Medicines & Healthcare products Regulatory Agency

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Regulating Medicines and Medical Devices

The Impact of the Revised EU FIH Guidelines on Toxicity Assessment and Dose Escalation

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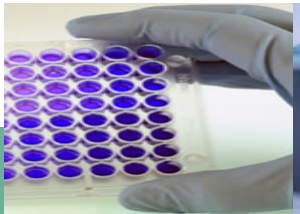

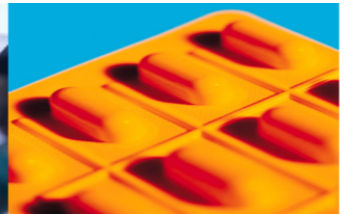


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European Council leaders have now endorsed an agreement on a 21-month transition period between March 2019, when the UK officially leaves the EU, and 31st December 2020.

The headline of the agreement, applying to the transition period, is that the UK will no longer be a Member State of the EU, but access to one another's markets will remain unchanged until at least the end of the implementation period.

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For the MHRA, there are some specific aspects of the proposed withdrawal agreement which will have an impact on how we work during the implementation period. These include:

MHRA will observe, but not actively participate in, EMA and EU committees and groups.

MHRA will not conduct assessments as a “leading authority” on behalf of the EU. The exact definition of what this applies to is still being negotiated between the UK and EU.

During the implementation period, the EU will accept UK batch release, legal establishment of Marketing Authorisation Holder (MAH) and other key roles in the UK.

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We will still be able to discuss issues with EU counterparts and share information as now.

Implications for Devices functions and the work of NIBSC are still being clarified.

The UK Government's position will continue to be in favour of collaborative working in the EU regulatory system, associate membership of the EMA, and to agree a comprehensive system of mutual recognition, where relevant.

We continue, as we have been doing, to plan for both potential outcomes – ongoing collaboration with the EU and preparing for standalone regulatory operations.


Every Day When I Wake Up
I Thank The Lord I'm Welsh

The Impact of the Revised EU FIH Guidelines on Toxicity Assessment and Dose Escalation in the UK

Absolutely nothing whatsoever!!

So why did we update the guideline?

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- First in Human integrated ("umbrella") protocol with sequential parts: **Single Ascending Dose, Food Effect, Multiple Ascending Dose, & Pharmacodynamic arm**
- ANSM authorization on June 26, 2015
- CPP (Ouest VI) approval on July 3, 2015
- Small molecule, **me-too drug**, inhibitor of Fatty Acid Amid Hydrolase (FAAH), **10th of the same class**
- **No safety issues with any drugs of the same class already administered in humans**, some discontinued in phase 2- 3 for lack of efficacy (e.g. PF-04457845).
- Did not belong to the definition for « **high risk compounds** » of EMA 2007 Guidance

The protocol stated:

Animal toxicology studies of repeated daily dosing of BIA 10-2474 for up to 13 weeks in mice, dogs and monkeys and up to 26 weeks in rats have been conducted.

Treatment with BIA 10-2474 produced no signs of toxicity in mice, rats, dogs and monkeys up to the no observed adverse effect level (NOAEL).

SUNDAY 10 JANUARY: D5 OF COHORT 50MG/DAY

- Mild transient **blurred vision** at 11:00am in one subject (S2508)
- **Mild headache** at 3:30pm (reported at 6:30pm)
- Worsening at 6:30pm with occurrence of **moderate headache, slurred speech (dysarthria), drunken feeling (cerebellar syndrome), floating specks and diplopia. Relationship to study drug always considered as possible**
- **The transfer to emergency was decided not due to life-threatening or severe condition but for obtaining a neurologist advice and other explorations including imaging to exclude another reason. Admitted at 8:50pm**
- **All subjects hospitalized in the same ward, and therefore aware of the transfer and its reason**
- After discussion with the Emergency physician, Biotrial physician declined that subject be sent back to Biotrial CPU during the night after evaluation was completed even if the clinical status remained stable
- Resident neurologist did not consider the clinical status of the subject justified MRI in emergency. Therefore **CT and angio scan done and considered as normal.** Treatment with low doses of aspirin and Tanganil was initiated. A MRI was planned for the next morning and subject expected to come back to Biotrial CPU after.
- Biotrial expected to be informed by the hospital if subject clinical status aggravated or abnormalities found in imaging (current legal rules when a physician sends a patient to the hospital)

MONDAY 11 JANUARY: D6 OF COHORT 50MG/DAY

- Biotrial administered the other volunteers their 6th dose the next morning at 8:00am, at 5-10min intervals as **no alarming information was provided by the hospital regarding the hospitalized subject (who was expected to come back in the Biotrial CPU within the morning), and the other participants of the cohort did not report similar CNS AE.**
- At **9 AM Biotrial called the Hospital emergency** and it was indicated that there was no news and that subject was undergoing the MRI
- At **10 AM the Hospital emergency** called Biotrial to inform that **MRI showed a massive stroke of the pons** (in this 49 year-old subject)
- At noon, after discussion with the resuscitation unit team, Biotrial was informed that the **stroke was really atypical**. The code was broken for this subject
- **Decision to stop dosing for all subjects taken: study terminated. Information shared by Biotrial with all participants**
- Further worsening of this subject's symptoms during the day (coma).
- A posteriori, Biotrial was informed that the subject clinical status remained stable the whole night and started to become slightly confused and agitated 15 min before the initiation of dosing of the remaining subjects

WITHIN THE 50 MG DOSE COHORT

- From **Day 5** gradual neurological symptoms in one subject (S2508) resulting in his hospitalization (first SAE), followed by rapid progression of symptoms severity **on Day 6** leading **to brain death** on Day 9
- On **Day 7,** 1 subject (S2501) complained of an **amnesia** explored by MRI in the evening (minimal abnormality in hippocampus) and sent back to Biotrial CPU by the hospital team
- **On Day 8, 2 additional subjects became symptomatic:** S2507 **(slurred speech, cerebellar syndrome, headache, blurred vision)** and S2505 (**headache and weakness of right hemibody**) and admitted to the hospital as well as S2501 (whose amnesia persisted).
- **On Day 8, MRI done for all active subjects of the cohort: 4 subjects with and 2 subjects without MRI abnormalities**
- **On Day 9, 1 asymptomatic subject** (S2503 **had in fact microbleeding in MRI done on Day 8)** was admitted and became symptomatic later when in hospital
- **On Day 10, 1 asymptomatic subject** (S2502**, MRI normal**) was admitted and remained asymptomatic.

- In 4 volunteers, MRI done 24 to 60 hours after last dosing showed **abnormalities of highly variable intensity, affecting the hippocampus and pons.** In 1 subject, MRI (performed 60 h after dosing) revealed only **minor punctiform** hypersignal of **right hippocampal body** no longer seen 2-4 days later.. In 1 subject no MRI abnormalities found.
- Abnormalities were identical in hippocampus and pons in 4 volunteers, and **expanded in thalamus and cerebral cortex in the most severely affected volunteer, suggestive of cortical damage**.
- MRI characterized by:
  - → Hyperintense lesions on diffusion weighted images indicating **possible cytotoxic oedema and/or inflammatory cell infiltration**
  - → Hyposignal on Susceptibility Weighted Imaging (SWI), suggesting the presence of hemoglobin, reflecting **microbleeds**.
  - → Pathologic hypersignal on FLAIR (Fluid Attenuated Inversion Recovery) possibly related to an **increase in water content, demyelination, gliosis or necrosis**.
  - → In the most severely affected volunteer, diffused hypersignal increased **in posterior part of brain stem**, suggesting **vasogenic edema**.

The tragedy is still under investigation in France and, as such, the Investigator's Brochure and primary reports have not been released for review. However, the results were discussed at the ACT meeting in Palm Springs last year.

The protocol is available to down-load. It is apparent, from this document, that the pharmacology package was very sparse.

There is also no information as to how NOAELs were calculated.

MAKE SURE YOU KNOW WHAT IS AND WHAT ISN'T A NO OBSERVED ADVERSE EFFECT LEVEL (NOAEL) !

The EMA co-ordinated two reviews, one nonclinical and one clinical into the incident.

The EU nonclinical experts had access to the IB and the primary reports.

Following the review, it was decided to revise the 2007 Risk Mitigation guideline.

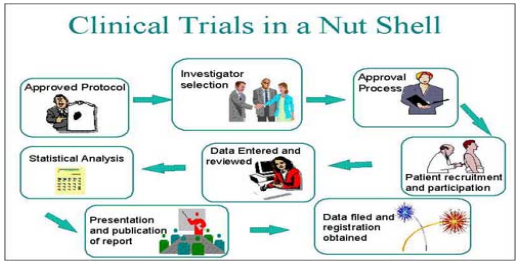
20 July 2017
EMEA/CHMP/SWP/28367/07 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products

Adopted by CHMP for release for consultation	10 November 2016
Start of public consultation	15 November 2016
End of consultation (deadline for comments)	28 February 2017
Adopted by CHMP	20 July 2017
Date of coming into effect	01 February 2018

Keywords	First-in-human, phase I, early clinical trials, investigational medicinal product, risk mitigation, integrated protocols, multiple ascending dose, dose escalation.

The new revision concerns the extension of the existing EU guidance to address FIH and early phase CTs with integrated protocols, and recommendations regarding the non-clinical and emerging clinical PK, PD and safety data to support them.



The emphasis on the revision is that the overall study design should be scientifically justified and careful consideration should be given to the inclusion of each study part considering the data each will provide and the time available for integrated assessment.

Safety should not be compromised in the interests of speed of acquiring data or for logistical reasons.

The revision of the guideline **has not called for an increase in the amount of nonclinical data** required to support FIH trials.

HOWEVER, THE GUIDELINE HAS AGAIN EMPHASISED THE CRITICAL VALUE OF PHARMACOLOGY AND THE MODE OF ACTION OF AN IMP.

When planning FIH/early CTs, sponsors and investigators should identify the potential factors of risk and apply appropriate risk mitigation strategies.

Industry, particularly in the USA, has expressed a fear that the requirement for them to justify their decisions may lead to more conservative decisions regarding program design and overly precautionary programmes and delays, in an effort to avoid regulatory risk. They claim that there is also a concern for the potential impact on Phase I designs and timelines, with potential impacts of diverting early CTs from Europe.

The UK saw a 50% INCREASE in Phase I, FIH trials in the second half of 2017, which has continued over the first 6 months of 2018.

Paracelsus, the Swiss Renaissance physician, wrote

“All things are poison, and nothing is without poison, only the dose permits something not to be poisonous”.

From this, we have the Toxicologist’s creed

“It’s the dose that counts!”

Careful dosing selection of an IMP is a vital element to safeguard the subjects participating in FIH and early CTs.

The section on “Estimation of the First Dose in Human” was less than one page long in the 2007 version.

In the revised guideline, “Dosing Selection for FIH and Early Clinical Trials” is almost 4 pages long!!

However, not surprisingly as author of this section, this represents the methods MHRA has long followed!

The planned dosing selection should also take into account a reasonably rapid attainment of the trial objectives without exposing excessive numbers of subjects.

The starting dose and a maximum exposure, as well as dose escalation steps during the CT, should be justified and outlined in the protocol.

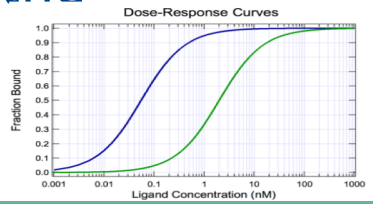
Decision-making criteria for adapting the planned dose escalation steps based on emerging clinical data should also be described in detail.

- Exposures at NOAEL in most relevant species used to estimate equivalent exposure for humans
  - State-of-art modelling (*e.g.* PK/PD and PBPK); allometric factors.
- Exposure at PD effects in relevant PD studies
  - MABEL (Minimal anticipated biological effect level); PAD (pharmacologically active dose); ATD (anticipated therapeutic dose) range in humans
- The novelty of the active substance, pharmacodynamic characteristics, the relevance of the animal models, uncertainties related to the estimation of the MABEL, PAD and the expected exposure in humans.

The starting dose for healthy volunteers should be a dose expected to result in an exposure lower than the PAD, unless a robust justification can be made for a higher dose.

Depending on the level of uncertainty regarding the human relevance of findings observed in nonclinical studies and the knowledge of the intended target, the starting dose should either be related to the MABEL, PAD or NOAEL.

A justification for the starting dose should be included in the protocol and may be included in the IB.



Similar considerations also apply for the identification of a safe starting dose in patients.

The goal of selecting the starting dose for FIH/early CTs in patients, *i.e*. where there are no previous data in healthy volunteers, is to identify a dose that is expected to have a minimal pharmacological effect and is safe to use.

The starting dose should also take into account the nature of disease under investigation and its severity in the patient population included in the CT. In some instances, a starting dose that is substantially lower than the human expected therapeutic dose may not be appropriate.

Criteria for dose increases during a CT should be outlined in the protocol.

The maximum fold increase in dose/exposure from one cohort to the next, as well as a maximum number of cohorts to be evaluated, should be stated.

The dose increment between two dose levels should be guided by the dose/exposure-toxicity or the dose/exposure-effect relationship defined in the non-clinical studies and adapted following review of emerging clinical data from previous cohorts.

The size of the dose increments should take into account the steepness of the dose/exposure-toxicity or dose/exposure-effect curves and uncertainties in the estimation of these relationships.

Furthermore, if there is evidence of non-linear PK potentially resulting in a supra-proportional increases in exposure, smaller dose increments, particularly in the later parts of SAD/MAD, should be considered.

If emerging clinical data reveal substantial differences from non-clinical or modelling and simulation data, adjustment of the planned dose levels may be warranted.

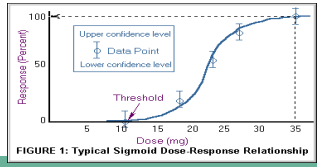
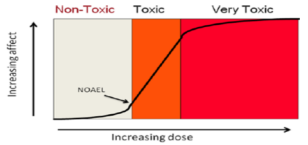


FIGURE 1: Typical Sigmoid Dose-Response Relationship

An expected maximum exposure level, which should not be exceeded in the study without approval of a substantial amendment, should be pre-defined in the protocol for each study part.

This is usually based on the NOAEL in the most relevant nonclinical species.

The maximum exposure should be justified based on all available data, including PD, PK, findings in toxicity studies and exposure at the expected therapeutic dose range.



In general, the maximum exposure of healthy volunteers should be within the estimated human pharmacodynamic dose range.

However, exposure levels exceeding the pharmacodynamic dose range can, if scientifically justified and considered acceptable from a safety perspective, be carefully explored, taking into consideration uncertainties/risk factors.

For trials or trial parts that include patients, the maximum tolerated dose (MTD), if applicable, should be clearly defined and not be exceeded once it has been determined.

Moving from Single to Multiple Dosing

The selection of an appropriate dosing interval and duration of dosing for all multiple dosing cohorts and study parts should take into account the specific PK and PD characteristics of the IMP, the available non-clinical safety data, and all data from subjects in previous single dose cohorts.

Particular attention should be paid to linear *versus* non-linear PK in the expected concentration range, the PK half-life *versus* duration of action, and the potential for accumulation.

Multiple dosing parts can explore different dosing regimens and schedules, such as a move from once daily dosing to twice daily dosing.

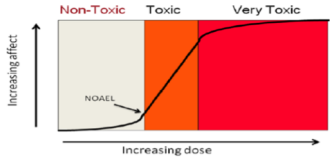
A maximum duration of dosing should be stated in the protocol for every cohort. The expected exposure after multiple dosing should have been covered during preceding SAD parts/trials.

If, however, emerging clinical data following multiple dosing suggests tolerance to adverse effects seen in a SAD part of a study, higher exposures in a MAD part can be considered, provided this option is pre-specified and below the set maximum exposure, or by a substantial amendment to the protocol.

Sadly, even today, there appears to be a perception that effects related to primary pharmacology should not be considered adverse.

As long as this belief persists, there will always be the potential for another tragedy, particularly as qualitative and quantitative differences may exist in biological responses to a new IMP in animals compared to humans.

The authors of the BIAL IB concentrated on trying to establish NOAELs.



It is my personal opinion, that we must move away from fixating on NOAELs and NOELs and, instead, concentrate on what the data are telling us, *i.e.* a weight of evidence approach.

Fixating on a “safe dose” and applying “safety factors” is the refuge of someone who does not know how to progress from nonclinical to clinical studies.

It is essential that pharmaceutical development moves away from an almost rigid tick box mentality of conforming to regulatory guidelines.

It is also essential that Regulators do not try to hide behind prescriptive guidelines.

Animal studies need to be carefully designed to provide the most useful data to decide whether it is safe to progress to humans.

FIH clinical trial protocols should have sensible starting doses, dose escalation steps and dose exposure caps. Inclusion and exclusion criteria and dose stopping criteria also have to reflect nonclinical data.

A rigid adherence to science rather than regulatory guidelines is the only way to avoid future AVOIDABLE tragedies.

Problem Areas and How to Resolve Them

Scientific Advice!!

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Risk comes from not knowing what you're doing!

Warren Buffett

The MHRA has, for many years, provided scientific and regulatory advice to sponsors.

Scientific advice can be requested during any stage of the initial development of the medicinal product (before submission of a marketing authorisation application), and also during the pre-submission period for a variation to an existing marketing authorisation.

Meetings can also be held with the MHRA to discuss pharmacovigilance, advertising, proposal changes to labelling or package leaflets or post-authorisations regulatory advice relating to a product range.

The MHRA prefers to meet face-to-face with companies but in exceptional circumstances, video-conferencing may be arranged.

Telephone and tele-conference meetings are generally not considered satisfactory to discuss complex scientific and regulatory issues.

The MHRA Licensing Division held about 420 Scientific Advice meetings with Companies in 2017.

The MHRA Clinical Trials Unit has held over 120 meetings with companies, academic institutes or hospital groups over the last 12 months!

The CTU's email helpline fields about 250 queries a month.

Scientific advice can also be obtained from the CHMP.

The Scientific Advice Working Party (SAWP) has been established as a standing working party with the sole remit of providing Scientific Advice and Protocol Assistance to applicants.

It is the SAWP/CHMP responsibility to give Scientific Advice to industry by answering to questions based on the documentation provided by the company in the light of the current scientific knowledge.


AND THAT'S MY LAST SLIDE. ANY COMMENTS?
YOU STOLE AN HOUR OF MY LIFE. SOMETHING INSIDE ME DIED. I WILL NEVER HAVE ANOTHER GOOD DAY.
ZZZZ
I WENT IN WITH LOW EX— PECTA— TIONS.
AVOIDS THE DELUSION THEY WANT TO LISTEN TO YOU!
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Any Further Questions ?

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