must at least equate with the longest time to onset of clinical signs in preclinical animal studies, in any species, and for the medicinal product or its surrogate, taking into account potential differences in pharmacokinetics and pharmacodynamics. This information must be understood by the clinician and used to refine clinical practices.	See modified text.
294-300 4.4.2.4 (BEBO)	Some concrete examples on sequential dosing would be helpful. Also, the use of placebo in FIM studies is quite common, e.g. 4 subjects receiving *verum* and 2 subjects receiving placebo in the same cohort. This issue should be discussed with sequential dosing.	See modified text.
294-300	It is suggested to amend the section on the sequential dose administration is not entirely clear. It is therefore proposed an	See modified text.

(EFPIA)	amendment for better clarity. ***"For trials with high-risk medicinal products, an initial sequential dose administration design should be employed within each cohort in order to minimise risk. Any non-sequential dose administration within each cohort should be justified. There must be an adequate period of observation between*** *the administrations of the medicinal product to the* ***first, second and subsequent*** ~~***administrations depending***~~ *subjects in a cohort to allow any significant adverse events to be captured, and adequately assessed and managed. The duration of the interval of observation should be fully justified and will depend* ***on the properties of the product, the data available including non-clinical PK and PD if available already existing experience with comparable medicinal products and identified risk factors.*** ~~***The duration of the interval of observation should be fully justified***~~***"***	
294 (FCP)	The sentence about "an initial sequential dose administration design" needs to be clarified , probably by examples. It can lead to misinterpretation such as dosing one subject per day. Dosing one subject per day may be appropriate in some cases, although we consider it would be more appropriate to dose 2 subjects (including a placebo and an active treatment) on the first day without more risks. Two or more subjects may be dosed on the same day only if there is no reason to expect major safety concerns due to adverse events of delayed onset and if the clinical staff can provide appropriate resuscitation if needed. Specific recommendations on drug dosing , number of subjects per cohort and intervals between cohorts were made by the July 2006 early Clinical Trial Taskforce Joint ABPI/BIA Report . These recommendations provides a reasonable approach and may be included in this guideline. We recommend adding practical examples in an appendix to clarify the sequential administration. Recommendations of ABPI BIA Taskforce may be appropriate	See modified text.
296 (EFPIA)	There must be an adequate period of observation between first, second	See modified text.

	and subsequent administration, …Is the intention that the dose should be staggered to at least three occasions? Two should be the minimum.	
300 (PDA)	Delete “fully” Rationale: Avoid absolutes	Agreed. Text modified.
301 (BMS)	In cases of particularly high-risk drugs, such as those described in lines 85-91, dosing and observation of a single (healthy preferred) subject in the first dosing cohort would provide the best opportunity to limit the number of subjects at risk for serious reactions. Suggest starting with a single dose in a single subject. (The first dose could be given unblinded, or in a block size of 2 along with a blinded placebo subject, to address the potential concerns noted above related to line 263). Consideration should also be given to the need or not of adopting this approach for subsequent dosing cohorts.	See modified text.
302-304 (GCPA)	Does the CHMP/EMEA want to suggest that ‘time of a clinical development programme’ is a legitimate criterion in determining cohort size?	See modified text.
4.4.2.4 (Eucrof)	In “high risk” medicinal products a sequential design is certainly preferable. The guideline should specify how this can be done (starting with 1 actively treated subject compared to 1 placebo subject, followed by 3 active versus 1 placebo, if a higher number is considered necessary the full cohort could then be included). The calculation of the period of time between 2 subjects has to be based on the PK/PD parameters. For the sequential dose administration design an example should be given: Example 1: Start with 1 active and 1 placebo, then treat 3 active and 1 placebo, if the number of subjects per cohort should be higher than 4+2, all other subjects could be entered then to complete the cohort. Example 2: The dosing within one dose group can be done staggered, i.e. a cohort of a few subjects (e.g. 2 on verum and 1 on placebo) on one day. This first cohort of subjects in a dose group sequentially dosed	See modified text.

	with e.g. at least an interval of 1-2 times Tmax between the subjects.	
4.4.2.5 Precautions to apply between cohorts		
305 (UoG)	There is a key point that is addressed in our report available at http://www.rss.org.uk/first-in-man-report . If a judgement is to be made in a controlled manner about proceeding to the next dose-step in a trial it implies that responses at the given step are may have to be compared to placebo cases from that step only. (This will certainly be the case if it is the first dose step and might arguably be suitably the case even if it is not.) This has to be addressed in the design. For example the trial of TGN1412 used 6 active versus 2 placebo. This means that at the end of step 1 there were only 2 placebo volunteers to determine if escalation should proceed. Of course, the violence of the reaction seen during that trial was so extreme that this was irrelevant. However, that is not the point. The trial has to be designed in such a way that escalation can proceed (if appropriate) under a variety of circumstances. At some point in the guideline the issue of proposed statistical analysis has to be addressed and it has to be pointed out that the design will have to be justified in terms of the proposed analysis (and vice versa) and that this may apply not only to the final analysis that would be used were the trial to proceed to completion but also the analysis that has to be used to determine whether the trial will proceed or not.	See modified text.
305-312 (EFPIA)	For biological products, which could often meet the criteria for high-risk products, the half-life is typically very long and immunogenicity needs to be assessed, hence the follow up visits could continue for several months or more. A study that needs to wait for such follow up visits before progressing to the next cohort would be excessively long and impractical, and while useful for information, not essential for subject safety. Some guidance on a pragmatic compromise would be helpful.	See modified text.

306 (EBE)	During the clinical evaluation of high-risk medicinal products, extra caution should be taken to avoid endangering the health of human subjects in such trials. Careful consideration of "*all* the results from *all* subjects" in each cohort prior to dosing the next cohort could substantially delay the conduct of the study. It may not be necessary to review *all* collected data, instead relying on the thorough review of data most relevant to monitoring potential adverse effects.	See modified text.
306 (Roche)	During the clinical evaluation of high risk medicinal products, extra caution should be taken to avoid endangering the health of human subjects in such trials. Careful consideration of "*all* the results from *all* subjects" in each cohort prior to dosing the next cohort could substantially delay the conduct of the study. It may not be necessary to review *all* collected data, instead relying on the thorough review of data most relevant to monitoring potential adverse effects.	See modified text.
306 (Takeda)	**Precautions to apply between cohorts** ……**all the results from all subjects** need to be considered before administration of the first dose of the next cohort FIH studies traditionally capture endpoints related to a molecules' clinical pharmacology together with number of exploratory parameters whose relevance is unknown at the time of FIH. A requirement of hold **all results from all subjects** prior to administration of the first dose of the next cohort is, therefore, unduly restrictive and dose escalation should be based on criteria related to the molecules clinical pharmacology and safety parameters, including vital signs and labs. Text should be modified to read: For further cohorts, **relevant clinical pharmacology parameters and all safety results** need to be carefully considered before administration of the first dose of the next cohort.	See modified text.
306 (ABPI)	For a biological (e.g. antibody) product, waiting for <u>all</u> data from a particular cohort could extend the cohort timing for several months (e.g. if waiting for several half-lives). It may be more appropriate to wait for sufficient data to escalate the dose once the Cmax has been reached and passed, and once the safety data covering this period has been obtained	See modified text.

	(e.g. lab results, AEs, ECGs etc). This may then allow dosing every week or every other week (depending on half life) thereby creating a more 'sensible' time frame for biological FIM studies. For further cohorts, relevant safety data from all subjects of the first cohort (and subsequent cohorts) need to be carefully considered before administration of the first dose of the next cohort … … If the dose escalation decision is to be based on a subset of the data collected for a cohort (e.g. a data cut at a given time interval) this must be justified.	
306-307 (MSD)	"For further cohorts, all results from all subjects of the first cohort (and of subsequent cohorts) need to be carefully considered before administration of the first dose of the next cohort." We request further clarification regarding the sentence. We would propose that acute safety after an agreed upon period be available and evaluated before administration of the first dose of the next cohort. However, in some case not all results such as PK and PD are readily available and therefore acute safety should be the key determining factor to progress to the next cohort.	See modified text.
306-307 (BIA)	It is impossible to have <u>all</u> data available on a real time basis during the study. For a biological product, waiting for all data from a particular cohort could extend the cohort timing for several months. This will make FIM studies incredibly long and costly. Modify as follows: For further cohorts, **any available PK and PD** results from all subjects of the first cohort (and of subsequent cohorts) need to be carefully considered before administration of the first dose of the next cohort.	Agreed. Text modified.
306-308 (IFAPP)	Measurement/full evaluation of PK data prior to any scheduled dose escalation may be extremely time-consuming with regards to the trial itself and may also decrease the value of the conclusion drawn from PK data by compromising overall assay quality	See modified text.

	Suggest reconsidering this recommendation, maybe rendering it optional (e.g. “is strongly recommended”)	
306-309 (ACRO)	ACRO suggests that lines 306-309 be revised to read: ADD: “For further cohorts, all the **safety** results from all subjects of the first cohort (and of subsequent cohorts) need to be carefully considered before administration of the first dose of the next cohort. In addition, any **relevant and critical** PK and PD data from the previous cohorts should be compared to known, **relevant** non-clinical pharmacokinetic, pharmacodynamic and safety information.”	Agreed. Text modified.
306-311 4.4.2.5 (FCP)	Precautions between cohorts The requirement to review all data is impractical, and not necessarily justified. It would have been better to have specified which safety data is useful for decision making as well as to define a duration of observation. Most safety concerns occurred at peak plasma concentrations rather than later on and in most of the cases data from the first 24 or 48 hours post-dose would be sufficient. These safety studies are usually conducted in a limited number of subjects per cohort which includes placebo subjects. We suggest allowing some flexibility by rather defining a minimum number of subjects to be dosed and analysed before progression to next higher dose level. We also agree that in some cases, it may be appropriate to have all planned subjects dosed and analyzed. However, depending on the size of the cohort and the properties of the drug, having 1 or 2 subjects not yet dosed , will not necessarily change the conclusions of the safety assessment. Therefore, we suggest to pre-specify in advance the number of subjects needed and associated relevant safety data required rather than requiring all data from all subjects We recommend to remove all line 306 and 311 “For further cohorts, the **relevant results (specify parameters as well**	See modified text.

	as duration of observation) from a relevant number of subjects (minimum number required)of the first cohort (and the subsequent cohorts) …Administration in the next cohort should not occur before **a relevant number (specify minimum number required)** of participants in the previous cohort have been treated and relevant **data/results (specify parameters and duration of observation)** from these participants reviewed	
306-312 (EFPIA)	The requirement to review all data is impractical and may introduce potential delay to safety review and assessment due to data turnaround time. Often more subjects are enrolled per dose group/cohorts for objectives other than safety/tolerability to allow dose-escalation; therefore, it is more important that the number of subjects needed and associated data elements required to assess safety and tolerability be pre-specified in advance, rather than requiring all data from all subjects. A rewording is thus proposed. *"For ~~further~~ **subsequent** cohorts, ~~all the results~~ **the prespecified data elements** from ~~all~~ **a prespecified number of** subjects of the ~~first cohort (and of subsequent~~ **preceding** cohorts~~)~~ need to be carefully considered before administration of the first dose of the next cohort. ~~In addition, any PK and PD data from the previous cohorts should be compared to known nonclinical PK, PD and safety information.~~ In addition, any observed responses should be compared to the responses that were anticipated **based on prior information from clinical or nonclinical data**. Unanticipated responses may require a revised dose escalation. Administration in the next cohort should not occur before ~~all~~ **an adequate number (prespecified) of** participants in the previous cohort have* been treated and data/results from these participants reviewed."	See modified text.
306-312 (Drusafe)	The requirement to review all data is impractical and may introduce potential delay to safety review and assessment due to data turnaround time. Often more subjects are enrolled per dose group/cohorts for objectives other than safety/tolerability to allow dose-escalation; therefore, it is more important that the number of subjects needed and associated data elements required to assess safety and tolerability be pre-specified in advance, rather than requiring all data from all subjects.	See modified text.

	Propose: "For subsequent cohorts, the prespecified data elements from a prespecified number of subjects of the preceding cohorts need to be carefully considered... In addition, any observed response should be compared to the responses that were anticipated based on prior information from clinical or nonclinical data… Administration…should not occur before an adequate number (prespecified) of participants…."	
306-314 (EBE)	Add the word "*available*" for any data collected. The requirement is not that all PK and PD data would have to be analyzed before escalating to the next dose level. Add the words: *"In addition, any available PK and PD data from the previous cohorts should be compared to known non-clinical PK, PD and safety information. …. Administration in the next cohort should not occur before all the participants in the previous cohort have been treated and available data/results from these participants reviewed."*	See modified text.
306-314 (AMGEN)	Add the word "available" for any data collected. The requirement is not that all PK and PD data would have to be analyzed before escalating to the next dose level. Add the words: *"In addition, any available PK and PD data from the previous cohorts should be compared to known non-clinical PK, PD and safety information. …. Administration in the next cohort should not occur before all the participants in the previous cohort have been treated and available data/results from these participants reviewed."*	See modified text.

306-314 (Drusafe)	This section should be clarified. We recommend adding the word "available" for any data collected. *We recommend revising: "In addition, any available PK and PD data from the previous cohorts should be compared to known non-clinical PK, PD and safety information. …. Administration in the next cohort should not occur before all the participants in the previous cohort have been treated and available data/results from these participants reviewed."*	See modified text.
306-314 (BIO)	Not all PK and PD data would have to be analyzed before escalating to the next dose level. We suggest addition of the word "available" so that the text reads "In addition, any available PK and PD data from the previous cohorts should be compared to known non- clinical PK, PD and safety information. … Administration in the next cohort should not occur before all the participants in the previous cohort have been treated and available data/results from these participants reviewed."	See modified text.
306-314 (EuropaBio)	Add the word "available" for any data collected. The requirement is not that all PK and PD data would have to be analyzed before escalating to the next dose level. Add the words: *"In addition, any available PK and PD data from the previous cohorts should be compared to known non-clinical PK, PD and safety information.* *…. Administration in the next cohort should not occur before all the participants in the previous cohort have been treated and available data/results from these participants reviewed."*	See modified text.

307 (ABPI)	Any PK and PD data from previous cohorts should be compared to known non-clinical and clinical PK, PD and safety information and used to help anticipate exposure and response for subsequent cohorts.	Agreed. Text modified.
307-309 Cancer Research	PK and PD data may not always be available immediately or only initial or summary data available. Is this statement intended to mean that further cohorts should not be performed until all data is available or that the data should be compared if available? In addition, any available PK and PD data from the previous cohorts should be compared to known non-clinical pharmacokinetic, pharmacodynamic and safety information.	See modified text.
310 (EuropaBio)	"unanticipated responses may require a revised dose escalation" We believe that this implies several amendments, and will increase the need a dedicated phase I Committee within Competent Authorities (See General comments) We would welcome a clarification on the criteria that will be used for the assessment of "unanticipated responses. Who will be responsible for the assessment: sponsor, investigator, IDSMB, CA; EC? How to document? Should it be included in the study report?	Depending on the nature and severity of the response all those with responsibility for oversight of the trials should be involved in assessment of the response and its impact on the trial.
310-11 (IFAPP)	Change in dosing schedule should be subject to protocol amendment Eventual dosing schedule changes should be handled strictly according to methods normally applied to protocol amendments. Inserting alternative dosing schedules in the same protocol is suggested to be excluded.	Detailed procedure not meant to be part of this guideline..
311 & 312 (BARQA)	To reduce errors and to ensure the veracity of subsequent judgements the data should be Quality Control (QC) checked before medical review. Administration in the next cohort should not occur before all the	Agreed. Text modified.

	participants in the previous cohort have been treated and data/results from these participants subjected to Quality Control (QC) checks and reviewed.	
309-311 Cancer Research	Non-clinical data is not usually usable as part of the definition of "expected events", is this allowed here? It is not clear whether "responses" means intended pharmacological responses or unintended toxicological responses; this should be clarified. If the former meaning of "responses" is intended then, as complete or partial responses are relatively unlikely in a phase 1 trial, does "observed responses" include changes in PK/PD endpoints?	See modified text.
311 (ABPI)	Administration in the next cohort should not occur before a defined number of subjects in the previous cohort have been treated and critical safety data/results from these participants are reviewed	See modified text.
311-312 4.4.2.5 (BEBO)	We strongly recommend that a detailed summary of all results in a given cohort be given to the IEC for inspection and that interim IEC approval is needed to start with the next cohort	Detailed procedure not meant to be part of this guideline.
311-312 Cancer Research	The generation of some PK and PD data may be protracted. Waiting for all data would greatly slow the drug development process. Administration in the next cohort should not occur before all the participants in the previous cohort have been treated and indicative toxicity data/results from these participants reviewed.	See modified text.
311-312 (JPMA)	**In case the investigational drug requires long term monitoring (ex. several months monitoring are necessary because of long half-life), it is not practical to go to the next cohort after the 'complete review' of the previous cohort. In this guideline, although the long term monitoring is recommended if appropriate, how should we consider the timing to go to the next cohort when evaluating the above-exemplified drug?**	See modified text.

	Change the sentence on Line 311-312 to" Administration in the next cohort should not occur before all the participants in the previous cohort have been treated and data/results concerning critical parameters for safety from these participants reviewed."	
311-312 (WP)	While we agree that additional precautions may be necessary for PHRM, we believe that dosing between cohorts should not be delayed pending results from participants receiving placebo. We recommend that the statement, *"Administration in the next cohort should not occur before all the participants in the previous cohort have been treated and data/results from these participants reviewed."* be revised to: *"Administration in the next cohort should not occur before all the participants who have received the active medicinal product in the previous cohort have been treated and data/results from these participants reviewed."*	See modified text.
311-312 (GCPA)	Is it always necessary to complete the study in one cohort before moving to the next cohort?	See modified text.
311-314 (BMS)	It is often not necessary for safety purposes to complete the analysis of all pharmacodynamic data before proceeding to the next dose, nor to complete the entire planned cohort before a modest dose escalation. Suggest change to "Administration in the next cohort should not occur until all data/results relevant to assessment of safety as predefined in the protocol have been reviewed from the previous cohort."	See modified text.
312 (J&J)	We recommend defining who should review the data/results, i.e., trial sponsor and IDSMB, if appropriate. Add the underlined text: *Administration in the next cohort should not occur before all the participants in the previous cohort have been treated and data/results*	See modified text.

	from these participants reviewed by the sponsor and the Independent Drug Safety Monitoring Board (IDSMB), if appropriate.	
313-314 (UCLH)	As above, this sentence is rather clumsy. Suggest the following ‘’ Time intervals between cohorts should be guided by non-clinical and clinical PK and PD data and if available, data from comparable medicinal products’’.	Agreed. Text modified.
4.4.2.6 Dose escalation scheme		
(AREC)	The protocol should specify an upper dose limit beyond which investigators may not proceed.	See modified text.
315 (MSD)	The dose escalation scheme and precautions to apply between cohorts are reasonable for truly high risk molecules but would markedly (and appropriately) slow development of such agents. Please clarify that this applies only to identified high risk molecules.	Agree. See modified text: precautions should be taken according to the risk identified.
315 (EFGCP)	Practical examples of suitable schemes should be given like starting with only one subject, pilot subjects in all dose levels, etc.	See modified text.
315 (EFPIA)	A certain amount of data is usually collected from one dose level before the Safety Monitoring Committee reviews it and the next dose level is started. However it is not clear if we would need to await a full evaluation of the data from the previous dose level before moving to the next one and if so then, an example of the type of data to be considered should be provided. We wonder how much detail will be needed into the protocol knowing that, at the moment the term "at least" is often used when talking about time intervals – which has been judged so far, acceptable.	See modified text.
316 (BIA)	One of the issues with immunological products is that they frequently do not have dose response curves like conventional molecules and are either all on or all off. The quality and the type of the immunogenic response are more relevant for such products. A practical application of the choice of a starting dose covering the range of product types that	See modified text.

	may be characterised as high risk should be discussed.	
316-319 (ABPI)	Knowledge of the exposure-response curve is important, not just the dose-response curve. This requires measurement of concentrations in pre-clinical pharmacology studies and appropriate exposure-response modelling.	Agreed. Text modified.
317 (EFPIA)	Statement is rather confusing, therefore rewording is proposed. "*Further dose increases should proceed with caution because ~~the initial dose would have been low and~~ there may be a steep dose-response* ***or dose-toxicity*** *curve*".	See modified text.
319 (AMGEN)	Consider adding typical dose escalation decisions include geometric rather than arithmetic schemes (typically half log increments) because of the biologic basis of receptor occupancy issues except at higher doses where smaller increments may be needed because of incipient toxicity.	See modified text.
319 (EBE)	Consider adding typical dose escalation decisions include geometric rather than arithmetic schemes (typically half log increments) because of the biologic basis of receptor occupancy issues except at higher doses where smaller increments may be needed because of incipient toxicity.	See modified text.
319	Consider adding typical dose escalation decisions include geometric rather than arithmetic schemes (typically half log increments) because of the biologic basis of receptor occupancy issues except at higher doses where smaller increments may be needed because of incipient toxicity.	See modified text.
319 (ABPI)	Consider adding typical dose escalation decisions including geometric rather than arithmetic schemes (typically half log increments) because of the biologic basis of receptor occupancy issues except at higher doses where smaller increments may be needed because of incipient toxicity.	See modified text.
315-325 FRAME	Dose escalation schemes may not be as feasible for clinical studies on biological products where low doses or repeat dosing may trigger immunogenicity.	See modified text.

	Insert after line 325: The value of dose escalation for the clinical assessment of potentially immunogenic products must be assessed prior to administration of the IMP to volunteers, particularly where there is an intention to assess therapeutic benefit and immunogenicity may affect such a potential benefit (i.e. patient trials).	
	Consistent with the provisions of the Declaration of Helsinki, there should be clear guidelines on the way in which consent is sort. The notion of informed consent requires that volunteers are presented with facts, understand them and are able to make an informed choice as to whether to participate in a clinical trial. Coercion that plays on the volunteers' financial or medical need must not feature in obtaining informed consent. Individuals must, therefore, be screened by an independent clinician to determine whether they have understood the facts pertaining to the potential benefits and risks of participating in a trial and undergo some psychological evaluation. The guidelines should be appended with a section that discusses informed consent that encapsulates the following recommended changes: The validity of informed consent will depend on the nature, quality and clarity of the information provided to clinical trials participants, the recruitment process and adherence to the guiding principles of the Declaration of Helsinki. Potential trials subjects must be given information about the possible risks of an IMP that takes into account all the preclinical evidence and any information available about related products that have already been through clinical trials. If an IMP is a novel product, one with a complex and partly defined mechanism of action, or one that during preclinical studies gave equivocal results, these facts must be clearly disclosed within the consent form and the IMP described as a potential high risk IMP. In	See modified text.

	these instances, it is especially important to ascertain whether potential trial subjects fully comprehend the risks of participating in the trial, in terms of their health and well-being. In the case of patients, informed consent will require the patients being able to weigh the potential risks against any therapeutic benefit and make a decision whether to opt for alternative treatment or management of their condition. It is essential that all complex terminology that cannot be avoided is explained as fully as possible within a glossary appended to the consent form. The information given to potential trials volunteers must be scrutinised by lay persons without any vested interest in the clinical trial to ensure that it is comprehensible to the reasonable competent volunteer. In any case, consent should only be considered to be truly informed when volunteers have been given the opportunity to consult with a clinician who has no interest in the trial, and only once all his/her concerns have been addressed. The volunteer's capacity to consent and understanding of the fact pertaining to the trial should be assessed in the presence of an independent psychologist. A record of meetings between potential trials volunteers and clinicians or psychologists should be kept and made available to the clinician responsible for the clinical trial.	
319 4.4.2.6 (EANM)	Dose escalation scheme should include monitoring of response by in vivo imaging whenever possible Add sentence: **Monitoring of specific binding or metabolic changes using in vivo nuclear imaging modality may provide a convenient tool to assess even small changes in administered dose.**	This subject is too specialist for the current guidance
319 (BIO)	We suggest the addition of typical dose escalation decisions including geometric rather than arithmetic schemes (typically half log increments) because of the biologic basis of receptor occupancy issues, except at	See modified text.

	higher doses where smaller increments may be needed because of incipient toxicity.	
319 (EuropaBio)	Consider adding typical dose escalation decisions include geometric rather than arithmetic schemes (typically half log increments) because of the biologic basis of receptor occupancy issues except at higher doses where smaller increments may be needed because of incipient toxicity.	See modified text.
320 (EFPIA)	Typographical error. The dose/toxicity or dose/effect relationship	See modified text.
320 (Drusafe)	Typographical error The dose/toxicity or dose/effect relationship	See modified text.
320 (BIO)	Typographical error The dose/toxicity or dose/effect relationship	See modified text.

320 (BIA)	The steepness of the dose response curve is seldom known. We suggest to revise as follows: The dose increment between two dose levels should be guided by the dose/toxicity or dose/effect relationship defined in non-clinical studies, depending on whichever is steeper where this information is available. The steeper the increase in the dose/toxicity or dose/effect curves, the lower the dose increment that should be selected. The choice of the next dose level should include some estimate of the potential pharmacodynamic effects and adverse effects (if any). Information on exposure, effect, and safety from the preceding dose in human should be taken into account. In practice, the steepness of the dose response curve is seldom defined non-clinically. Where this information does not exist, it is appropriate to escalate larger steps (< 10 fold) at pharmacologically inactive doses, with ever reducing escalations where safety signals are of concern.	See modified text.
324 4.4.2.6 (FCP)	Dose escalation scheme Drug concentrations from the previous dose are not in most of the cases necessary to make the decision to progress to next higher dose level. This is why we recommend to add “if needed” after exposure line 324 We recommend “Information on exposure if needed, e and safety from the preceding dose in human should be taken into account	
320-325 Cancer Research	Could this paragraph be simplified? Using non-clinical data to attempt to estimate human dose/toxicity and dose/effect relations would be over-complicated and of limited predictive value. Delete “The dose/toxicity or dose/effect relation observed in non-clinical studies, depending on which is steeper, should guide the dose increment between two dose levels. The steeper the increase in the dose/toxicity or dose/effect curves, the lower the dose increment that	See modified text.

	should be selected."	
320-325 (ABPI)	The steepness of the dose response curve in man is seldom known. Suggest revise this paragraph to read: 'The dose increment between two dose levels should be guided by the dose/toxicity or dose/effect relationship defined in non-clinical studies which ever is steeper where this information is available. The steeper the increase in the dose/toxicity or dose/effect curves, the lower the dose increment that should be selected. The choice of the next dose level should include some estimate of the potential pharmacodynamic effects and adverse effects (if any). Information on exposure, effect, and safety from preceding doses in man should be taken into account. In practice, the steepness of the dose response curve is seldom defined non-clinically. Where this information does exist, it is appropriate to escalate larger steps (< 10 fold) at pharmacologically inactive doses, with ever reducing escalations where safety signals are of concern.'	See modified text.
320-321 (EFPIA)	Traditional toxicity studies usually use only a limited number of dose levels; assessment of the 'steepness' of the dose/toxicity relationship may be impracticable in this regard, rendering the phrase 'which is steeper' unworkable**.** Consider modifying the text. "***The dose increment between two dose levels should be guided by the dose/toxicity or dose/effect relationship defined in non-clinical studies which ever is steeper where this information is available. The steeper the increase in the dose/toxicity or dose/effect curves, the lower the dose increment that should be selected. The choice of the next dose level should include some estimate of the potential pharmacodynamic effects and adverse effects (if any). Information on exposure, effect, and safety from the preceding dose in human should be taken into account***	See modified text.
4.4.2.7 Stopping rules and decision making		

4.4.2.7 (Drusafe)	It is stated that stopping rules should be defined for individual subject, cohort and trial. This is broad, could cover an endless number of scenarios and might be focused somewhat and determined on a case by case basis. The regulators should consider limiting the stopping rules to specific clinical safety concerns. The use of an IDSMB is fairly uncommon in Phase1 studies and its utility might be limited because these studies can be easily conducted in a single blind fashion, are often done at a single site and are closely monitored by Phase 1 unit Ethics Committees. In addition, finding IDSMB members with sufficient Phase 1 experience may cause delay that is unwarranted given the low potential of an IDSMB for meaningful input. The guidance implies that the involvement of an IDSMB would be the norm, since the sponsor would have to provide justification if an IDSMB were not used. Given the practical limitations described above, the guidance should only propose the involvement of an IDSMB for high risk products, where the sponsor has particular cause for concern rather than recommend use of an IDSMB, with justification for its absence.	See modified text.
(AREC)	AREC considers that in such studies the use of an Independent Drug Safety Monitoring Board should be mandatory.	See modified text.
326 (EACPT)	Stopping rules: The benefit of the introduction of an Independent Drug Safety Boards should be discussed under practical conditions.	See modified text.
326 (Takeda)	**Stopping rules and decision making** Dose escalation should be undertaken following a review of all available data by the principal investigator and the sponsor physician, with the possible involvement of a pharmacokineticist / statistician if required.	See modified text.
327 (EFPIA)	In a single dose study it is inappropriate to have stopping criteria for an individual patient. It is suggested to revise the sentence to read: "*The protocol should define stopping rules for the ~~individual,~~ cohort and trial.*"	See modified text.
327 (BIA)	It is inappropriate to have stopping criteria for an individual patient in a	See modified text.

	single dose study. Suggest to revise the sentence as follows: The protocol should define stopping rules for the **~~individual,~~** cohort and trial.	
327 (Anapharm)	Stopping rules and decision making: in order to establish clearer and safer lines for stopping rules, the use of standardized rating scales for the classification of the severity of adverse events, changes in electrocardiogram and clinical laboratory tests such as the *National Cancer Institute Common Toxicity Criteria* or the *Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events* should be promoted. It might harmonize evaluation of investigators and safety reviewers and clarify the decision making process.	Agreed. Text modified.
327-329 Cancer Research	Is this the same as the independent safety monitoring board as mentioned in line 259?	See modified text.
327-329 (WP)	We believe that use of an independent expert safety monitoring board in a Phase 1 environment is not practical. The lack of resources to fulfil this role is further compounded by the time commitment that would potentially be required to commit to frequent meetings (i.e., weekly/bi-weekly for typical SAD or MAD studies) and short duration of these studies. We recommend that the statement, "*Sponsors should consider the use of an Independent Drug Safety Monitoring Board (IDSMB) and if this is not considered appropriate, this should be justified*." to "*Sponsors should consider the use of an Independent Expert ~~Drug Safety Monitoring Board (IDSMB) and if this is not considered appropriate, this should be justified~~*."	See modified text.
327-329 (ACRO)	The function of an IDSMB is unclear, if not unnecessary, within the context of a Phase I clinical trial, as the trial protocol will define clear processes and responsibilities for making decisions about stopping rules for the individual subject, cohort and trial. ACRO suggests that lines 327-329 be revised to read:	See modified text.

	ADD: "The protocol should define stopping rules for the individual subject, cohort and trial. Sponsors should consider, **as appropriate**, the use of an Independent Drug Safety Monitoring Board (IDSMB)." DELETE: "**and if this is not considered appropriate, this should be justified**".	
327-330 4.4.2.7 (BEBO)	See our remarks for lines 224-255, Section 4.4.1.The IEC should be the body of choice in making decisions about dosing, dose escalations, cohort changes and stopping/ postponing of the study.	See above
327-330 (SPC)	4.4.2.7 Stopping rules and decision making The use of an Independent Drug Safety Monitoring Board (IDSMB) is usually employed to assure safety monitoring while maintaining the blind when safety data contains significant background events and trend monitoring is important. Safety and tolerability is the primary goal of FIH studies and background significant adverse events are unusual for the phase 1 studies. The clinical investigators and sponsor usually have strong active safety surveillance of all FIH and can unblind individuals or groups of study participants when safety question arise. When particular expertise is helpful in assessing issues related to safety, arrangements other than IDSMB are more efficient and can be arranged far earlier in the study design process. This early involvement provides more extensive understanding of the overall NME profile and allows for efficient utilization of broad a broad spectrum of experts. ISDMB-related activities do produce delays in dose progression and tend to diffuse responsibilities in safety decision making. Phase 1 studies have been conducted with IDSMB are usually for addressing management of higher dose levels in later studies. Except for pharmacological effects, it is the rare NCE that has toxicities associated with xenobiotic effects. There may be an unusual circumstance for which an IDSMB should be constituted for phase 1 studies, but those should be the exceptions.	See modified text.
328 4.4.2.7	Same comments as previously. The use of an Independent Drug Safety	See modified text.

(FCP)	Monitoring Board (IDSMB) is rarely useful in early drug development. We would rather recommend to justify the need for an IDSRB or an alternative such as a relevant expert rather than justifying in almost all circumstances the absence of need of an IDSRB We recommend "Sponsors should consider the use of a relevant expert and/or an Independent Drug Safety Monitoring Board if needed. The protocol should … " Rather than "Sponsors should consider the use of an Independent Drug Safety Monitoring Board (IDSMB) and if this not considered appropriate, this should be justified"	
328 (EBE)	It is the responsibility of the sponsor to secure safety for the volunteers participating in the trial and to define stopping rules for the individual subjects, cohorts and trial. The process and responsibilities for making decisions regarding dosing / dose escalation should be clearly described in the protocol. How to organise this process is the sole responsibility of the sponsor, including whether or not an IDSMB is justified. The following text should be deleted: *"Sponsors should consider the use of an Independent Drug Safety Monitoring Board (IDSMB) and if this not considered appropriate, this should be justified"*.	See modified text.
328 (EFPIA)	There are companies that have medical units that perform Phase I trials in house – including FIM trials. Similarly, toxicology and medical departments within large Sponsor companies have an in-depth compound-specific toxicological and medical knowledge. This specific experience, expertise and knowledge can hardly be found with "external" monitoring boards. An Independent Drug Safety Monitoring Board with only external experts is not to be recommended. If an independent opinion is warranted, it is suggested a Drug Safety Monitoring Board with Sponsor's physicians and one independent physician with knowledge of	See modified text.

	the drug target. The decisions on how to proceed with the study should then be made unanimously by the members of this group. Thus, in line with previously mentioned comment on the same topic, a rewording is proposed. "*Sponsor ~~should~~ **may** consider the ~~use~~ **utility** of an Independent Drugs Safety Monitoring Board (IDSMB) ~~and if this is not considered appropriate, this should be justified~~. The protocol should define clear processes and responsibilities for making decisions about dosing of subjects and dose escalation **or any stopping criteria".***	
328 (ABPI)	DSMBs should be avoidable in many cases if the sponsor and/or the investigator is unblind. There is a case to be made for investigators not being blinded in these studies.	See modified text.
328-329 (BIA)	The current wording suggests that use of an Independent Drug Safety Monitoring Board will be the rule rather than the exception. Please note that IDSMBs are generally indicated for large phase III trials (see FDA and EU guidance). Where there is a well defined risk management strategy including a plan for monitoring safety, for management of any adverse reactions, clear stopping rules and escalation criteria, it should be possible for an experienced investigator and an expert, fully-engaged sponsor to make appropriate decisions on review of the available data. Modify as follows: Sponsors **may** consider the use of an Independent Drug Safety Monitoring Board **~~and if this is not considered appropriate, this should be justified~~**.	See modified text.
328-330 (ABPI)	DSMBs should be avoidable in many case if the sponsor and/or the investigator is unblind. There is a case to be made for investigators not being blinded in these studies. The current wording suggests that an DSMB will be the rule rather than exception. This is questionable for a single dose study where there is a well defined strategy for managing risk, including a plan for monitoring	See modified text.

	safety and management of any adverse reactions, including well defined stopping and dose escalation criteria. Under these circumstances, it should be possible to manage the dose escalation internally with the sponsor and investigator reviewing the data. The protocol should clearly define how subject safety will be protected when study centre staff are blinded to treatment allocation. The sponsor ~~should~~ may consider the ~~use~~ utility of an Independent Drug safety Monitoring Board (IDSMB) ~~and if this is not considered appropriate, this should be justified~~. The protocol should define clear processes and responsibilities for making decisions about dosing of subjects and dose escalation or any stopping criteria."	
328-330 (BMS)	The default need not be an IDSMB for every study, as would be implied by requiring a justification if an IDSMB is not used. Emphasis should be on the need for clear stopping rules and primary responsibility of the Investigator and Sponsor. Clarification of eventual further involvement of the EC and/or Competent Authority would be helpful if this is envisioned. Propose to revise possibly as follows: "Sponsors should consider the use of an Independent Drug Safety Monitoring Board (IDSMB~~) and if this is not considered appropriate, this should be justified~~. The protocol should in any case define clear processes and responsibilities for making decisions about dosing of subjects and dose escalation, with the primary responsibility remaining that of the Investigator and Sponsor.	See modified text.
4.4.2.7	Line 327 "The protocol should define stopping rules for the individual subject cohorte and trial": it's really difficult to define clear and detailed stopping rules because we are in an unexpected situation (first in man administration, new product, unexpected side effects. Line 328: IDSMB : what is a definition of independent ? Is the IDSMB can be replaced by the Ethical Committee ?	See modified text.

4.4.2.8 Monitoring for adverse events/reactions		
331 (EFPIA)	It is suggested to reword the title to better reflect the content of the section *"Monitoring **and communication of** ~~for~~ adverse events/reactions*	See modified text.
332-346 (MRC)	Again all studies of first in man use should have a risk assessment of likely adverse effects and an action plan in the event of each of these possible events. The location and facilities available during conduct of the trial should be based on this assessment. Conducting a full assessment requires as much information as possible and MRC supports the recommendations in the Expert Report (as above) regarding improved access to unreported trial results and adverse effects, through regulators or other appropriate mechanisms. It is also important that the assessment of possible adverse effects is communicated effectively to trial participants in a proportionate manner, such that participants understand which events they should alert the investigator to. This does not detract in any way from the responsibility of the investigator and sponsor to monitor for such events but could enhance such monitoring. In relation to 'Long-term monitoring' there may be other considerations, such as advice on blood or organ donation in future and follow up for potential teratogenic effects.	See modified text.
333 (EFPIA)	The following addition is proposed as in line with normal practice. *"The mode of action of the high-risk medicinal product**, findings in the non-clinical toxicity studies** and any anticipated responses should be used to identify likely adverse reactions."*	See modified text.
334 (EFPIA)	An amended sentence is proposed although this is by definition an impossible requisite. Maybe better to say that clear communication ways shall be in place to allow quick decisions?	See modified text.

	"All clinical trial staff should be trained to identify those reactions and how to respond to those ***or any other adverse events or reactions****."*	
334 (Drusafe)	The term clinical trial staff should be clarified, since it may include technicians as well as nurses and physicians. It would be impractical to train technicians. All medically qualified clinical trial staff (nurses and physicians) should be trained to identify those reactions and how to respond to those and any other adverse events or reactions.	See modified text.
334 (BIA)	This would appear to be a bit excessive that <u>all</u> clinical trial staff should be trained to identify those reactions and how to respond to those or any other adverse events or reactions. Modify as follows: **Appropriate** clinical trial staff should be trained to identify those reactions and how to respond to those or any other adverse events or reactions.	See modified text.
336 (ICAPI)	*4.4.2.8 Monitoring for adverse events/reactions* Surely, if there is a 'predictable risk of a certain type of severe adverse reaction', a human trial would not be ethical and should not be conducted? Given the inherent limited reliability of animal models (see above) there is always an element of risk when conducting first-in-man trials. This should therefore be appreciated at all levels and appropriate treatment protocols devised. This should occur as a matter of course in *any* trial where there is *any* risk of *any* kind of adverse reaction. In cases where there is any risk of adverse reactions occurring, a treatment strategy should be described in the protocol.	See modified text.
338 (BARQA)	The sentence starting with; "There should be rapid .." should be on a new line, otherwise it looks like this is only relevant in the case where there is a predictable risk. In fact this is a requirement whether there is	See modified text.

	a predictable risk or not. Also it should be emphasised that the access should be available 24/7. This should include the availability of specific antidotes where they exist and a clear plan of supportive treatment. There should be constantly available, rapid access to the treatment allocation codes (when relevant).	
338 (J&J)	This paragraph should also refer to the need for medical staff for emergency treatment. Add underlined text: *This should include the availability of specific antidotes where they exist, a clear plan of supportive treatment, <u>and availability of medical staff and emergency treatment.</u>*	See modified text.
338 (ABPI)	Long term monitoring has obvious benefits, but it is a little unclear how to prospectively decide how long a monitoring program may be. As well as having an expedited plan for informing about SUSARs there should also be a process for updating the subjects with any change to the risk benefit analysis that may be relevant to the subject's willingness to continue participation. The length of the monitoring period within and outside the research site should be justified on the grounds of pharmacokinetics, pharmacodynamics and safety endpoints as part of the strategy to manage risks in the clinical trial.	See modified text.
340 (EFPIA)	Is this not always required? Is it thus necessary to stress this?	Yes.
341 to 343 (BARQA)	As well as having an expedited plan for informing about SUSARs they should also be updating the subjects with any change to the risk benefit analysis that may be relevant to the subject's willingness to continue	See modified text.

	participation. Sponsors should ensure that processes are in place, before the trial starts, for expedited reporting of any SUSARs to the national competent authority (ies), ethics committee(s), investigator(s) and that subjects are informed of any changes that may be relevant to the subject's willingness to continue participation.	
341-354 (ABPI)	From a pre-clinical perspective, if a plausible signal for malignancies was identified pre-clinically then it is unlikely that such a molecule would be developed. Carcinogenicity studies would not have been performed at this stage of development and may not be relevant for a human specific target. The idea of extended monitoring may therefore be more applicable to long term effects on immune suppression but it is not quite clear in the guidance how this will be adjudicated.	See modified text.
347 (Takeda)	**Long Term Follow Up** The guideline recommends long term follow up for participants in FIH trials. However, given the small number of subjects involved, long term monitoring will lead to variability in the number and type of events captured and increasing difficulty in assigning a relationship to study drug. Follow up should be maintained according to current GCP practice. Specific sentence should be added for biological / immunological agents which may require additional follow up.	See modified text.
347-354 (EFPIA)	**From a pre-clinical perspective, if a plausible signal for malignancies was identified pre-clinically then it is unlikely that such a molecule would be developed. Carcinogenicity studies would not have been performed at this stage of development and may not be relevant for a human specific target. The idea of extended monitoring may therefore be more applicable to long term effects on immune suppression but it is not quite clear in the guidance how this will be adjudicated.**	See modified text.

	However, Long-term monitoring – this is a very vague proposal. How will this be carried out? How will an infection or malignancy be evaluated to determine it was a consequence of drug exposure? Any findings will be difficult to interpret at time points too far removed from the treatment period. It is suggested to specify the type of study design and special circumstances that would absolutely require long term monitoring. Finally, it is to be noticed that the following sentence "Special considerations should be given to potential long-term consequences on physiological systems and potential long-term safety problems" from L28-280 is here as well repeated.	
347-354 (Drusafe)	Long-term monitoring – this is a very vague proposal. How will this be carried out? How will an infection or malignancy be evaluated to determine it was a consequence of drug exposure? Any findings will be difficult to interpret at time points too far removed from the treatment period. **Specify the type of study design and special circumstances that would absolutely require long term monitoring.**	See modified text.
347-354 (BIO)	This section on long-term monitoring is very vague. How will this monitoring be carried out? How will an infection or malignancy be evaluated to determine it was a consequence of drug exposure? Any findings will be difficult to interpret at time points too far removed from the treatment period. We request specification of the type of study design and special circumstances that would absolutely require long term monitoring.	See modified text.
348-354 (AMGEN)	The sentence from 280-281 is repeated here. Additional clarification is needed. Add the words: *"Special considerations should be given to potential long-term consequences on physiological systems and potential long-term safety*	See modified text.

	problems (e.g., mechanisms that deplete cell populations). … In these circumstances, it may be necessary to implement follow-up for an appropriate period of time for the participants after the end of the study (i.e., until there is no longer measurable drug in the serum or until recovery of a PD effect).”	
348-354 (EBE)	The sentence from 280-281 is repeated here. Additional clarification is needed. Add the words: *“Special considerations should be given to potential long-term consequences on physiological systems and potential long-term safety problems (e.g., mechanisms that deplete cell populations). … In these circumstances, it may be necessary to implement follow-up for an appropriate period of time for the participants after the end of the study (i.e., until there is no longer measurable drug in the serum or until recovery of a PD effect).”*	See modified text.
348-354 (Drusafe)	The sentence from 280-281 is repeated here. Additional clarification is needed. *We recommend revising: “Special considerations should be given to potential long-term consequences on physiological systems and potential long-term safety problems (e.g., mechanisms that deplete cell populations). … In these circumstances, it may be necessary to implement follow-up for an appropriate period of time for the participants after the end of the study (i.e., until there is no longer measurable drug in the serum or until recovery of a PD effect).”*	See modified text.
348-354 (EuropaBio)	The sentence from 280-281 is repeated here. Additional clarification is needed. Add the words: *“Special considerations should be given to potential long-term consequences on physiological systems and potential long-term safety problems (e.g., mechanisms that deplete cell populations). … In these*	See modified text.

	circumstances, it may be necessary to implement follow-up for an appropriate period of time for the participants after the end of the study (i.e., until there is no longer measurable drug in the serum or until recovery of a PD effect).”	
348-354 (BIO)	The sentence from 280-281 is repeated here. Additional clarification is needed. We suggest the alternate wording “Special considerations should be given to potential long-term consequences on physiological systems and potential long-term safety problems (e.g., mechanisms that deplete cell populations). … In these circumstances, it may be necessary to implement follow-up for an appropriate period of time for the participants after the end of the study (i.e., until there is no longer measurable drug in the serum or until recovery of a PD effect).”	See modified text.
349 (EFPIA)	The sentence implies that for all FIM trials, it is mandatory that one should justify the length of monitoring period outside the research site, whereas, it may only be applicable for certain instances. It is suggested to reword it. *“The length of the monitoring period within”,* ***and if deemed appropriate*** *outside, the research site should be* ~~*justified*~~ ***described*** *as part of the strategy to manage risks in the clinical trial.”*	See modified text.
349-350 (EBE)	The sentence implies that for all FIH studies, it is mandatory that one should justify the length of monitoring period outside the research site, whereas, it may only be applicable for certain instances. Consider rewording sentence to *“The length of the monitoring period within”, <u>and if deemed appropriate</u> outside, the research site should be <u>described</u> as part of the strategy to manage risks in the clinical trial.”*	See modified text.
349-350 (Roche)	The sentence implies that for all EIH studies, it is mandatory that one should justify the length of monitoring period outside the research site, whereas, it may only be applicable for certain instances.	See modified text.

	Consider rewording sentence to "The length of the monitoring period within", and if deemed appropriate outside, the research site should be described as part of the strategy to manage risks in the clinical trial.	
349-350 (BIA)	The length of the monitoring period should be justified on grounds of pharmacokinetics, pharmacodynamics and safety endpoints. Suggest to revise the sentence as follows: The length of the monitoring period within and outside the research site should be justified **on the grounds of pharmacokinetics, pharmacodynamics and safety endpoints** as part of the strategy to manage risks in the clinical trial.	See modified text.
350-354 (RP LTD)	Immunological compounds may alter the immune system permanently. We propose an obligation to Sponsors and Investigators to issue a pass to study participants. This pass should include contact details for the notification of adverse events with a late onset. The pass should provide adequate information on the medicinal product including potential long-term effects and precautions regarding future prescriptions and participation in studies. The subject's family doctor should receive the same information in writing.	See modified text.
351 (AMGEN)	Adding an example here would be valuable. As currently written, any immune modulator could be construed to require a long-term monitoring plan despite the fact that a single dose is being studied. Add the words: *"(e.g. therapeutics effecting a demonstrable PD effect persisting beyond the duration of the study)"*	See modified text.
351 (EBE)	Adding an example here would be valuable. As currently written, any immune modulator could be construed to require a long-term monitoring plan despite the fact that a single dose is being studied.	See modified text.

	Add the words: *"(e.g. therapeutics effecting a demonstrable PD effect persisting beyond the duration of the study)"*	
351 (EFPIA)	Adding an example would be valuable. As currently written, any immune modulator could be construed to require a long-term monitoring plan despite the fact that a single dose is being studied. *"For example, high-risk medicinal products* ***(e.g. therapeutics effecting a demonstrable PD effect persisting beyond the duration of the study)*** *that may have the potential to alter the immune system for long periods and/or may cause delayed unexpected adverse reactions such as infections or malignancies".*	See modified text.
351 (Drusafe)	Adding an example here would be valuable. As currently written, any immune modulator could be construed to require a long-term monitoring plan despite the fact that a single dose is being studied. *Add "(e.g. therapeutics effecting a demonstrable PD effect persisting beyond the duration of the study)"*	See modified text.
351 (BIO)	Adding an example here would be valuable. As currently written, any immune modulator could be construed to require a long-term monitoring plan despite the fact that a single dose is being studied. We suggest addition of "(e.g. therapeutics effecting a demonstrable PD effect persisting beyond the duration of the study)".	See modified text.
351 (EuropaBio)	Adding an example here would be valuable. As currently written, any immune modulator could be construed to require a long-term monitoring plan despite the fact that a single dose is being studied.	See modified text.

	Add the words: *"(e.g. therapeutics effecting a demonstrable PD effect persisting beyond the duration of the study)"*	
351 to 354 (BARQA)	If they are requiring potential long term follow-up will this mean that plans should be made for the long term tracing of volunteers involving retention of extensive personal contact data?. Does this mean that in high risk studies they should not use subjects who are travellers or indigents? In these circumstances, it may be necessary to maintain a contact plan for the long-term follow-up of the participants after finalisation of the study.	See modified text.
352 (EFPIA)	If such is suspected, then suggest using patients, as it is probably more difficult to (1) justify in normal volunteers and (2) harder following normal volunteers for the length of time necessary to monitor for such delayed unexpected adverse reactions.	See modified text.
353 (EFPIA)	Based on the requirements of the draft guideline a long-term follow up <u>for several years</u> might have to be established for NCEs which fulfil the criteria of high-risk medicinal products and affect the immune system. This may be difficult to establish in the context of Phase 1 studies because of lacking compliance of participants. Taking into account the small number of individuals included, a higher rate of infections or increase in the rate of malignancies will generally not be possible to detect in this limited population. Therefore the need for such a monitoring and the benefit for the participants in the trial should be considered very carefully. "*In these circumstances, it may be necessary to implement long-term follow-up for the participants after finalisation of the study**, if the properties of the substance and the results of the trial suggest a particular need.***"	See modified text.

353 (EuropaBio)	With regard to the long term follow-up after the finalization of the study, we would welcome further clarification on this particular aspect of the requirement. If this long term follow up is considered as part of the CT, the results and final study report could be delayed for an unnecessary length of time. If considered stand-alone from the CT, how should this be implemented regarding the EudraCT application, administrative management and study report?	This could be conducted as a new long term safety study.
354 (ABPI)	Consideration perhaps should be given to adding a statement where individuals that have received a long acting IMP that suppresses some aspects of immune function subjects should be advised on the risk of travel to areas of high endemic infections on the impact of vaccine efficacy. Expand this sentence to read: 'In these circumstances, it may be necessary to implement long-term follow-up for the participants after finalisation of the study and to ban travel to areas that require vaccination(s) and present a high risk of infectious disease until immune function has returned to baseline.'	See modified text.
4.4.3 Site of the clinical trial		
355-366 (MRC)	The MRC recognises the importance of availability of medical care whenever this may be needed. Once again, the proximity and level of facility a study should have access to should be determined on a case-by-case basis. The recommendation of 'immediate access' is open to interpretation and may not be applicable to all circumstances.	See modified text.
355-366 (ABPI)	For first-in-man studies, consideration should be given to making the trial open to the sponsor and/or investigator. The study should be conducted in clinical research units where the data can be made available on an on-going basis for prompt decisions for either adapting or stopping dose escalation. First in man studies of compounds where the risk profile is difficult to predict (see above) should be conducted in a hospital based unit with rapid access to appropriately primed resuscitation facilities. The guidance should specify what is meant by appropriate training of	See modified text.

	investigators – for example it could say “training in, and previous experience of, first in man studies ”. There is no mention of a minimum resuscitation standard. For example, the Resuscitation Council UK ALS guidelines are, we believe, accepted across Europe.	
355-366 (RP LTD)	We would propose to expand on guidance for the clinical conduct of such studies, in particular the facilities of the site and qualifications of Principal Investigator and other medical staff. There should be no geographical risk in studies in man. Clinical trials with potential high-risk medicinal products should be conducted within a hospital. Whilst appropriate facilities must be in place within the research unit to deal with the initial treatment of life-threatening emergencies, too little emphasis is given to the prevention of an emergency in the first place. There needs to be early access to acute medical and Critical Care services at the first sign of an emerging significant adverse event as demonstrated by the events in Northwick Park Hospital. This may prevent the deterioration of a subject, thereby decreasing the risk of complications occurring. Furthermore it will ensure that all treatments required (including resuscitation) are immediately available and undertaken by specialists. Problems associated with the transfer of patients are kept to a minimum. Locations requiring an ambulance service to transfer patients to a nearby hospital should be considered inappropriate for the conduct of studies involving potential high-risk medicinal products. Principal Investigators should be senior medical doctors who have acquired the necessary skills and knowledge through several years of training and supervised work as Co-Investigators in line with training in other medical specialties and should be able to produce evidence for this. Principal Investigators and Research Physicians should operate within the limits of their knowledge and skills and avoid doing harm to any person in their care. They should provide medical care to their patients according to best medical practice. The delivery of all aspects of acute, emergency and Critical Care medicine is not within the competence of any one individual. It is therefore essential that these services can be provided by clinical specialists in diverse fields, rapidly when required. The Principal Investigator should ensure that an	See modified text.

	adequate clinical environment is provided taking into account any potential risk of a study. They should ensure that a study is designed and conducted in such a way that it is scientifically valid, conducted to all applicable standards and guidelines, meets its objective and most importantly is safe for those participating in the research. We propose to expand on guidance in the following areas: • Specific reference to the prevention of serious adverse events and early intervention through immediate and direct access to hospital specialists • Exclusion of geographical risks Reference for doctors to operate within the limits of their competence	
358-361 Cancer Research	"Immediate access" is a very strong term. For example, within many hospitals transport within the hospital site may require a short ambulance journey, is this "immediate access"? Could the phrase "rapid access" be used instead?	See modified text.
356 (EFGCP)	More emphasis should be put on the assessment of suitability of the site. *The suitability of the site should be verified by the responsible ethics committee according to an agreed list of criteria. The implementation of an accreditation system for clinical research units performing FiM trials should be considered.*	See modified text.
356 (EuropaBio)	We would welcome clarification on what constitutes "appropriate clinical facilities"? Would it be feasible to have an FIM site authorization system in Europe, inspected and accredited by the Member State Competent Authority?	Noted
356-358 (EPFIA)	We cannot see why other first in man studies require another clinical setting as specified here *"First-in-man trials ~~with high-risk medicinal products~~ should take place in appropriate clinical facilities and be conducted by medical*	See modified text.

	staff with appropriate level of training and expertise and an understanding of the investigational medicinal product, its target and mechanism of action".	
357 (EFGCP)	Site of medical trial This line requires that medical staff should have an appropriate level of training and expertise, however, like in ICH GCP, it does not provide standards.	See modified text.
357 (ECRIN)	Site of medical trial This line requires that medical staff should have an appropriate level of training and expertise, however, like in ICH GCP, it does not provide standards.	See modified text.
358 (EFGCP)	…be conducted by medical staff with appropriate level of training and expertise….. *…be conducted by trained investigators who have acquired the necessary expertise in conducting early clinical drug trials (i.e. phase I-II) under well controlled circumstances. These studies should be conducted by medical staff with appropriate level of training and experience in early clinical drug development. Training in Good Clinical Practice, safety training and Basic Life Support should be considered mandatory for investigator and site personnel.*	
(AREC)	Facilities on site should include 24-hour cover by staff trained and current in ALS. A written agreement should be in place between the clinical research unit and its nearby Intensive Care Unit regarding the responsibilities and undertakings of each in the care and transfer of patients. Staff should be fully aware of these and the procedures described should be regularly trialled. Particular care is needed to ensure staff training is current and that there are robust arrangements for updating staff and dealing with changes in personnel.	See modified text.
359-361 (IFAPP)	What does "immediate access to facilities" imply? Does it mean that only hospitals will be allowed to run these trials? The term "ready availability of ICU facilities" should also be specified.	See modified text.

	Does it mean e.g. that ICU beds have to be reserved?	
362 (EACPT)	Multi centre first-in-man single dose escalation trials for high-risk medicinal products require a consistently communication between all sites. Any parallel study should be avoided. .... If several sites are planned for the study, this should be justified and an adequate information communication system between sites should be described, following a clear time protocol without any parallel study.	See modified text.
362 (IPOPI)	It is vital that a trial with a high risk potential should be conducted at the same place and preferably with the same staff.	See modified text.
362 (FECS)	This is a key aspect to the paper. Add the word "initially". This should replace the word "preferably" at the end of line 362. It should read "products should initially be conducted as a single protocol at a single site".	There may be circumstances that can justify conducting this type of trial at more than one site. E.g. rare diseases or oncology studies.
362 (EFPIA)	"First-in-man single dose escalation trials for high-risk medicinal products should preferably be conducted as a single protocol at a single site, as this helps to assure the well-being of all trial participants particularly if new safety findings are identified". In the case of FIM trials in patients, especially oncology, a single site would not be ethical as would significantly prolong recruitment and development of a potential much needed therapy for an unmet medical need. In addition, what is meant with "single protocol"? We wonder whether this is related to umbrella/interleaved protocols. A modified section is thus proposed. "*First-in-man single dose escalation trials ~~for high-risk medicinal products~~ should preferably be conducted as a single protocol at a single site, as this helps to assure the well-being of all trial participants particularly if new safety findings are identified**; however exception***	See modified text.

	can be made on a case-by case basis*"*.	
362-363 (ABPI)	Please clarify the concerns regarding conducting a first-in-human clinical study with a potentially high-risk medicinal product at several sites. Where an adequate communication system is in place, conduct of the study at several sites should not compromise patient safety First-in-human single dose escalation trials for high risk medicinal products should preferably be conducted at a single centre. Where the trial is multi-centre an adequate information communication system should be put in place to ensure new safety findings are transmitted to all participating sites.	See modified text.
362 – 364 (EBE)	*"First in man single dose escalation trials for high-risk medicinal products should preferably be conducted as a single protocol at a single site, as this helps to assure the well-being of all trial participants particularly if new safety findings are identified."* Change as follows: *"First in man single dose escalation trials for high-risk medicinal products" medicinal product requiring special attention" should preferably be conducted as a single protocol at a single sites experienced in the conduct of clinical trials. Where different sites are involved in a sequential trial design an appropriate plan needs to be in place as this helps to assure the well-being of all trial participants particularly if new safety findings are identified."*	See modified text.
362-364 (EBE)	"First in man single dose escalation trials for high-risk medicinal products should preferably be conducted as a single protocol at a single site, as this helps to assure the well-being of all trial participants particularly if new safety findings are identified." In the case of EIH studies in patients, especially oncology, a single site would not be ethical as this would significantly prolong recruitment and development of a potentially much needed therapy for an unmet	See modified text.

	medical need. Change as follows: *"First in man ~~single~~ dose escalation trials for high<u>er</u>-risk medicinal products should preferably be conducted as a single protocol at ~~a single~~ site<u>s</u> <u>experienced in the conduct of clinical trials</u>. Where different sites are involved in a sequential trial design an appropriate plan needs to be in place ~~as this helps~~ to assure the well-being of all trial participants particularly if new safety findings are identified."*	
362-364 Cancer Research	This is written from a healthy volunteer perspective, for cancer patient studies, especially in rarer forms of cancer, multiple sites are often required for adequate patient recruitment. Can patient studies be excluded from this statement?	
362-364 (Roche)	"First in man single dose escalation trials for high risk medicinal products should preferably be conducted as a single protocol at a single site, as this helps to assure the well being of all trial participants particularly if new safety findings are identified." In the case of EIH studies in patients, especially oncology, a single site would not be ethical as would significantly prolong recruitment and development of a potential much needed therapy for an unmet medical need.	See modified text.
362-366 (BIA)	Please clarify the concerns regarding conducting a first-in-man clinical study with a potentially high-risk medicinal product at several sites. Where an adequate communication system is in place, conduct of the study at several sites should not compromise patient safety. Suggest to revise as follows: First-in-man single dose escalation trials for high-risk medicinal products should preferably be conducted as a single protocol. Where the trial is multi-centre an adequately defined information communication system should be put in place to ensure new safety findings are transmitted to all participating sites.	See modified text.
364 (ICO)	It is crucial to emphasize the importance of single centre trials or maximum 2-3 centre trials for the sake of safety	See modified text.

365 (EuropaBio)	We would welcome further guidance on what constitutes an "adequate information communication system". Should this system be described in the protocol and should it be reviewed and approved by the Competent Authority and Ethics Committee?	See modified text.
356-366 (CAG)	Especially in cases where adverse events are not likely attributable to pre-existing conditions, please advise that costs of medical treatment for adverse events (acute or semi-acute) potentially attributable to the study product are best borne by the study sponsor or clinical trial site.	This issue is outside the scope of this guideline.
4.4.3 (Eucrof)	What is the an "appropriate clinical facilities" ? From a French point of view, it's a Phase I unit which has been agreed by the Competent Authority. Do we have to set up the same approval Phase I unit system in the different European countries ? What is the definition of "facilities for the treatment of medical emergency" ? Does it mean that the Phase I unit has to be **in** hospital which has got an emergency department and/or an intensive care unit facilities ? "Ready availability of an ICU facilities" *for the first cohort of subjects within a dose group, could be discussed on the anticipated possible side effects.* About "an adequate information communication system" we could propose the French system, a centralized national database which is on process since 1988. This system is the only system which can guarantee the sentence: "the safety of subjects participating in first in man studies is the paramount consideration" (line 8). If this guideline is voted in Europe (EMEA) what will happen for the first in man studies performed outside of Europe (USA, Asia), ? Will this studies performed outside of Europe be accepted by the EMEA? Our suggestion is that this guideline has to be applied for all first in man studies performed.	See modified text. European Member States have the responsibility for clinical trials performed only in their own country. Indeed, the guideline should be carefully considered for all first-in-human clinical trials.