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The EMEA Guideline on First-in-Human Clinical Trials and Its Impact on Pharmaceutical Development

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INTRODUCTION

On March 13, 2006, TGN1412, a monoclonal antibody, was administered to humans for the first time. Severe, life-threatening toxicities ensued. The science behind these adverse events and the immediate responses to this event have been described in another article (Horvath and Milton 2009). The TeGenero incident was a wake-up call to the pharmaceutical industry, the clinical trials community, and the regulatory agencies. The incident was investigated thoroughly by several different groups, including the Expert Group on Phase One Clinical Trials (chaired by Professor Gordon Duff), the Royal Statistical Society, and the Early Stage Clinical Trial Taskforce. Each of these groups issued reports that summarized the causes of the adverse events and proposed ways that such adverse events could be avoided in future first-in-human (FIH) studies (Expert Group on Phase One Clinical Trials 2006; Medicines and Healthcare Products Regulatory Agency [MHRA] 2006; Early Stage Clinical Trial Taskforce 2007; Senn et al. 2007; Royal Statistical Society 2007). At the same time as these reports were being created, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMEA) was working on creating a guideline on strategies to identify and mitigate risks for FIH clinical trials with investigational medicinal products.

THE CREATION OF THE EMEA GUIDELINE

In January 2007, there was an announcement that a guideline on "Requirements for First-in-Man Clinical Trials for Potential High-Risk Medicinal Products" would be created, and approximately six months later, the guideline was finalized (EMEA 2007c, 2007d). The draft guideline was released for consultation on March 22, 2007, with the end of the consultation period (the deadline for comments) being May 23, 2007. Comments on the draft guideline were received from over fifty-eight different organizations, companies, and institutes. The summarized comments on the draft guideline and the CHMP's response to these comments are all available on the EMEA's Web site, as is the original draft guideline (EMEA 2008). This transparency is in contrast to the FDA's practice of removing draft versions from the Web page after finalization. The FDA also does not provide the responses to the comments that the interested parties have submitted to the docket. Obtaining the submitted comments from the FDA Web site is feasible but not easily achieved. The EMEA then hosted a workshop on the draft version of the guideline on June 12, 2007 (EMEA 2007a). The workshop covered background information on the TGN1412 case, the details of the draft guideline, and the comments that were provided on the draft guideline. Breakout sessions that covered the major areas of the draft guideline were also held. The guideline was adopted by the CHMP on July 19, 2007, and came into effect on September 1, 2007 (EMEA 2007c).

As an aside, it should be noted that within two weeks of the TeGenero incident, the CHMP issued a concept paper on the "Development of a CHMP Guideline on the Non-Clinical Requirements to Support Early Phase I Clinical Trials with Pharmaceutical Compounds" (EMEA 2006). However, the timing of the release of this concept paper was purely coincidental since it had been agreed on with the Safety Working Party (SWP) in February 2006. In addition, the thrust of the concept paper was to expedite the initiation of clinical trials in a manner similar to the FDA's Guidance on Exploratory INDs (FDA 2006). The current (2008–2009) work plan for the

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Abbreviations: ABPI, Association of the British Pharmaceutical Industry; BIA, BioIndustry Association; CHMP, Committee for Medicinal Products for Human Use; CMC, Chemistry, Manufacturing & Controls; CPMP, Committee for Proprietary Medicinal Products; CTA, Clinical Trials Authorization; CTX, Clinical Trials Exemption; DMARD, disease modifying antirheumatic drug; DMPK, drug metabolism and pharmacokinetics; EMEA, European Medicines Agency; EU, European Union; FAHMP, Federal Agency for Medicines and Health Products; FDA, Food and Drug Administration; FIH, first-in-human; GAD, L-glutamic acid decarboxylase; GLP, good laboratory practice; HED, human equivalent dose; ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; IMP, investigational medicinal product; IND, investigational new drug; LAD, leukocyte adhesion deficiency; MABEL, minimum achievable biological effect level; MHRA, Medicines and Healthcare Products Regulatory Agency; MOA, mechanism of action; MRSD, maximum recommended starting dose; NCE, new chemical entity; NHV, normal healthy volunteer; NOAEL, no observed adverse effect (dose) level; PAD, pharmacologically active dose; PK, pharmacokinetics; PD, pharmacodynamics; SWP, Safety Working Party; SSD, safe starting dose.

SWP indicates that a draft guideline will be released for review in 4Q 2008 (EMEA 2007e). The national health authority in Belgium, the Belgian Federal Agency for Medicines and Health Products (2006), has produced a document, ''Guidance to the Conduct of Exploratory Trials in Belgium,'' that is a working document concerning the conduct of clinical exploratory trials in Belgium. This document was produced under political pressure and is not yet finalized. Despite these limitations, this document complements the EMEA guideline since it provides additional detail in certain areas.

The finalized EMEA guideline differed from the draft guideline in several ways, including the title. The title of the finalized guideline is ''Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products'' (EMEA 2007c), whereas the title of the draft guideline was ''Guideline on Requirements for First-in-Man Clinical Trials for Potential High-Risk Medicinal Products'' (EMEA 2007b). The subtle change in title highlights a change in the intent of the guideline from ''potential high-risk medicinal'' products to all investigational medicinal products (IMPs). Implicit in this is the belief that any IMP is potentially high risk unless data exist to the contrary. In addition, the scope of the draft guidance was expanded from a focus on biologics to include both biologics and new chemical entities (NCEs). These changes arose based on the written comments that were provided by interested stakeholders, as well as discussions at a workshop that was held on the draft guidance. Some of the comments that were provided by interested parties who were primarily focused on the development of biologics seem to imply that biologics were being unduly singled out and that, if such a guideline were to be implemented, it should apply to both biologics and NCEs. The decision to expand the scope of the guideline to apply to both biologics and NCEs is a prudent decision because it places the focus on the pharmacology of the target and the properties of a product rather than the categorization of a given clinical candidate. Despite the fact that the guideline applies to both biologics and NCEs, the heritage of the guideline is quite clear, and the guideline reads very much like a biologics guideline into which some mention of NCEs has been inserted.

THE CONTENT OF THE EMEA GUIDELINE

The guideline is wide-ranging in scope and is intended to assist sponsors in the transition from nonclinical to early clinical development. It identifies factors influencing risk for new investigational medicinal products and considers quality aspects, nonclinical and clinical testing strategies, and designs for FIH clinical trials. Strategies for mitigating and managing risk are given, including the calculation of the initial dose to be used in humans, the subsequent dose escalation, and the conduct of the clinical trial.

The guideline is not a stand-alone document and should be read in conjunction with several nonclinical and clinical EU guidelines. These guidelines include the following:

- Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (ICH M3), CPMP/ICH/286/95
- Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH S6), CPMP/ICH/302/95
- The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarisation (QT Interval Prolongation) by Human Pharmaceuticals (ICH S7B), CPMP/ICH/423/02
- Safety Pharmacology Studies for Human Pharmaceuticals (ICH S7A), CPMP/ICH/539/00
- Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies (ICH S3A), CPMP/ICH/384/95
- Position Paper on the Non-Clinical Safety Studies to Support Clinical Trials with a Single Micro Dose, CPMP/SWP/2599/02
- Guideline for Good Clinical Practice (ICH E6), CPMP/ICH/135/95
- General Considerations for Clinical Trials (ICH E8), CPMP/ICH/291/95
- EUDRALEX Vol. 10—Clinical Trials (in particular, chap. 1: Application and Application Form, and chap. 2: Monitoring and Pharmacovigilance)

It should be noted that an expert working group has been established to write an addendum to the ICH S6 guidance (ICH 2008a). A clarification (and sometimes amplification) of this guidance is needed as substantial experience and new information has been gained since 1997. Disharmony across regulatory regions was identified to be a result of differences in implementation and interpretation of the S6 guidance and in part because of regional specific ''Points to Consider'' documents. The addendum will address species selection, study design, reproductive/developmental toxicity, carcinogenicity, and immunogenicity, although at this time, it is unclear as to the exact details and impact of the addendum. It is hoped that the addendum will reach Step 2 (i.e., be available for review) in November 2009 and Step 4 (i.e., adoption) in June 2010.

In section 4, the EMEA guideline acknowledges that

> for many new investigational medicinal products, the non-clinical safety pharmacology and toxicology programme provides sufficient safety data for estimating risk prior to first administration in humans. However, for some novel medicinal products this non-clinical safety programme might not be sufficiently predictive of serious adverse reactions in humans and the non-clinical testing and the design of the first-in-human study requires special consideration. When planning a first-in-human clinical trial, sponsors and investigators should identify the factors of risk and apply risk mitigation strategies accordingly as laid down in this guideline. In addition to the principles expressed in this guideline, some special populations such as paediatrics may deserve specific considerations.

The focus of risk identification and risk mitigation before performing a FIH study is a somewhat new approach. Previously, the approach had been primarily focused on hazard identification (a description of the danger; i.e., what are the target organ[s] and adverse effects caused by the agent) with a lesser emphasis on risk identification (the likelihood of a toxic effect at expected exposure levels and conditions) and risk mitigation. The distinction between hazard identification and risk identification may appear to be a subtle one, but the difference is important. A compound that may have a high or hazardous profile may pose no risk to humans if exposure levels are low and the toxic potency is low. In addition, the mention of the pediatric population is an interesting one because it is very rare (if it has ever occurred before) that the first time that a novel IMP was administered to a human would be to a child rather than to an adult. One can only speculate as to why this population was specifically mentioned unless the intent was for the guideline to be used for first-time administration to a new subject population.

Various risk factors that should be taken into account are described in the guideline at both a high level and at a very detailed level. At the high level, the guideline states, ''Predicting the potential severe adverse reactions for the first-in-human use of an investigational medicinal product involves the identification of the factors of risk. Concerns may be derived from particular knowledge or lack thereof regarding the mode of action, the nature of the target, and/or the relevance of animal models.'' This statement makes the point that absence of evidence is not the same as evidence of absence and starts to lay the groundwork for the conclusion that new products should be regarded as having high risk unless data exist to the contrary.

The guideline then describes in great depth the criteria that should be discussed in the Clinical Trial Authorization (CTA) application for an FIH study. The list is lengthy and is not intended to be a checklist, since the guideline also notes that the criteria should be taken into account on a case-by-case basis. However, the mere existence of such a list will inevitably mean that it will be viewed as a checklist. Similarly, the guideline describes in great length the information that should be available related to the following:

1. Demonstration of the relevance of the animal model (i.e., animal species)
2. Pharmacodynamics
3. Pharmacokinetics
4. Safety Pharmacology
5. Toxicology
6. Estimation of the first dose in humans.

It should be noted that the risk assessment will be performed on a ''case-by-case'' basis and that a ''weight-of-evidence'' approach will be used. This confirms the approach advocated by ICH S6 and suggests that such an approach is just as valid for NCEs as it is for biologics. In the opinion of the authors, this is an important and appropriate principle, especially with the realization that some NCEs (e.g., PEGylated small molecule compounds) and some synthetic compounds (e.g., peptides and oligonucleotide compounds) may have properties similar to biologics.

The guideline notes that novel mechanisms of action (MOA) do not necessarily add to the risk, per se, but consideration should be given to the novelty and extent of knowledge of the supposed mode of action. This statement alludes to the fact that we may not know the primary MOA at the time of the FIH study, as was the case with pregabalin (Lyrica®, Pfizer; Silverman 2008). At the time of the FIH study for this compound, it was believed that the MOA was activation of L-glutamic acid decarboxylase (GAD). Subsequently, it was discovered that this was not the MOA and that pregabalin's true MOA was binding to the $\alpha_2\delta$ subunit of voltage-gated calcium channels. According to the guideline, the type of knowledge that may be required includes the nature and intensity (extent, amplification, duration, reversibility) of the effect on the specific target and nontargets and subsequent mechanisms, if applicable. This simple statement contains two important points, namely, the importance of nontarget-mediated (i.e., off-target) effects and the importance of the downstream effects of the interaction of the product with its target. It is presumed that *nontarget* in this context is synonymous with ''nonintended target.'' Additional information related to the nature of the dose response (steepness, shape, linearity, presence of a maximum effect) is also recommended. The guideline identifies certain modes of action that might require special attention. These include targets that have pleiotropic effects or are ubiquitously expressed (e.g., as often occur in the immune system) and those that have a biological cascade or cytokine release, including those leading to an amplification of an effect that might not be sufficiently controlled by a physiologic feedback mechanism (e.g., in the immune system or blood coagulation system). Monoclonal antibodies against the T cell targets CD3 or CD28 are given as examples of products that have this latter type of MOA.

The analysis of the risks associated with a given MOA not only should be based on data generated for a particular target but should also take into account data generated from the previous exposure of humans to compounds that have related modes of action and evidence from genetically modified animal models (transgenic, knock-in, or knock-out). Interestingly, the guideline does not describe the use of data from humans with genetic polymorphisms in the intended target or related to the intended MOA. Such data would be far more informative than the corresponding animal data. For example, the primary pharmacologic effects of administration of an anti-CD18 monoclonal antibody (i.e., leukocytosis and increased susceptibility to infection) are predicted by the phenotype of individuals with leukocyte adhesion deficiency (LAD), related to one of several functional defects in this selectin (Sharar et al. 1991; Etzioni 2007).

In addition to an understanding of the intended MOA, it is expected that the sponsor will provide a detailed description of the nature of the target. This information may include information on the structure, tissue distribution, cell specificity, disease specificity, regulation, polymorphisms, level of expression,

and biological function of the human target, including "downstream" effects, and how it might vary between individuals in different populations of healthy subjects and patients.

Because the selection of the starting dose for an FIH study will be based on animal data from either toxicology or pharmacology studies, it is not surprising that the guideline also recommends that the sponsor should address the relevance of the animal models (species). This topic is addressed in two separate sections of the guideline. The guideline emphasizes that a weight-of-evidence approach should be used for determining the relevance of the animal models and that if the animal models are of questionable relevance for the investigation of the toxicological and/or pharmacological properties of the IMP, then this should be considered as adding to the risk. That is, the results of preclinical testing are relevant only to the extent that the target biology and compound pharmacology are comparable to humans. For this reason, it is incumbent on the sponsor to demonstrate convincingly the relevance of the chosen animal species.

The EMEA guideline describes the assessment of the relevance of the animal models as taking into account many factors, including the target, its structural homology, distribution, signal transduction pathways, the nature of the pharmacological effects, and metabolism and other pharmacokinetic aspects. The guideline places a clear emphasis on the need to ensure that the species used in the toxicology studies are pharmacologically relevant, with lesser emphasis on similarity of the metabolism of the clinical candidate in animals and humans (as has typically been the case for NCEs). The use of nonrelevant species in toxicology studies is strongly discouraged. Although pharmacological relevance is often part of the justification of the selection of the species to be used for the safety evaluation of biologics, it is rarely the case for NCEs, where the selection of the species used for the toxicology studies traditionally uses exposure and/or metabolism data. In reality, such data are most often used to justify the selection of the dog (for NCEs) and monkeys (for biologics) as the nonrodent species to be used in the toxicology studies. The rat is almost universally used as the rodent species in safety assessment studies for NCEs (Baldrick 2008), with very little justification for the selection of this species other than historical precedent.

The description of the elements that are important in the selection of the relevant species clearly shows that this guidance was originally written with biologics in mind and was not intended to be applied to NCEs. Yet the preclinical studies for NCEs traditionally emphasize comparative in vitro metabolism and biodistribution studies as part of the species selection criteria. Little, if any, mention is given in the guideline to the distribution of the product within the body and the metabolism of the product by the body. For a biologic, it is usually assumed that the compound will distribute poorly to tissues and be essentially restricted to the blood due its size. By contrast, NCEs will more readily distribute throughout the body due to their relatively small size. The concentrations of NCEs in tissues will also be affected by the metabolism and/or active transport of these agents. Therefore, an assessment of the relevance of a given species should take into account not only the distribution of the target in different tissues but also the distribution of the compound to those tissues in which the target is expressed. It should be noted that little data exist related to the relationship between the distribution of an NCE in animals and in humans.

With so much weight being given to the importance of pharmacological relevance in the selection of the species to be used in the toxicology studies, it is possible that clinical trial participants could encounter greater risk if toxicologic mechanisms are not fully evaluated. The guideline clearly gives the impression that the risk will most likely arise from biologic mechanisms (i.e., the intended pharmacological mechanism) rather than from chemical mechanisms. This is not surprising given the genesis of this guideline (i.e., as a guideline focused on biologics and the traditional focus on exaggerated pharmacology as the mechanism of toxicity for most biologics). It is assumed (as stated in ICH S6) that metabolism of biologics will yield small peptides and individual amino acids and that classical biotransformation studies as performed for NCEs are not needed (ICH 1996). It is also commonly assumed that any metabolites that are generated do not have a pharmacological and/or toxicological profile that is different than that of the parent molecule. However, it should be noted that such assumptions may not be valid in all cases (e.g., for oligonucleotide-based products, fusion proteins, and immunoconjugates). In addition, most biologics are very selective and have limited cross-reactivity with targets other than the intended target. The opposite is true for NCEs, where metabolism can result in molecules with altered pharmacological and toxicological properties and where both the parent and the metabolites may cross-react with targets other than the intended pharmacological target. Consequently, this leads to the possibility that unless one is careful, a focus on MOA-based toxicity may underestimate the human toxicity risk for NCEs, especially if the toxicity is caused by a metabolite. Although the FDA (2008) has issued a guidance on the safety testing of drug metabolites, this guidance was not intended to address FIH studies. Clearly, the challenge in the selection of the relevant species serves to emphasize the need for an extensive, weight-of-evidence approach in which both pharmacological and metabolic relevance are considered.

The EMEA guideline also addresses several CMC aspects. Briefly, the guideline notes that the sponsor should determine the strength and potency of the product, that the material used in nonclinical studies should be representative of the material to be used in the FIH study, and that the sponsor should demonstrate that very small doses can be accurately administered if the doses to be used in the FIH study are very low.

Selection of FIH Dose

Because the adverse events observed with TGN1412 were observed after the administration of the first dose, it is not surprising that the selection of the FIH dose is a major topic in the EMEA guideline. The guideline states that all available

information has to be taken into consideration for the dose selection, and this has to be made on a case-by-case basis. In general, the no adverse effect (dose) level (NOAEL) determined in nonclinical 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 or adjusted by appropriate safety factors according to the particular aspects of the molecule and the design of the clinical trials. However, for IMPs where factors influencing risk have been identified (which in reality will most likely be all products except ''me-too'' products), the use of the above approach is not appropriate and the use of the minimal anticipated biological effect (dose) level (MABEL) approach is recommended. The MABEL is the anticipated dose level leading to a minimal biological effect level in humans. The guideline states that the calculation of MABEL should use all in vitro and in vivo information available from PK/PD data. Such data may include the following:

1. target binding and receptor occupancy studies *in vitro* in target cells from human and the relevant animal species
2. concentration-response curves *in vitro* in target cells from human and the relevant animal species and dose/exposure-response *in vivo* in the relevant animal species
3. exposures at pharmacological doses in the relevant animal species

As was mentioned previously for calculating the FIH dose using NOAEL data, safety factors should also be applied to the calculation of a FIH dose using the MABEL approach. However, the EMEA guideline does not give insight as to the magnitude of the safety factor that should be used. The FDA ''Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers,'' which was issued in July 2005, addresses the use of a safety factor in detail (FDA 2005). This guidance states that the default safety factor that should normally be used is 10 and that this value is a historically accepted number although no justification for the selection of this value is provided. The FDA guidance indicates several considerations for increasing the safety factor, consistent with the EMEA guideline. The FDA guidance also describes situations under which the safety factor may be decreased. These situations include me-too products and when the duration of the toxicology study is longer than the proposed clinical schedule in healthy volunteers. In the latter situation, it is assumed that the toxicities are cumulative and are not related to the C_{max} of the product (i.e., are acute events). The FDA guidance focuses on the use of the NOAEL to establish the maximum recommended starting dose (MRSD) for the FIH clinical trial. However, the guidance also addresses the pharmacologically active dose (PAD) but does not provide much detail on this topic because the ''selection of a PAD depends upon many factors and differs markedly among pharmacological drug classes and clinical indications; therefore, selection of a PAD is beyond the scope of this guidance.'' Despite this statement, the guidance does encourage the sponsor to calculate the PAD and the human equivalent dose (HED). The guidance further notes that if the pharmacological HED is greater than the MRSD, it may be appropriate to decrease the FIH dose for pragmatic or scientific reasons, especially for certain classes of products (e.g., vasodilators, anticoagulants, monoclonal antibodies, or growth factors). Unlike the EMEA guideline, the FDA guidance does not encourage the use of PK/PD in the calculation of the MRSD. In fact, the guidance states that ''although the process outlined in this guidance uses administered doses, observed toxicities, and an algorithmic approach to calculate the MRSD, an alternative approach could be proposed that places primary emphasis on animal pharmacokinetics and modeling rather than dose. In a limited number of cases, animal pharmacokinetic data can be useful in determining initial clinical doses. However, in the majority of investigational new drug applications (INDs), animal data are not available in sufficient detail to construct a scientifically valid, pharmacokinetic model whose aim is to accurately project an MRSD.'' The reluctance to incorporate PK/PD in the determination of the MRSD appears to be based on the fact that using such data would rely on multiple untested assumptions regarding the behavior of the product in humans. It should be noted that a major effect of the EMEA guidance should be to prevent a clinical trial application in which it is considered that ''animal data not available in sufficient detail.''

According to the Duff Report, the selection of the starting dose for the TGN1412 clinical trial was based on the approach described in the FDA's guidance (Expert Group on Phase One Clinical Trials 2006; TeGenero 2006). The NOAEL from the repeat-dose cynomolgus monkey toxicology study was 50 mg/kg. An allometric conversion factor of 3.1 was used to convert this dose to the HED on a body surface area basis (16 mg/kg). A safety factor of 10 was then applied which yielded a MSRD of 1.6 mg/kg. The company then applied a further safety factor of 16 and selected a starting dose of 0.1 mg/kg. Overall, the safety factor used was 160. The rationale for the use of the additional safety factor is unclear and highlights the rather arbitrary nature of safety factors. Often, the actual safety factor used is based on a combination of the standard approach (i.e., a safety factor of 10), pragmatism (i.e., the dose strengths available for use in the study), and tradition (i.e., the use of round numbers). For TGN1412, it seems more likely that the dose of 0.1 mg/kg was chosen arbitrarily and that the resulting safety factor was calculated retrospectively. The topic of calculating the safe starting dose for pharmaceuticals in general, and TGN1412 in particular, has been discussed by Horvath and Milton (2009).

There are many challenges related to the calculation of the MABEL, the most notable of which is the definition of what is ''minimal.'' However, the guideline does not provide insight into this topic. In addition, despite describing in detail the factors that should be taken into account in the calculation of

MABEL, the guideline does not provide an example of how MABEL could be calculated. The Duff Report does give examples of MABEL calculations for two other products, although neither of these examples is easy to follow (Expert Group on Phase One Clinical Trials 2006). Members of the Association of the British Pharmaceutical Industry and the BioIndustry Association (ABPI/BIA) subsequently calculated probable receptor occupancy (included in the Duff Report) and presented their calculations of the MABEL for TGN1412 at an EMEA workshop held to discuss the draft guideline for FIH clinical trials for potential high-risk medicinal products (EMEA 2007a). More recently, Lowe et al. (2007) have published examples of how the dose of FIH studies can be calculated, including the calculation of MABEL for a monoclonal antibody. To date, there are no examples of how to calculate MABEL for an NCE. Regardless of which method of calculating the starting dose for TGN1412 (i.e., NOAEL, PAD, or MABEL) might have been the most appropriate, the complete absence of any discussion of the anticipated PD effects of the FIH dose within the TGN1412 clinical trial application is a glaring omission.

Although the EMEA guideline describes two different (NOAEL and MABEL) approaches for the calculation of the FIH dose, the sponsor is not restricted to using just these two approaches. Sponsors should look at the totality of the data available to them and evaluate several different approaches to the calculation of the safe starting dose (SSD) and then take the most conservative approach. The calculation of the SSD as described in the EMEA guideline applies only to studies that will be performed in NHVs. The guideline acknowledges that ''other approaches may also be considered in specific situations, e.g. for studies with conventional cytotoxic IMPs in oncology patients.''

Another draft regulatory guidance, ICHM3(R2), also addresses the issue of the selection of the SSD (ICH 2008b). ICHM3(R2) is a document whose purpose is to recommend international standards for, and promote harmonization of, the nonclinical safety studies recommended to support human clinical trials of a given scope and duration and marketing authorization. The draft guidance describes five approaches to nonclinical studies to support exploratory clinical investigations. These approaches range from support to clinical trials that use microdoses to clinical trials that include doses in the therapeutic range. Whether this guidance, in its finalized form, will provide harmonization or clarity remains to be seen since regional guidances also need to be taken into consideration, and such regional guidances may not be in strict alignment with the finalized ICH guidance.

Clinical Study Design

Finally, the EMEA guideline provides input into the design and conduct of the FIH study, with numerous recommendations for limiting and managing the risk to humans. These recommendations include the sequence and rate of dose administration in the first dose cohort, the dose escalation scheme, and the creation and use of stopping rules. The use of healthy volunteers should be fully justified because the expression of the pharmacological target (due to differences in phenotype and/or genotype) in healthy subjects may be different to that in patients. In addition, it is important that the healthy volunteers be able to tolerate any potential side effects. In designing the study, it is important that the sponsor considers, based on the available data, what could be the worst that could happen in the trial—to expect the unexpected and to be prepared for the worst.

The guideline has clearly focused on the safety of the volunteers that will participate in the first cohort in the study but does not provide much, if any, guidance as to the maximum dose that should be administered in the study based on the sponsor's knowledge of the pharmacology of the molecule and the animal toxicology data. This is a somewhat surprising omission because it is imperative that we perform the same kind of risk assessment at all dose levels that we perform for the first dose level. If the MABEL approach is used successfully for the calculation of the SSD, the administration of the product to the first dose cohort should be uneventful. The lack of observed toxicity in that first dose cohort should not be interpreted as meaning that the product will have a benign safety profile. It is quite possible that severe toxicities will be observed at higher dose levels and that all that has been achieved is to delay the inevitable consequence of the administration of a toxic product to a human population that will derive no therapeutic benefit from the product. In principle, then, it would seem prudent to estimate the PK/PD results of each dose level in the FIH trial and to revisit these projections after reviewing results of the first cohort. Such a practice will place increased emphasis on ''real-time'' PK/PD analysis and may lead to slower dose escalation as apparent safety alone may be insufficient to allow proceeding to the next dose level.

To address the issue of the potential for effects at higher dose levels, the guideline advocates the creation of stopping rules and a cautious approach to dose escalation. With regard to dose escalation, the guideline clearly states that PK and PD data (as well as safety data) obtained from a dose cohort should be compared to available nonclinical data before the decision to escalate to the next dose cohort is made. On the surface, this seems to be a simple task to perform, but the guidance does not provide insight into how PK/PD will be used in the dose escalation decision in one vital area, namely, interindividual variability. It is unclear whether the dose escalation decision should be based on the mean or individual PK (or PD) parameters, although based on discussion with a European regulator, the use of mean data would most likely be acceptable. Such a distinction is very important for highly variable products that have a narrow therapeutic window.

THE IMPACT OF THE TEGENERO INCIDENT ON PHARMACEUTICAL DEVELOPMENT

Since the TeGenero incident took place, those of us engaged in preclinical development have been swamped with suggestions

TABLE 1.—Potential impact of the TeGenero incident on the different disciplines.

Function	Points to Consider and Potential Impacts
Pharmacology	• Design and conduct of animal efficacy studies – Relevance of animal species and models of disease – Number of species or models used – Number of times a given efficacy study should be performed – Increased group size for statistical rigor – Conduct of studies "in the spirit of GLP" – Increased use of PK/PD • Better understanding of the pharmacology of the target – Consequences of modulating the target – Polymorphisms and variability of expression of target in animals and humans – Duration of effect, including "on-off" rate and rate of regeneration of target – Definition of a minimal effect • Better tools – More robust and sensitive PD assays – More PD assays for NCEs – Preditive cytokine release assays
Toxicology	• Enhanced role of target expression in selection of Tox species – How do we address differences in target expression based on supplier, age, gender, etc.? – Do we need to determine tissue distribution of target for a chemical? • What is more important for a chemical on-target or off-target toxicity? • Revisions to standard testing paradigms – Robust PD markers for both NCEs and biologics – Inclusion of limited toxicity assessments in animal efficacy studies – Increased number of animals/group in order to improve statistical rigor – Selection of Tox species for NCEs based on pharmacological responsiveness and not just metabolic stability – Cautious interpretation of studies that do not show toxicity
PK/ADME	• Greater need for PK/PD modelers in nonclinical studies • Robust PD markers for both NCEs and biologics • More nonclinical studies to define PK/PD than are presently conducted
Clinical	• FIH studies may be more protracted – Caution will be required at every dose level – Any adverse event that was not observed in animal toxicology studies may halt dose escalation – Slow IV infusions (60 min) instead of bolus administration – Sequential administration of product to subjects within a cohort – Possibly larger cohort size • Clinical protocols will need to be flexible to allow for changes to dose levels and PK/PD sampling schemes without undue delay to the conduct of the study • Slow conduct of clinical trial due to lag time between cohorts due to stopping rules and increased reliance on PK/PD for dose escalation • Need to build a PK/PD model in real-time based on data obtained from FIH study • Greater scrutiny of any observed side effect • Additional resources may be required – Real-time (bedside) PD assays – Expedited bioanalytical sample and PK analysis – "Rescue" procedures for patients that develop adverse events – Cross-functional approach to dose escalation decisions • Increased costs for FIH study
Regulatory	• Will need better competitive intelligence regarding other compounds with similar MOAs • Greater use of the Scientific Advice process in the EU before the FIH study
CMC	• Will need to provide a greater range of dose strengths for the FIH study • May need to provide solution doses to aid flexibility in dose escalation (oral products)

for reducing the risks for the subjects who participate in FIH studies from a variety of sources (expert reports, editorials, guidelines, etc.), and it can be difficult to reconcile them all. These suggestions affect the disciplines of pharmacology, pharmacokinetics and pharmacodynamics, and toxicology. However, once we have understood what is now required of us, we are left to determine who should implement the recommendations in the guideline. There are many potential implications of the EMEA guideline and many points to consider. Some of these points to consider and potential impacts are summarized in Table 1.

It is clear that FIH clinical trials will be conducted in an even more cautious manner and that they will take longer to conduct and be costlier. It may be reasonable to speculate that sponsors would move FIH clinical trials away from the EU. However, it is also reasonable to anticipate that the FDA would

default to the approaches described in the EMEA guideline, even though they may not issue their own guidance on this topic. Historically, many sponsors developing biologics have conducted their FIH trials in the EU, particularly prior to the replacement of the Clinical Trial Exemption (CTX) with the Clinical Trial Application (CTA). It will be interesting to see how the regulatory environment for FIH studies continues to evolve. For example, will the expectation be that the same cautious approach should be taken each time that the product is studied in a new population for the first time (e.g., patient vs. NHV; children vs. adults; single dose vs. multiple dose; drug-drug interaction studies)? Will the role and/or rigor of the pharmacology or toxicology review be increased? For example, the EMEA do not presently require the individual study reports for review prior to approving the FIH protocol but may decide that going forward, these documents should be made available to them as part of their review, as is the case in the United States. Despite the increased awareness of the risks inherent in FIH studies with high-risk medicinal products, there does not seem to have been much, if any, effect on the conduct of FIH clinical trials in the United Kingdom. At the 2008 annual meeting of the Drug Information Assocation, sponsors were encouraged to seek advice from the MHRA before submitting their IMPDs. The MHRA have a flexible approach and prefer to review medicinal products on a case-by-case basis rather than a ''by-the-book'' basis. The MHRA are more frequently advising sponsors that their products are not high-risk medicinal products than they are advising them that their products are high-risk medicinal products. In the period 2007 to May 2008, 267 Phase 1 clinical trials were conducted in the United Kingdom. Of these, the MHRA identified five products (< 2%) as being high risk, and only one of these products was discussed with an external advisory group. In addition, there does not appear to be an impact on the review cycle for the IMPD. In April and May 2008, 46 Phase I clinical trial applications were reviewed with an average review time of 12.5 days (Jones 2008).

Undoubtedly, the TeGenero incident has brought pharmaceutical testing into the spotlight, particularly for trials using human volunteers. The period from the time of the TeGenero incident until early July 2008 was very quiet in terms of adverse events in Phase I clinical trials with NCEs or biologics. In early July, a participant in a Phase 1 study to evaluate the bioavailability of RhuDex® in a new formulation suffered a heart problem several days after administration of the drug and subsequently died (MediGene 2008). RhuDex® is an orally administered disease-modifying antirheumatic drug (DMARD) that is designed to inhibit T cell activation by blocking the CD80 receptor, which will lead to a decrease in inflammatory cytokines. RhuDex® has been administered to approximately eighty individuals, and positive safety data have been announced in a Phase IIa trial in patients with rheumatoid arthritis. At this point in time (approximately 2 weeks after the tragic death of the clinical trial participant), it is uncertain as to the role of the drug in this adverse event, but the reporting of the event by the press in the United Kingdom shows a keen interest in the protection of the safety of volunteers in clinical trials (Sweeney 2008).

Despite all of these concerns and the changes in the regulatory environment, not much will change in how we prepare for FIH studies. We will be essentially conducting the same work that we have previously, although we will be looking at the data and literature in a far more critical manner. There will be an increased need for integration of data and interpretations across disciplines, rather than the current, somewhat line-function-based approach. In reality, the distinction of roles based on line functions is outdated, particularly for companies that are developing biologics where the toxicity is due to exaggerated pharmacology. In this case, it is difficult, if not impossible, to tell where pharmacology ends and toxicology begins. For this reason, it is essential that toxicologists developing biologics become better acquainted with pharmacology (and immunology). The pharmacologist and toxicologist should work very closely together or even be one and the same person. This will open up opportunities for the toxicologist to act as a leader on cross-functional project teams, at least as it pertains to the identification and mitigation of risks in the FIH clinical trial. The toxicologist may be able work in close collaboration with the clinician to use preclinical data to forecast what pharmacodynamic activity will occur at each dose level in the FIH study rather than the standard current practice of advising what dose levels are not acceptable for the FIH dose. This enhanced requirement for a pharmacology-based approach to nonclinical safety assessment would logically extend to the pharmacology/toxicology reviewers in regulatory agencies, despite recent trends in the opposite direction (e.g., CDER assuming responsibility for CBER projects at the FDA).

CONCLUSIONS

At first blush, the TeGenero incident appears to have had rapid and far-reaching effects on the preclinical development programs to support FIH clinical trials. The most tangible of these is creation of the EMEA guideline for identification and mitigation of risk in FIH studies. This guideline builds on the foundation of ICH S6, in which a case-by-case, science-driven approach to safety testing is described, and the FDA guidance for estimating FIH starting doses, with additional emphasis on understanding and projecting the likely effects of the first pharmacologically active dose administered to humans. For perhaps the first time, this approach is now implicitly condoned for NCEs as well as for biologics and emphasizes a thorough understanding of the pharmacology in addition to the toxicology. We may never be able to tell whether the guideline has indeed improved the safety of the clinical trial participants due to the extreme rarity of the types of events such as the TeGenero incident. The EMEA guideline will, however, undoubtedly reduce the risk for participants in clinical trails, although there will be consequences of this added caution. It is likely that there will be an increase in the cost and time required to develop a product and a decrease in productivity of development organizations, particularly prior

to Phase II testing. In addition, the pharmaceutical industry may be less willing to develop products for novel and unvalidated targets, especially for the treatment of small patient populations. It is probable that if the EMEA guideline had been in place at the time of the TeGenero clinical trial, the events that unfolded after the administration of TGN1412 to the first dose cohort would not have occurred. However, it is quite possible that the guidance may have simply delayed the inevitable tragic consequences of the administration of TGN1412 to healthy volunteers until a higher dose level.

Regardless, the EMEA guideline is here to stay, and it is up to us to determine how to safely and effectively develop products in this new regulatory environment. Whatever we do, we should ensure the safety of the clinical trial participants and work diligently to ensure that the events of March 2006 do not occur again.

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