EFFECTIVE IMPLEMENTATION OF THE REVISED EMA FIRST-INTO-HUMAN (FiH) GUIDANCE TO ACCELERATE YOUR EARLY CLINICAL DEVELOPMENT

Dr Annelize Koch and Dr Simon Hutchings review the revised EMA FiH guidance effective February 2018, and suggest how these guidelines can be used effectively to accelerate your early clinical development.

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Simon has over 10 years of experience in the drug development process, including pre-clinical pharmacology/toxicology, Phase I (including first-in-human) pharmacology/PK studies and investigator-led Phase II/Phase III trials. In addition to undergraduate and postgraduate qualifications in pharmacology, Simon also holds a Certificate in Human Pharmacology from the Faculty of Pharmaceutical Medicine (Royal College of Physicians).

Simon has extensive practical experience and scientific knowledge of the design, management and reporting of clinical development projects. He was a contributor to the revised 2017 EMA First-in-Human guidance and is Chair of the EUCROF Early Phase Research Working Group.

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Annelize has over 15 years of experience in the drug development process, including interpretation of preclinical pharmacology/toxicology, Phase I (including first-in-human) pharmacology/PK studies and Phase IIa trials. In addition to her medical degree, Annelize also holds a Certificate of Completion of Training (CCT) in Pharmaceutical Medicine (Royal College of Physicians) and is a Fellow of the Faculty of Pharmaceutical Medicine. Annelize has extensive experience in the running of Phase I studies as well as scientific knowledge of the design and management of clinical studies. Annelize has held medical positions at Paraxel and GSK.

UK EXPERIENCE IN FiH TRIALS

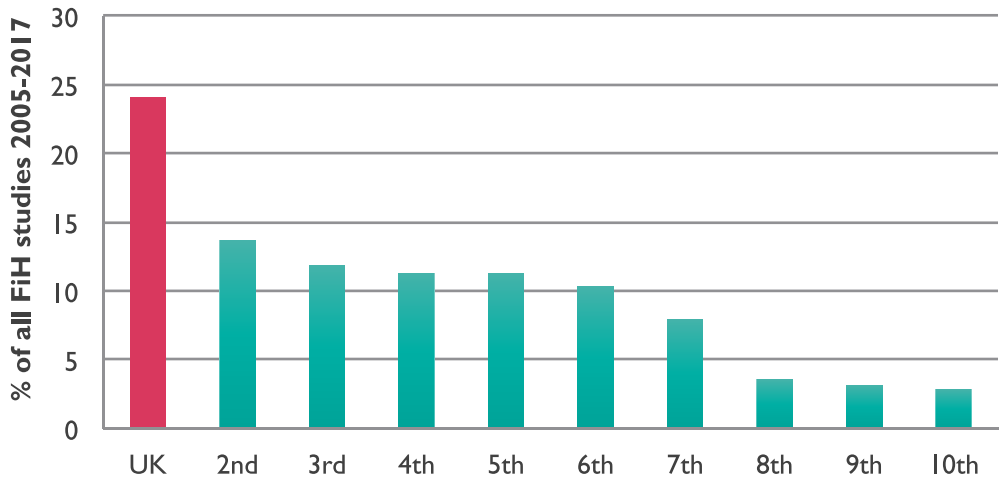
The UK has significant experience in FiH trials and has conducted almost 25% of the 2,006 FiH studies carried out in the European Union (EU) between 2005 - 2017. (Figure 1)

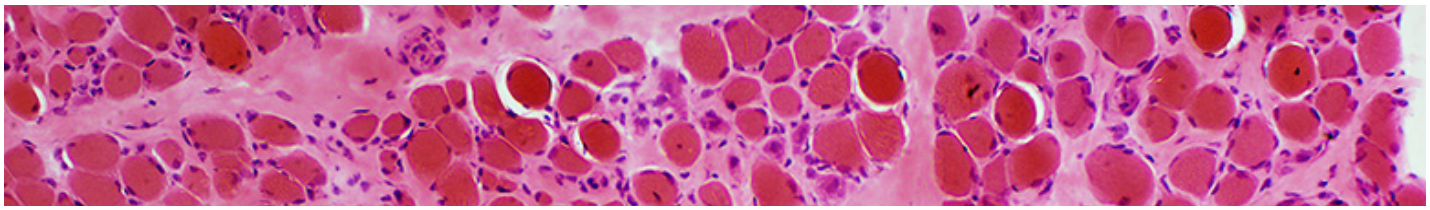
EU MEMBER STATES CONDUCTING FiH STUDIES

We contacted a number of regulatory authorities to provide individual country-level data for FiH and Phase I studies, we received responses from the UK, Sweden, Denmark, Germany and Belgium for 2016/2017.

During this period Germany conducted approximately 200 studies of which around 20% were FiH. The UK conducted around 150 studies, however a significantly higher proportion (>50%) of these were FiH, demonstrating the UKs experience and expertise for FiH studies (with Phase I units, Investigators and the regulators). Belgium conducted the third highest number of studies, followed by Denmark and Sweden.

Figure I: Graph of Top 10 EU Member States conducing FiH studies





Dr ANNELIZE KOCH:

How studies have shaped and helped produce the EMA FiH guidelines.

CASE STUDY: PAREXEL PHASE I UNIT – NORTHWICK PARK HOSPITAL, UK MARCH 2006

- TGN1412: humanised IgG mAb – First-in-class anti-CD28 'superagonist'
- Single Ascending Dose (SAD) study design
- First SAD cohort (6 active: 2 placebo) dosed at 0.1mg/kg
- 3 to 6-minute infusion, 10-minute intervals between volunteers.
- Calculation of starting does followed existing 2005 FDA guidance[1]

All six subjects that received the active dose had a severe systemic inflammatory response followed by respiratory and renal failure and disseminated intravascular coagulation. Later this reaction was identified as 'Cytokine Release Syndrome'[2].

THE REGULATORY RESPONSE

In response to this incident, the Expert Scientific Group (ESG) was set up by the MHRA to investigate the TGN1412 incident. Following their investigation, a report was published in 2006 which included 22 different recommendations to improve the safety of FiH trials [3]. As stated in the report "the preclinical development studies that were performed with TGN1412 did not predict a safe dose for humans, even though current regulatory requirements were met". It should be noted that the starting dose estimation did not consider a biologically active dose based on plasma TGN1412 levels or receptor occupancy. It further emphasised the importance of the relevance of animal models, and subsequently the EMA published the FiH Guidance in 2007 [4].

Dr SIMON HUTCHINGS:

THE 2007 EMA FiH GUIDANCE.

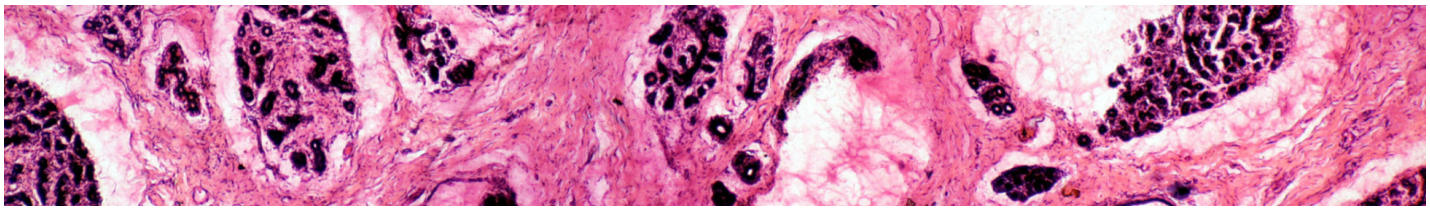
The first thing to note from the original 2007 EMA guideline [4] is the strong emphasis on risk identification and the subsequent mitigation of those risks associated with the first dosing of a novel, investigational medicinal product into humans. The guide also emphasised that a case-by-case approach should be taken, and that guidelines should not simply be used as a checklist for FiH trials; the guidelines should really be used in combination with good science and good pharmacology, considering all aspects when deciding the starting dose.

As with all drug development programmes, much information can be gathered during non-clinical studies with regards to the Mechanism of Action (MOA). However, the extent of knowledge of such mechanisms that can be ascertained from non-clinical studies can vary significantly between products. Where we have a lack of true knowledge of the MOA the guidelines state it will need to be noted as a risk. In general, the guidance states that all new or novel products should be regarded as having high risk, unless there is data existing to the contrary.

The guideline also suggested that there should be additional requirements for information included in applications for Clinical Trials Authorisation (CTA). This includes things such as demonstration of the relevance of the animal model and detailed description of the nature of the target, such as tissue distribution, cell specificity, level of expression and biological function. The guideline also suggested a more comprehensive knowledge and demonstration of the Pharmacokinetics (PK) in non-clinical species, and their relationship to Pharmacodynamics (PD).

A key concept of the guidance was the introduction of the concept of a Minimum Anticipated Biological Effect Level (MABEL). This recommended that we should use all available *in vivo* and *in vitro* PK and PD data, and not just rely on the No Observed Adverse Effect Level (which has a basis more in toxicology as opposed to pharmacology). It was stated in the Expert Scientific Group Report in 2006 that applying such an approach for the TGN1412 study would have resulted in a least a 20-fold lower starting dose [3].

There were additional aspects included in the 2007 FiH guideline that arose from the experience with the TGN1412 trial. One key aspect was precautions to apply between doses within a cohort, and introduced the importance of sentinel or dose-leader subjects. It also discusses precautions to apply between cohorts, i.e. what



information to look at in order to perform acceptable dose escalation.

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CASE STUDY: BIOTRIAL PHASE I UNIT, RENNES, FRANCE, JANUARY 2016

BIA-10-2474 is a Fatty Acid Amide Hydroxylase (FAAH) inhibitor, which is not a first-in-class compound, so other compounds from this class had been tested in the past [5,6].

The study employed an integrated Protocol with 4 separate parts: single ascending dose (SAD), multiple ascending dose (MAD), Food Effect and PD.

At the time of the incident, 78 subjects had already been exposed to BIA-10-2474: SAD (0.25 – 100 mg) and MAD cohorts (2.5 – 20 mg/day for 10 days), and during this BIA-10-2474 was well tolerated. For cohort 5, subjects received 50 mg per day for 10 days. In the evening of day 5, one subject was hospitalised for acute neurological symptoms, which then later progressed to the subject becoming brain dead within three days [6].

The remaining 5 subjects were dosed on day 6 as planned, but 4 subjects were subsequently hospitalised due to acute neurological symptoms before they stabilised and eventually started to improve.

The French Competent Authority (ANSM) set up the Temporary Specialist Scientific Committee (TSSC) to investigate the BIA-10-2474 incident. They noted that the study design had sentinel dosing for SAD cohorts, but not MAD. The dose escalation was also based on the safety data from the previous cohort, but PK data only from the last-but-one (n-2) cohort.

The TSSC report was published in April 2016 and included six further recommendations to improve the safety of FiH trials [6]. The EMA published a revision to the FiH guideline in July 2017 [7].

Dr SIMON HUTCHINGS:

THE 2017 REVISIONS TO THE EMA FiH GUIDELINE

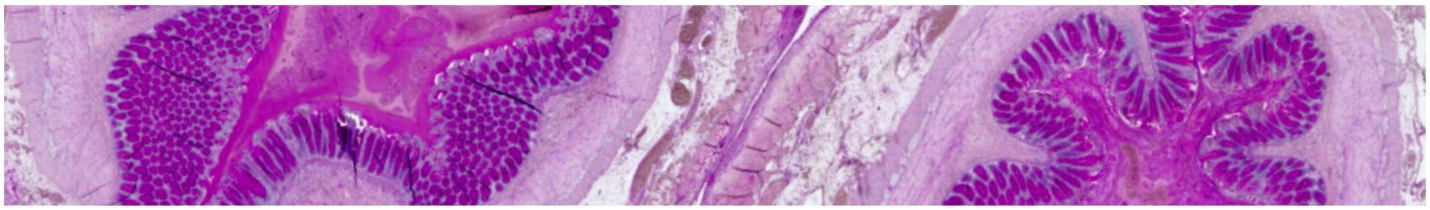
Much of the 2007 guideline remains in the 2017 revision, with an emphasis on good science and application of pharmacology and toxicology principles. What the revised guideline did introduce was specific recommendations for combination and integrated protocols (e.g. combined SAD/MAD/Food Effect/drug-drug interaction, among others).

The revised guidance emphasises that dose selection and escalation should be reviewed based on all emerging human PK and PD data from previous cohorts and should not be considered fixed based on the original assessment of the non-clinical data. Pre-clinical or non-clinical PK should be sufficient to support interpretation of the data from *in vivo* PD models in order to estimate Pharmacological Active Doses (PAD) and Anticipated Therapeutics Dose (ATD) ranges. The key aspect for this is that in pharmacodynamic non-clinical models we really need to have an idea of the exposure (i.e. the levels of drug in the blood) in those models in order to try and translate to a human scenario.

The other major aspect of the revised guidance of note is that there were no significant changes to the quality and non-clinical requirements for early phase studies. There was no update considered necessary to ICH M3 (R2) (the global non-clinical study requirement guidelines [8]) suggesting that the non-clinical studies that were performed prior to the 2016 BIA-10-2474 incident are considered sufficient. The interpretation and application of that data has been suggested as a possible deficiency contributing towards the unfortunate incident [5, 8].

Another aspect that the revised guidelines addressed is the progression from SAD to MAD parts, stating that this decision should be made based on PK-PD modelling where possible. It also stated that sentinel dosing should be used for all cohorts, both SAD and MAD, unless otherwise justified. Sentinel dosing requires on day one of the study that one participant is randomised to active and one participant is randomised to placebo. Both subjects are then observed for a minimum of 24 hours before the remainder of the cohort is dosed.

It is often asked if the new guidance requires submission of interim reports to Competent Authorities or Research Ethics Committees when moving between the SAD and



the MAD parts of the study. The guidance says that this should be considered, but it is not mandatory. So, for instance in the UK the MHRA does not require interim reports to be submitted when moving between different study parts within the same protocol, provided that the decision-making criteria for moving between parts is clearly defined in the protocol.

In general, the guidelines have been revised to promote more safe, effective, and science-based clinical trial design and therefore can be used to accelerate early clinical development. It is important to remember that guidelines are exactly that – they are not a set of rules that must be followed, and deviations from guidelines are often permissible if they are scientifically justified.

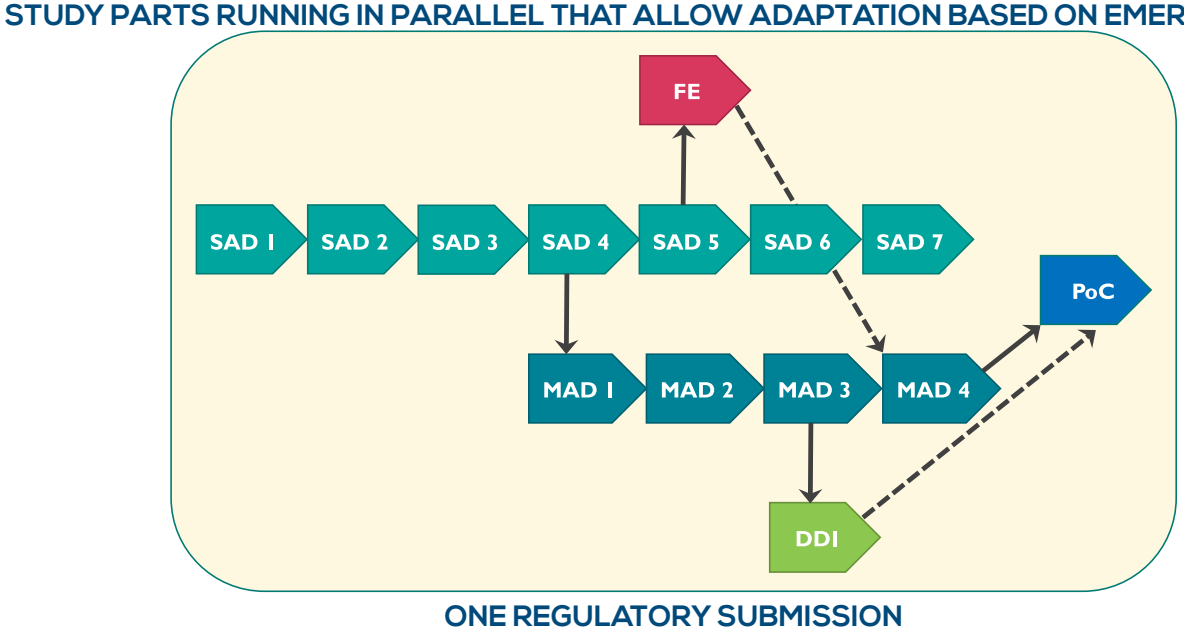
OBJECTIVES OF EARLY CLINICAL DEVELOPMENT.

The key objectives of early stage clinical development are to determine if a drug candidate meets the target product profile in terms of safety, pharmacokinetics, pharmacodynamics and proof-of-concept wherever possible. The reasoning for this is to allow a go or no-go decision as early as possible in the development programme. If the trial is going to fail, it is better to fail early, and therefore fail cheaply.

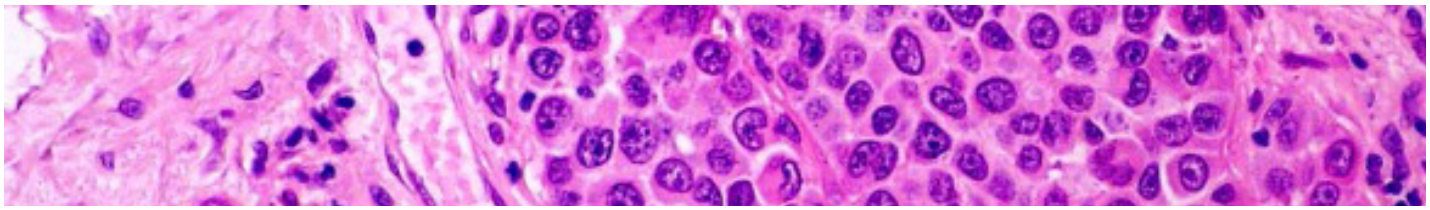
Examples of studies performed to meet the objectives of early clinical development include Single Ascending Dose, Multiple Ascending Dose, Food-Effect, drug-drug interaction, Gender Effect, Thorough QT assessment and Proof of Concept.

Traditionally, each of these objectives would be addressed by a separate study and therefore a separate regulatory submission, which can be arduous and represents a burden in terms of time and resource. To limit this, it became more common to combine certain aspects of early clinical development into one protocol and therefore one regulatory submission – the most common being combining the Single-Ascending Dose aspect to the Multiple Ascending Dose. This was expanded to include Food Effect or Drug-Drug Interaction studies, among other components.

Figure 2: Diagram example of Integrated Protocols



WHAT IS A TRULY INTEGRATED PROTOCOL?



ADAPTIVE PROTOCOLS

Adaptive protocols are considered as protocols with really defined boundaries within which we can operate without the need for substantial amendment. This allows adjustments to certain elements of the study in response to emerging data. For example, the number or size of cohorts is considered an adaptive element. In early cohorts, we may only need to recruit lower subject numbers, and as we move up the dose levels and therefore (conceptually) move up the dose-response curve, we might look to increase the subject numbers, which would increase the amount of data we are able to obtain at what we suspect to be therapeutic dose levels, and also minimise exposure of volunteers to suspected sub-therapeutic dose levels.

Another important aspect for FiH studies is deciding blood sampling or physiological assessment timings. At the non-clinical stage it really is an educated guess as only after we have seen the data for the first few cohorts that we know whether those estimates or timings, particularly for things like PK samples, were appropriate. Having adaptive elements where we have flexibility regarding blood sampling (up to an agreed maximum blood volume) is advantageous and avoids the need for substantial amendments.

For overlapping or parallel combined studies, we don't need to specify in advance which cohort we are going to start the Multiple Ascending Dose for instance, or after which dose level we start the Food-Effect study part. We can have decision-making criteria which allows this to be flexible.

Substantial amendments will typically only be required for unanticipated changes. Everyone who has been involved in clinical development will know that substantial amendments usually mean delays, take time and therefore incur an increased cost.

THINGS TO CONSIDER WITH ADAPTIVE PROTOCOLS

Adaptive Protocols are complex. They require experienced, pragmatic Competent Authorities who understand what we are trying to achieve with these types of studies. Adaptive Protocols also require experienced Phase I units with appropriate experience and Quality Management Systems in place to effectively run such studies.

It also should be noted that in order to make these studies as efficient as possible, rapid turnaround of PK/PD data is advantageous, therefore having on-site laboratories in Phase I units is highly desirable.

Additionally, there is a real increase in expectation for clear decision criteria, including the use of decision trees where relevant. This serves to show regulators exactly how we are going to adapt and what information we are going to use to make those decisions.

Dose selection/ escalation: Exposure-response

The relationship between dose or exposure and biological effect really underpins everything.

Minimum Anticipated Biological Effect Level (MABEL)

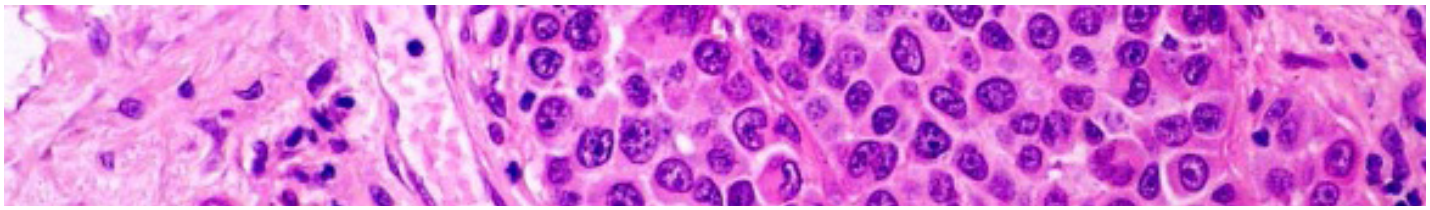
MABEL – seen in the early stages of the study, when you can first measure some biological activity, but it is nowhere near where we might anticipate a therapeutic dose lying.

Anticipated Therapeutic Dose (ATD)

This is seen as the biological effect increases. The ATD varies considerably between products, dose response curves or exposure response curves vary between different classes of compounds and mechanisms of action.

Unacceptable Toxicity

Within pharmacology, any drug or chemical will produce both unacceptable effects in addition to the original, intended effect at higher levels. Ideally, the product will have a wide interval between the ATD and unacceptable toxicity.



No Observed Adverse Effect Level (NOAEL)

NOAEL is a toxicological end-point, which could lie anywhere between MABEL and higher doses required for therapeutic benefit. This indicator is a good example of why regulators are keen to emphasise the use of both pharmacology and toxicology when using non-clinical data to estimate the starting dose.

Key points to consider for dose selection and dose escalation:

- The starting dose should be calculated using both toxicology and pharmacology
- The dose increment between cohorts should be guided by the exposure-effect, or the exposure-toxicity relationship in non-clinical studies and incorporating emerging clinical data. It should not be fixed.
- The exposure at the ATD range should typically not be exceeded, unless scientifically justified. This requires knowledge of the ATD, which may be more straightforward in some products where it is simple to demonstrate biological activity (particularly in healthy volunteers). For other products it can be very difficult to demonstrate biological activity, so this can be a challenge for certain products.
- It is stated in the guidelines that a trial design using a maximum tolerated dose approach is considered unethical for Healthy Volunteer studies. However, we do need to explore higher doses as part of the development process, such as for overdose or in the event of a drug-drug interaction (DDI), so how much above ATD range is acceptable? Is it justifiable, and how do we approach things such as exposure limits?

Exposure limits

The guidelines do state that exposure limits not to be exceeded should be explicitly stated in FiH protocols. But the message from regulators such as the MHRA is that we shouldn't consider exposure limits as a 'brick wall', but rather as 'a line in the sand', i.e. it may be acceptable to exceed an exposure limit if scientifically justified based on the emerging data during the clinical trial. This is one example of how interaction with a regulator via a substantial amendment would be required in order to exceed the stated exposure limits based on non-clinical studies.

Dr ANNELIZE KOCH:

RISK MITIGATION: STUDY DESIGN/ PROTOCOL

Key considerations around risk mitigation include the level of uncertainty around your IMP, are adverse events monitorable or reversible?

For the calculation of the starting dose, we need to consider the appropriate use of NOAEL vs Minimum Anticipated Biological Effect Level (MABEL) or the Pharmacological Active Dose (PAD)

The MHRA require investigators to be able to reference the starting dose proposed in the protocol, and it is an expectation that this is calculated independently in order to determine if it is in agreement with the starting dose estimated by the sponsor. It is also important to consider dose escalation and increments proposed for the study. You cannot just have n-fold acceptability, we need to look at pharmacological active doses and monitor this. It is also important to use PK-PD modelling to guide dose selection wherever possible.

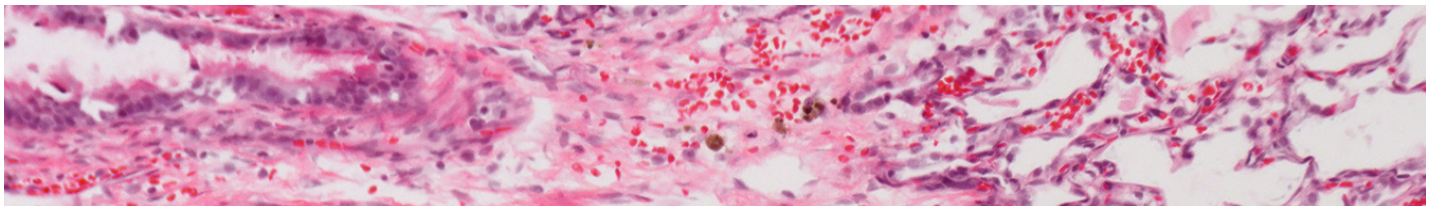
It is important to have clear criteria and decision making for dose escalation, and clear criteria to stop the study or specific cohorts. Exposure limits should be set for individuals, meaning we cannot use a mean value for the cohort; this imposes problems with variable data or outliers. If we see huge variability or outliers, we could increase those exposure limits, as it is an option with a substantial amendment.

As briefly discussed earlier, the key focus is going to be on emerging data. Throughout our study, we need to have a continuous review of all available data as it becomes available, including safety, PK and PD.

RISK MITIGATION: STAFF AND FACILITIES

As part of risk mitigation it is important to review how appropriate the staff and facilities are for the study. Facilities should have trained investigators with relevant medical and clinical pharmacology expertise, GCP training, a clear understanding of the specific characteristics of the IMP, and of its targeted mode of action, which are both important when we look at the starting dose calculation.

The study needs to be run in controlled conditions (e.g. inpatient care at an experienced, accredited Phase I unit), to allow the possibility of close supervision. Phase I units do not need to be located within hospital premises, but it



is important to have the ready availability of an intensive care unit and other hospital facilities, as well as clear procedures in place for transferring patients from the Phase I unit to the hospital's intensive care unit.

It is very clear that a single site is preferred for dose escalation studies, and this is mainly to gather data on collective experience. It is acknowledged that for some types of combined healthy volunteer-patient studies it may be that multiple sites are needed, and therefore the protocol needs to include appropriate measures to reduce any extra risks, for example, including all investigators in dose escalating meetings, even though they many not have access to the patients in the study; it helps to give an overview of the data collected so far.

MHRA PHASE I ACCREDITATION SCHEME (EST. 2007)

The MHRA Phase I Accreditation Scheme [9] was established in 2007 after the 2006 TGN1412 incident, providing detailed, specific requirements for Phase I units undertaking higher-risk (i.e. first-in-human) clinical trials. The scheme was designed to give assurance that accredited units "not only met, but surpassed the basic regulatory GCP aspects by having additional 'best practice' procedures that encompassed the highest standards for avoiding harm to trial subjects and for handling medical emergencies should they arise".

This is a voluntary scheme, and once a unit has enrolled they are subject to routine MHRA inspections every two to three years, they require a highly robust Quality Management System, and specific criteria for FiH Principal Investigators and staff training.

FREQUENT FEEDBACK PROVIDED DURING PROTOCOL REVIEW

We still occasionally see draft healthy-volunteer FiH protocols from sponsors which include reference to a Maximum Tolerated Dose, however it is clearly stated in the revised guideline this is not acceptable as an objective for a Healthy Volunteer study. Sometimes we find that the justification for the starting dose / escalation scheme is missing from the protocol. While it is common for sentinel dosing to be included in Single Ascending Dose studies, sometimes sentinel dosing is not included for the Multiple Ascending Dose part of the study, and the absence of this needs to be scientifically justified. In our experience sentinel dosing is required for all SAD and MAD cohorts.

Another aspect which we find during protocol reviews is a lack of flexibility or adaptivity in the protocol. It is very easy to state what you are going to do, and not account for how to adapt or change if things do not go to plan.

Additionally, we also see a lack of suitable assessment or sampling windows, and a lack of review of PK data for dose-escalation decisions. Although they are only guidelines and not rules, at the early protocol stage it is important to justify any deviations if this is the case.

Dr SIMON HUTCHINGS:

SUMMARY

The revised guideline is a welcome update, but largely reflects what was already in place by many EU Competent Authorities. The guideline also provides some much-needed clarity on how integrated or adaptive protocols can and should be used effectively, and these can answer many of the early clinical development questions to allow go or no-go decisions.

It is a guideline, not a set of rules to be followed blindly. Good science and volunteer safety is paramount, and there is an emphasis on the use of emerging data throughout the duration of the study and using this data for informed decision making for subsequent cohorts and study parts.

In conclusion, integrated and adaptive FiH and early phase studies can accelerate early clinical development without compromising the safety and wellbeing of participants.

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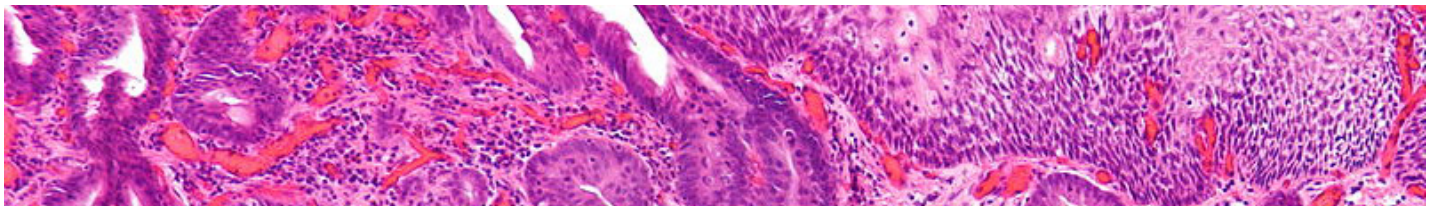

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