INTRODUCTION

For many decades the decision to start the dosing of a first-in-human (FIH) trials was mainly based on the No Observed Adverse Effect Level (NOAEL) in the most sensitive species as determined during the toxicological studies.

Following the life-threatening adverse event that occurred after the FIH administration of a CD28 super-agonist antibody, early testing in humans was revisited by a UK scientific expert group to specifically address the risk related to the administration of monoclonal antibodies in healthy subjects. Based on the resulting expert report (aka “the Duff Report”) the European Medicines Agency (EMEA) drafted a guideline that was followed by an extensive discussion across the scientific drug development community before reaching a general agreement that was translated into a new EMEA guidance. This new guidance underlines the need to better mitigate the risk when first-in-human dosing is concerned, and proposed an improved approach to the dose selection through the integrated quantitative analysis that combines all the pharmacology, safety and efficacy preclinical data. The objective of this new process is to define a starting dose in the FIH trial that is expected to result in a minimum anticipated biological effect.

Interestingly, while the early discussion focused on the risk related to antibodies and biological products in general, the final document did not try to give a definition of a high risk drug candidate, but instead proposed a risk mitigation strategy that should be equally applicable to all investigational medicinal products (IMP) whether they are small molecules or biologicals.

This paper aims at presenting diverse strategies supporting the choice of the starting dose that were seen in recent FIH trials conducted at the SGS Clinical Pharmacology Units (CPU).

EMEA APPROACH

The EMEA Guideline recognizes that the NOAEL adjusted with allometric factors or based on pharmacokinetics (PK) is the first approach to define the human equivalent dose (HED) and consequently the maximum recommended starting dose (MRSD) for a FIH trial.

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 trial.

However, when factors influencing risk are identified (e.g. related to the mode of action, the nature of the target, and/or the relevance of animal model(s)) the ‘Minimal Anticipated Biological Effect Level’ (MABEL) approach is recommended. The MABEL by definition is deemed to lead to a minimal biological effect in humans. It is calculated by using all in vitro and in vivo information available from pharmacokinetic/pharmacodynamic (PK/PD) data.

When the two approaches give different estimations of the first dose in man, the lowest value should be used, unless otherwise justified.
EXAMPLES OF STARTING DOSE APPROACH IN FIH TRIALS CONDUCTED AT SGS

The following 4 case studies give an overview of the increasing use of PK/PD in the selection of the starting dose of FIH trials conducted in the CPU's of SGS in the last two-year period.

When considering these FIH trials, conducted with drug candidates with different mechanisms of action, three methods of determination of the starting dose were used:

- based on the NOAEL and the allometric scaling of the human clearance
- based on the NOAEL and a "pharmacological NOAEL"
- based on the NOAEL, PK modelling and pharmacological activity

CASE STUDY 1 WHERE THE MRSD IS BASED ON BOTH NOAEL AND ALLOMETRIC SCALING OF CLEARANCE

Typically, from two 4-weeks toxicology studies the NOAEL of the most sensitive species was retained (25 mg/kg) to calculate the maximum recommended starting dose (MRSD) using the body surface area scaling and a standard safety factor of 10 (24 mg). MRSD was also calculated by using allometric scaling of the human clearance (simple allometric scaling, corrections by brain weight, maximum life span and body weight fixed exponent) and the same safety factor as mentioned above. The method giving the lowest estimate of clearance was retained.

The MRSD (377 mg) was then calculated as

\[ \text{MRSD} = \text{CL}_h \times \text{AUC}_{\text{NOAEL}} \times \text{Protein Binding Correction Factor} \]

The most conservative estimate of MRSD (25 mg) was used as the starting dose of the FIH trial.

CASE STUDY 2 WHERE MRSD IS BASED ON NOAEL AND "PHARMACOLOGICAL" NOEL

Where the MRSD extrapolated from the NOAEL established in two 4-week toxicity studies was corrected by the difference in the affinity to the target receptor across species and with a standard safety factor of 10 (1.3 mg) and further compared with MRSD (0.44 mg) extrapolated from the no observed effect level (NOEL) based on the target pharmacological activity. The starting dose of the FIH trial was lower than the MRSD based on the NOAEL to accommodate with the predicted pharmacological effect in humans. It is worthy to note that the NOEL concept was used here as method to approach the MABEL.

CASE STUDY 3 WHERE MRSD IS BASED ON NOAEL, PK MODELLING AND PHARMACOLOGICAL ACTIVITY

The in vivo preclinical information of the drug candidate was shown to support the concept of a relationship between the pharmacological effect and the exposure. Subsequently, three methods of calculation of MRSD were used:

- MRSD (10 mg) based on NOAEL from two 4-weeks toxicology studies and a standard safety factor of 10
- MRSD (0.5 mg) based on the pharmacologically active dose in an in vivo animal model and the safety factor as mentioned above
- PK modelling and extrapolation to humans

Again, the most conservative estimate of MRSD (0.5 mg) was used as the starting dose of the FIH trial.

CASE STUDY 4 WITH A DRUG WITH A LOW PERMEABILITY

A low permeability drug candidate leads to difficulties in the assessment of the most sensitive species in the toxicology studies. It is quite often that no adverse effects can be seen even at the highest dose of the toxicology studies. In this case, the NOAEL in the two 4-weeks toxicity studies were the two highest doses. Based on these results MRSD were respectively 960 mg and 1620 mg. It is worthy to note that in this case the safety factor (20) was greater than usual after considering that two metabolites that were identified in vitro might not be present in toxicological species in the same ratios.

The MRSD (80 mg) was then calculated by allometric scaling of the PK and using the lowest exposed toxicological species. Again, the most conservative estimate of MRSD (80mg) was used as the starting dose of the FIH.

DISCUSSION AND CONCLUSIONS

It is worth noting that within two years the Guidelines on FIH trials have evolved for the starting dose in FIH trials from a unique approach (e.g. conversion of NOAEL to human equivalent dose, HED), to a more global approach that combines the NOAEL approach, the pharmacokinetic interspecies scaling, and the dynamics of the drug candidate.

The present retrospective evaluation of FIH trials of small molecule non-high-risk drug candidates conducted at SGS shows that in the case where no risk factors have been identified, the choice of the starting dose generally combines the standard approach based on the FDA Guidance (extrapolation from NOAEL based on allometric factors), the scaling of human clearance and further extrapolation of the starting dose based on the...
exposure at the NOAEL and applying a standard safety factor of 10. Then the lowest starting dose is generally chosen as a conservative approach to the safety of the trial participants.

In the case where the pharmacological effects in humans is expected to blur the first evaluation of the drug candidate in humans (e.g. sedation), or when the expected pharmacological activity in humans is one of the study objectives of the FIH trial, then the NOAEL, PK modelling approaches are combined with the modelling of the pharmacological effect exposure so that the starting dose allows the evaluation of a wide range of the dose-effect relationship.

The last EMEA Guideline on FIH trials has emphasised the role of PK/PD simulation in the determination of the starting dose in FIH trials. This retrospective analysis indicates that even for non-high-risk drug candidates a PK simulation of the human starting dose is almost always added to the standard primary method based on NOAEL adjusted with allometric factors. The examples presented also show that dose-exposure/effect information is increasingly used for the determination of the starting dose pharmacologically active dose.

Noteworthy, in two cases, and although the corresponding drug candidates were not identified as high-risk molecules, a MABEL approach was used to choose the most conservative starting dose, which overall confirms the usefulness of this new approach to mitigate the risk that is ever related to the first dose given to humans.

This combined approach certainly provides a greater confidence when the choice of the starting dose in a FIH trial is considered.

**With innovative study designs, optimal facilities and strong regulatory intelligence, SGS can favorably impact client’s drug development timelines and decision-making process.**

---

**REFERENCES**

5. Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. FDA/CDER, July 2005

---

To receive future articles on current trends and regulatory updates, subscribe to SGS’ Life Science News at [www.sgs.com/lss_subscribe](http://www.sgs.com/lss_subscribe)

**CONTACT INFORMATION**

**EUROPE**  
+ 33 1 53 78 18 79  
clinicalresearch@sgs.com

**NORTH AMERICA**  
+ 1 877 677 2667  
clinicalresearch@sgs.com

[www.sgs.com/cro](http://www.sgs.com/cro)

**WHEN YOU NEED TO BE SURE**