SIMBEC-ORION

About Simbec-Orion

- Full- service international Contract Research Organisation
- Headquartered in the UK with more than 450 employees across Europe and North America
- Early stage clinical development, FiH, HV & patient studies from our purpose built MHRA-accredited facility
- Late stage trials conducted in collaboration with sites across Europe, North America & beyond
- Particular expertise in oncology & rare disease programs
- Predominantly supporting small to mid-size pharma & biotech companies, both in Europe & North America, with a comprehensive portfolio of services including central laboratories, IMP Management, Pharmacovigilance & Regulatory Support

SIMBEC-ORION

Introducing your moderator & presenter

Dr Danielle Webb has over 10 years of experience in clinical research, having joined Simbec-Orion in 2013.

Danielle has a PhD from the Welsh School of Pharmacy and has previous non-clinical experience in pulmonary pharmacology and pharmacokinetic modelling. Danielle also holds a Certificate in Human Pharmacology from the Faculty of Pharmaceutical Medicine (Royal College of Physicians).

Danielle has practical experience and scientific knowledge of the design, management, analysis and reporting of clinical development projects with an emphasis on first-in-human pharmacology, and phase I pharmacology and PK studies.

David Jones is a European Registered Toxicologist and a Fellow of the British Toxicology Society as well as a Chartered Biologist and a Fellow of the Royal Society of Biology.

David has previously worked with the MHRA as an Expert Nonclinical Assessor responsible for assessing non-clinical data for Clinical Trial Authorisation Applications and chaired over 100 scientific advice meetings every year.

David joins the Scientific Advisory Board at Simbec-Orion as our Pharmaco-toxicology Expert.

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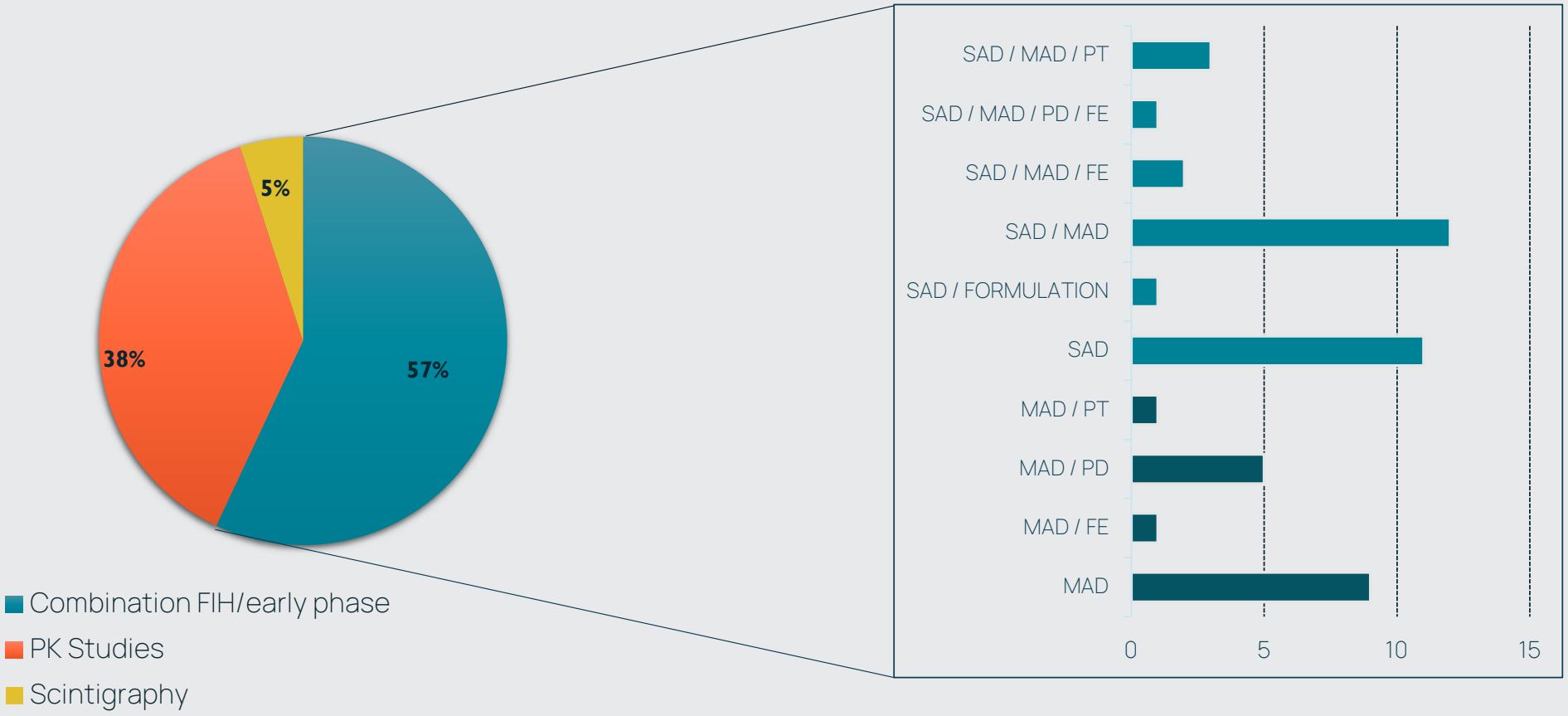
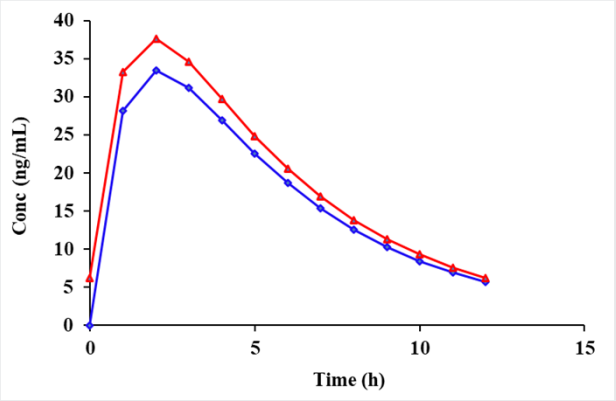
Early Phase Clinical Trials

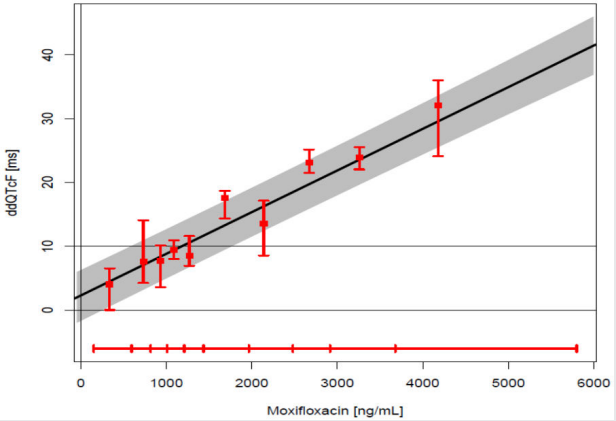
Simbec Orion Clinical Pharmacology Unit:
Recent Study Experience (prev. 10 years)



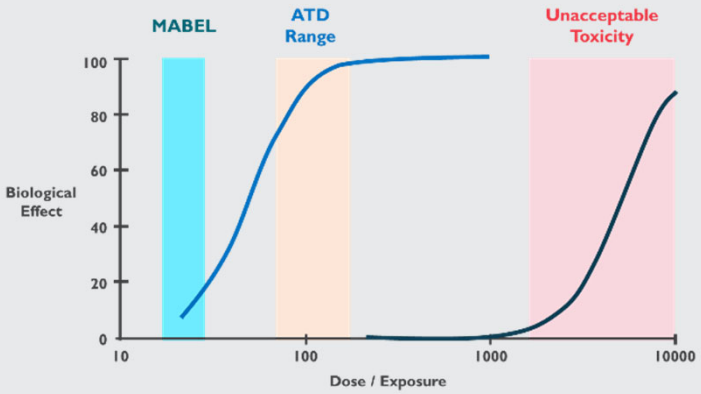
FIH & Early Phase Studies - Objectives

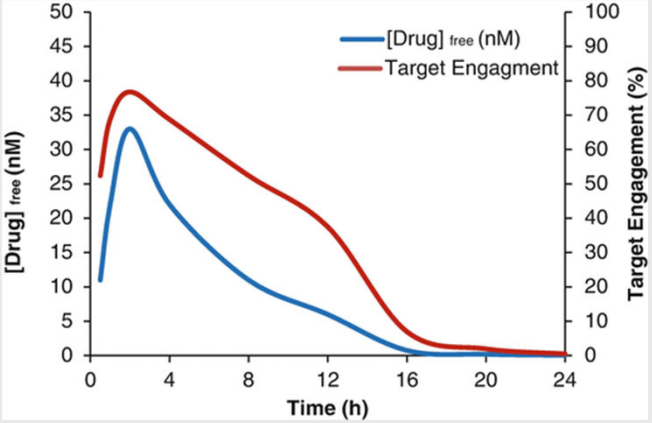
- Single Ascending Dose
- Multiple Ascending Dose
- Food-Effect
- Formulation Effect
- Drug-Drug Interaction
- Gender Effect
- Cardiac Safety
- Target Engagement
- Proof of Concept





Conc [ng/mL]





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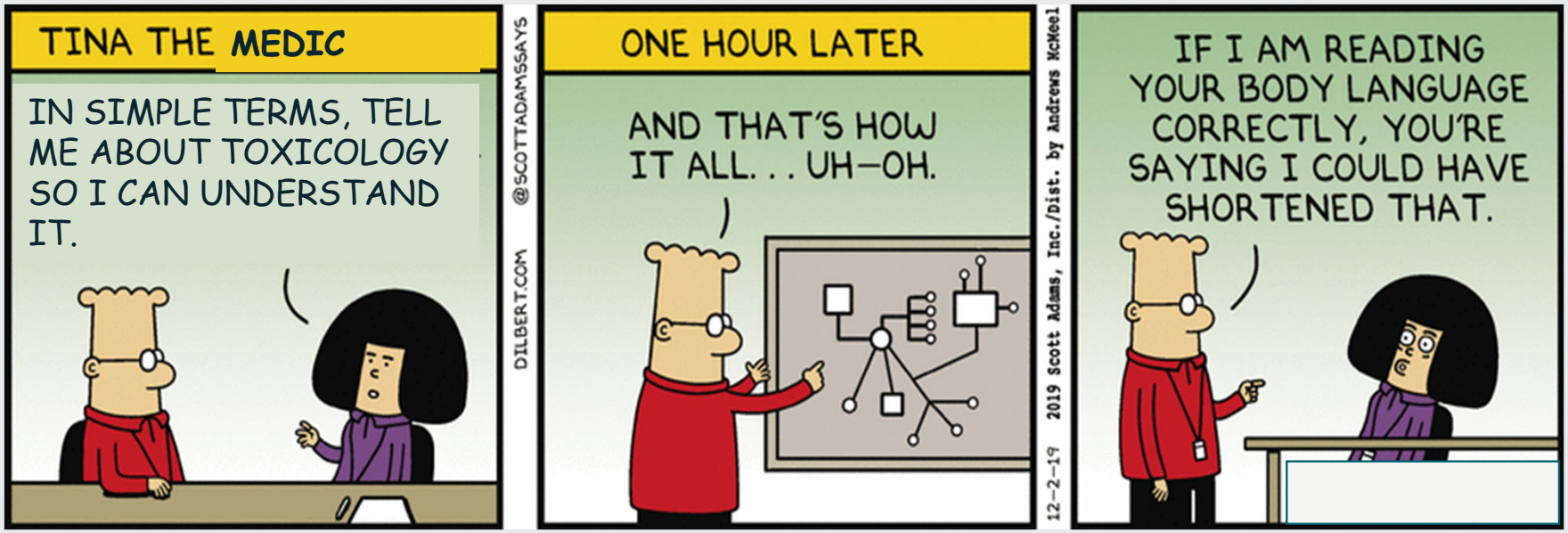
Nonclinical Considerations for Early Phase Clinical Trials

David R Jones, ERT, FBTS, FRSB
(davidrjones@hotmail.co.uk)
Independent Consultant PharmacoToxicologist


TINA THE MEDIC
IN SIMPLE TERMS, TELL ME ABOUT TOXICOLOGY SO I CAN UNDERSTAND IT.
DILBERT.COM @SCOTTADAMSSAYS
ONE HOUR LATER
AND THAT'S HOW IT ALL. . . UH-OH.
12-2-19 2019 Scott Adams, Inc./Dist. by Andrews McMeel
IF I AM READING YOUR BODY LANGUAGE CORRECTLY, YOU'RE SAYING I COULD HAVE SHORTENED THAT.


LEARNING
IS
FUN

What worries regulators?

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The Drug Regulator's Tightrope Walk

Protect public health …

… against negative consequences from unsafe or ineffective medicines.

… against negative consequences from failing to meet unmet medical needs.

When in doubt, be negative, "we need more information"

When in doubt, be positive, "it might be a patient's only hope"

Worry about false-positive decisions "Type-1 error"

Worry about false-negative decisions "Type-2 error"

Are the (dis-)incentives balanced right to influence regulators' behaviour?

no penalty for being negative!

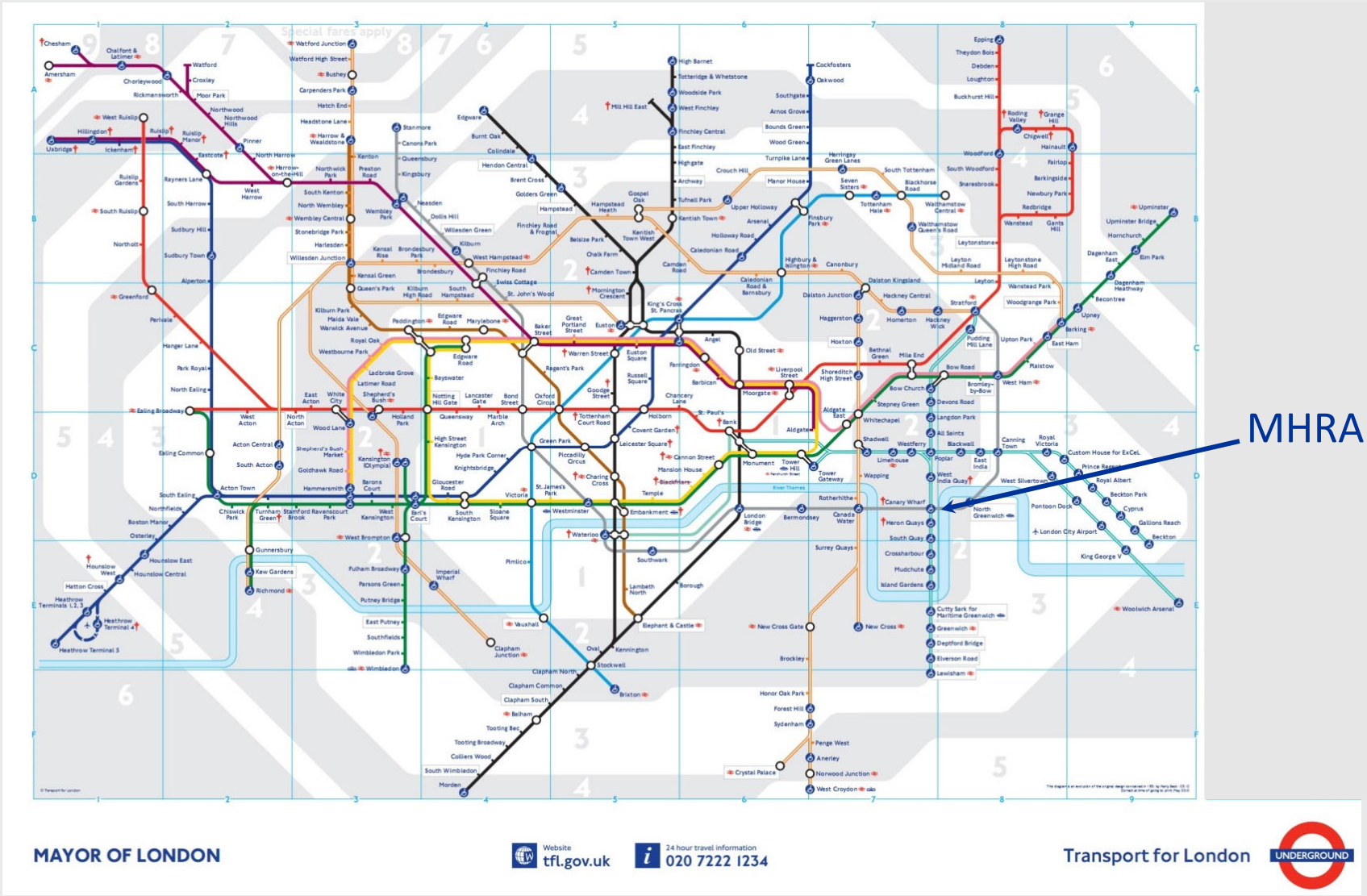
What are the consequences?

What are the consequences?

Enough of their problems….

Let’s turn to yours ☺

Regulatory Guidelines


MHRA
MAYOR OF LONDON
Website
tfl.gov.uk
24 hour travel information
020 7222 1234
Transport for London
UNDERGROUND


MHRA

Regulatory guidelines are like the modern map of the London Underground.

They don't completely represent the "real" world.

There's almost always more than one way to reach an objective and the recommended route might not be the one you should follow!

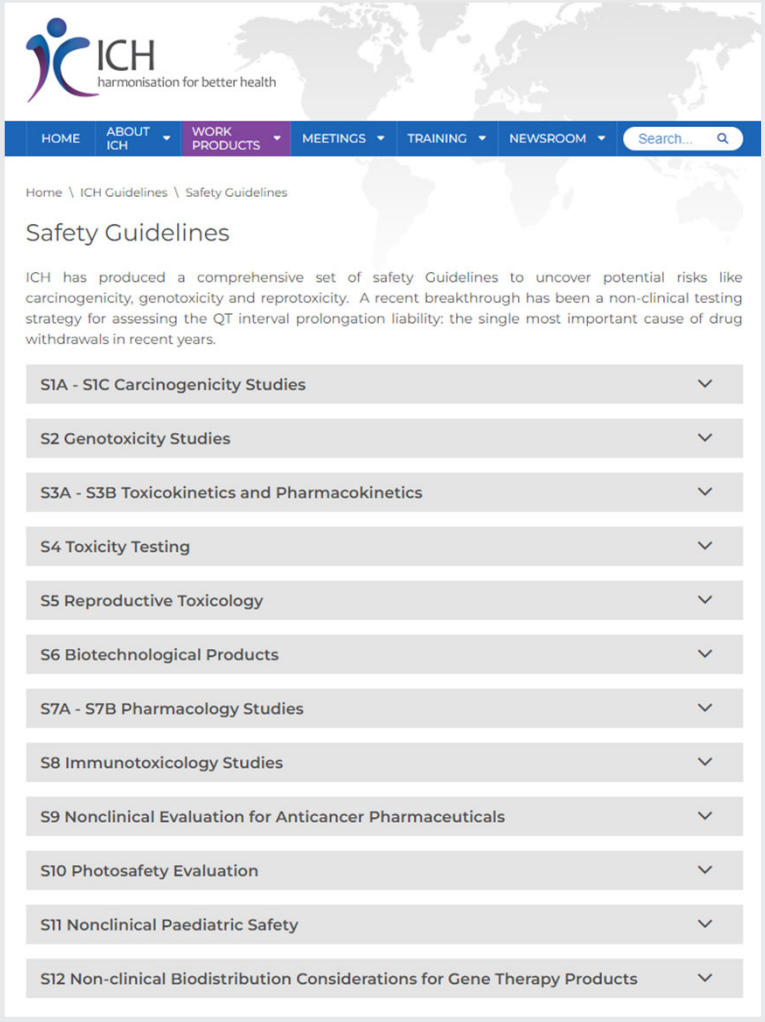
Samuel Johnson said “Patriotism is the last refuge of the scoundrel.”

I say “Rigorously following Regulatory Guidelines is the last refuge of those who don’t know how to develop medicines!!.”

I BELIEVE THAT YOU SHOULD NEVER FOLLOW A REGULATORY GUIDELINE IF THERE IS A GOOD SCIENTIFIC RATIONALE NOT TO!!!

In an ideal world, every Regulatory Guideline should simply say….

Important Non-Clinical Guidelines (www.ICH.org)



Not forgetting:

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

GUIDANCE ON NONCLINICAL SAFETY STUDIES FOR THE CONDUCT OF HUMAN CLINICAL TRIALS AND MARKETING AUTHORIZATION FOR PHARMACEUTICALS

M3(R2)

Current *Step 4* version

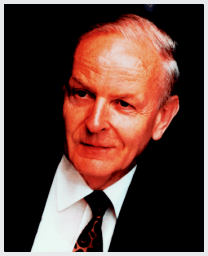
dated 11 June 2009

What's the point of nonclinical studies?

The goals of the nonclinical safety evaluation generally include a characterisation of toxic effects with respect to target organs, dose dependence, relationship to exposure, and, when appropriate, potential reversibility.

BUT the main goal is to determine whether or not it is acceptably safe to test the drug in humans.

Regulatory decisions are made based on safety considerations (Benefit *versus* Risk)



Gerhard Zbinden (a toxicologist even older than me!!) once said:

Don’t do something just because you can.

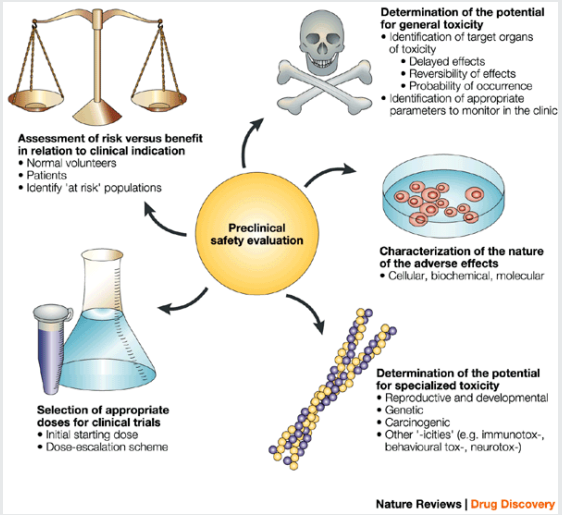
Don’t do something just because that’s the way you’ve always done it.

Don’t do something because others do it.

Don’t do something just because you think you’re expected to.

Don’t do something to generate results you can’t interpret.

The nonclinical safety evaluation, although usually limited at the beginning of clinical development, should be adequate to characterise potential adverse effects that might occur under the conditions of the clinical trial to be supported.



The appropriate non-clinical studies are the basis of extrapolation to indicate possible risks to humans.

These studies are a means to an end, not an end in themselves

Think ahead : The value of a toxicology study is only as good as its design.

The main thing is to make sure that the main thing really is the main thing.

The more the focus is on things that are not the main thing, the bigger the risk that the real main thing gets neglected, until something bad happens

nature

Published: 22 December 2016

Fatal French clinical trial failed to check data before raising drug dose

James Randerson

Nature (2016) | Cite this article

1143 Accesses | **3** Citations | **200** Altmetric | Metrics

Revelation from drug firm Bial prompts criticism from pharmacologists.

June 2009
CPMP/ICH/286/95

ICH Topic M 3 (R2)
Non-Clinical Safety Studies for the Conduct of
Human Clinical Trials and Marketing Authorization for Pharmaceuticals

Step 4

NOTE FOR GUIDANCE ON NON-CLINICAL SAFETY STUDIES FOR THE CONDUCT OF HUMAN CLINICAL TRIALS AND MARKETING AUTHORIZATION FOR PHARMACEUTICALS

(CPMP/ICH/286/95)

TRANSMISSION TO CHMP	July 2008
TRANSMISSION TO INTERESTED PARTIES	July 2008
DEADLINE FOR COMMENTS	October 2008
APPROVAL BY CHMP	June 2009
DATE FOR COMING INTO OPERATION	December 2009

This document applies to the situations usually encountered during the development of pharmaceuticals and should be viewed as general guidance for drug development.

Nonclinical safety studies and human clinical trials should be planned and designed to represent an approach that is scientifically and ethically appropriate.

For biotechnology-derived products, appropriate nonclinical safety studies should be determined in accordance with ICH S6.

For anti-cancer drugs appropriate nonclinical safety studies should be determined in accordance with ICH S9.

For these products, ICH M3(R2) only provides guidance with regard to timing of nonclinical studies relative to clinical development.

In principle, the duration of the animal toxicity studies conducted in two mammalian species (one non-rodent) should be equal to or exceed the duration of the human clinical trials up to the maximum recommended duration of the repeated-dose toxicity studies.

However, the NC3Rs have examined opportunities for use of one species for longer-term toxicology testing during drug development[1].

A number of products developed for COVID-19 only used a single species.

1 - https://www.sciencedirect.com/science/article/pii/S0273230020300507

The data generated from nonclinical studies are important, particularly to the design of the early stage clinical trials with respect to selecting the starting clinical dose level, dose escalation plan, dosing regimen, and route of administration.

The nonclinical data may help guide patient eligibility criteria and will often determine some important safety monitoring procedures.

BUT Nonclinical Does Not Necessarily Mean Animal.

Science based, non-animal approaches in drug development are not just possible, but are recommended in many cases.

The ICH S11 guideline (Nonclinical Safety Testing in Support of Development of Paediatric Pharmaceuticals) states:

"An understanding of the overall clinical development plan is needed to design an appropriate, efficient nonclinical plan. A weight of evidence (WoE) based decision should be made to determine whether additional nonclinical investigations are warranted."

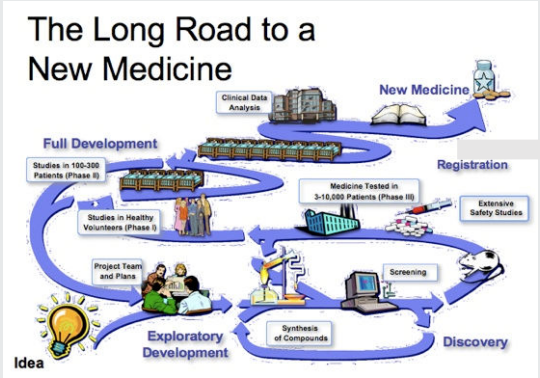
This is also true in all cases!!

Clinical Trials

The development of a pharmaceutical is a stepwise process involving an evaluation of both animal and human efficacy and safety information.

As a general matter, nonclinical studies are a necessary part of drug development for both rare and common diseases.

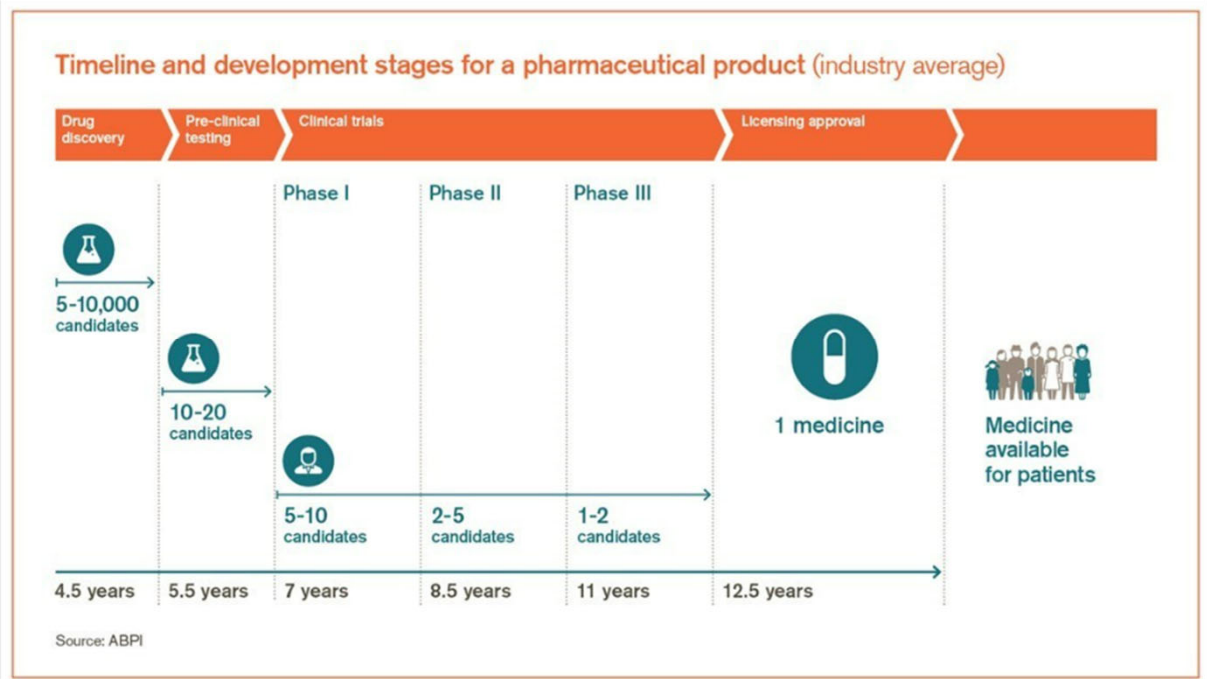
Nonclinical studies can contribute to a better understanding of the drug's mechanism of action.



It can be a slow and very expensive process!

Clinical Trials represent on average approximately 60% of a product total development costs.

In 2019, the average cost to bring a drug to the market was £2.09 billion.



Note that the UK will NOT be part of the EU Clinical Trials Regulation (CTR).

The UK Medicines and Medical Device (MMD) Act 2021 to confer power to amend or supplement the law relating to human medicines, veterinary medicines and medical devices; make provision about the enforcement of regulations, and the protection of health and safety, in relation to medical devices; and for connected purposes has received Royal Assent.

MAAs have the nonclinical overview, written summaries, tabular summaries and all the primary reports.

CTA applications have Investigator's Brochures and/or IMPDs.

CTA applications are not supported by primary reports in the UK and EU – Regulators are supposed to trust you not to tell them fibs!

MAKE SURE YOU KNOW WHAT YOUR DATA ARE TELLING YOU AND DON'T CONCENTRATE ON IDENTIFYING A NO OBSERVED ADVERSE EFFECT LEVEL (NOAEL) !

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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.

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Send a question via our website www.ema.europa.eu/contact

Decisions are made based on safety considerations (Benefit *vs.* Risk)

'*Do the data supplied support the use of this product, administered in this way, in the proposed dose for the proposed duration, to this 'type' of participant?'*

There is risk associated with all trials

The degree of acceptable risk depends on a number of factors including potential benefit.

SIMBEC-ORION

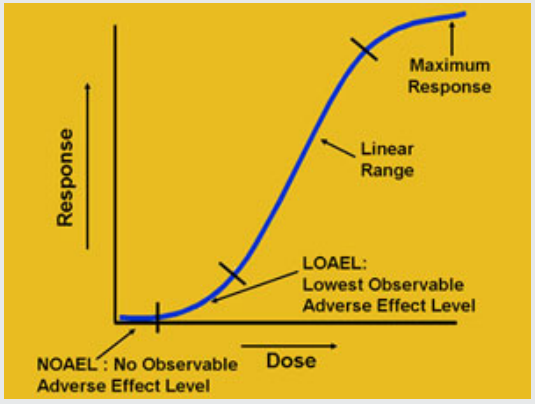
Starting Doses in First in Human Trials

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

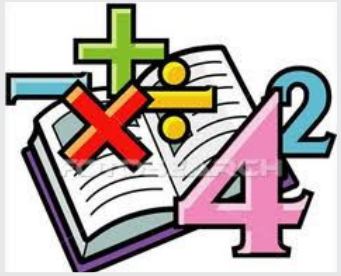
"It's the dose that counts!"



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

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

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



All available non-clinical information (PD, PK, TK and toxicological profiles, dose or exposure/effect relationships, *etc.*) should be taken into consideration for the calculation of the starting dose, dose escalation steps and the maximum dose.

Furthermore, clinical data (*e.g.*, PK, PD and reports of adverse events) emerging during the trial from previous dosed cohorts/individuals need to be taken into account, in line with pre-specified decision criteria.

Experience, both non-clinical and clinical, with molecules having a similar mode of action can also be useful.

Generally speaking, the no observed adverse effect level (NOAEL) should be determined in the non-clinical safety studies performed.

The NOAEL is a generally accepted benchmark for safety, but is actually outdated and very conservative, and can serve as the starting point for determining a reasonably safe starting dose.

The exposures achieved at the NOAEL in the most relevant (NOT MOST SENSITIVE) animal species used should be used for estimation of an equivalent exposure for humans.

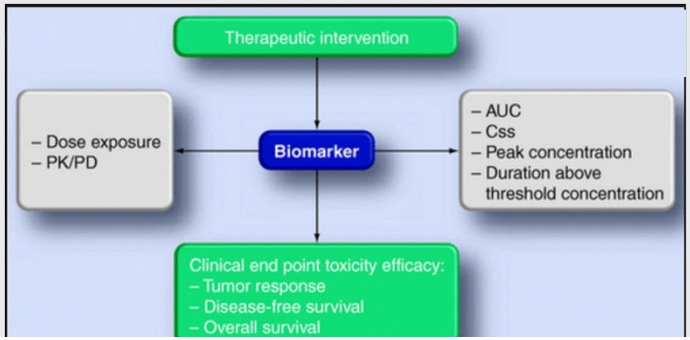
Estimation should be based on state-of-the-art modelling (*e.g.* PK/PD and PBPK) and/or using allometric factors.

Exposure showing PD effects in the non-clinical pharmacology studies, including *ex vivo* and *in vitro* studies in human tissues if feasible, should also be determined.

These data should be used to determine an estimation of the pharmacologically active dose (PAD) and/or anticipated therapeutic dose range (ATD) in humans.

Some sponsors also calculate the minimal anticipated biological effect level (MABEL) in humans.

When using these approaches, potential differences in sensitivity for the mode of action of the IMP between humans and animals need to be taken into consideration.

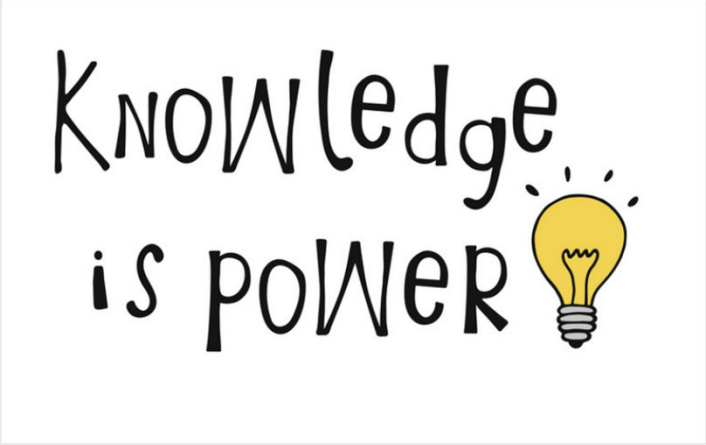


In addition, the calculation of the PAD, ATD and MABEL should consider target binding and receptor occupancy studies *in vitro* in target cells from human and the relevant animal species and exposures at pharmacological doses in the relevant animal species.

The starting dose for healthy volunteers should be a dose expected to result in an exposure lower than the PAD, unless a robust scientific rationale can be provided 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 PAD, NOAEL or MABEL.

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



In order to further limit the potential for adverse reactions in humans, safety factors are generally applied in the calculation of the starting dose in humans.

Safety factors should take into account potential risks related to:

- The novelty of the active substance;
- Its pharmacodynamic characteristics, including irreversible or long lasting findings and the shape of the dose-response curve;
- The relevance of the animal models used for safety testing;
- The characteristics of the safety findings;
- Uncertainties related to the estimation of the MABEL, PAD and the expected exposure in humans.

Furthermore, findings in the non-clinical studies and how well potential target organ effects can be monitored in the CT should also be addressed and may influence the safety factors used.

The reasoning behind the safety factors used should be detailed in the IB and protocol.

Starting Dose for patients

Similar considerations as outlined for healthy volunteers 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 many instances, a starting dose for patients that is substantially lower than the human expected pharmacological dose may not be appropriate.

In all cases, a rationale should be provided, and the subjects included in the CT should be informed.

If potential differences in target distribution, PK or safety profile of the IMP between HV and patients can be foreseen, consideration should be given to reverting to a SAD design (with dose escalation as appropriate) in the first patient cohort or starting t a dose that is lower than that identified as “safe” in HV.

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 (except for oncology products).

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

Target saturation should be taken into account when appropriate, then the maximum exposure should consider when complete inhibition or activation of the target is achieved, and no further therapeutic effect is to be expected by increasing the dose.

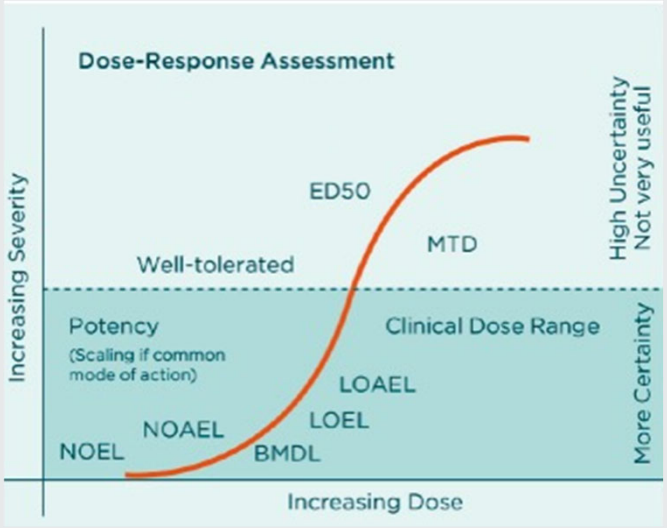
In general, the maximum exposure of healthy volunteers should be within the estimated human pharmacodynamic dose range.

Exposure levels exceeding the pharmacodynamic dose range can, if scientifically justified and considered acceptable from a safety perspective, be carefully explored.

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.

The potential therapeutic/clinically relevant dose (exposure) and the expected benefit/risk balance should always be considered when defining the dose range.

A trial design using a MTD approach is considered to be inappropriate for healthy volunteers.



Contraception Requirements

For women of childbearing potential (WOCBP) there is a high level of concern for the unintentional exposure of an embryo or fetus before information is available concerning the potential benefits *versus* potential risks.

The recommendations on timing of reproduction toxicity studies to support the inclusion of WOCBP in clinical trials are similar BUT NOT IDENTICAL in all ICH regions.

WOCBP can be included in early clinical trials without non-clinical developmental toxicity studies.

One circumstance could be intensive control of pregnancy risk over short duration (*e.g.*, 2 weeks) clinical trials.

Another circumstance could be where there is a predominance of the disease in women and the objectives of the clinical trial cannot be effectively met without inclusion of WOCBP and there are sufficient precautions to prevent pregnancy.

Where precautions to prevent pregnancy in clinical trials are used, inclusion of WOCBP (up to 150) receiving investigational treatment for a relatively short duration (up to 3 months) can occur before conduct of definitive reproduction toxicity testing in the UK and some EU member states and in the USA.

All female reproduction toxicity studies and the standard battery of genotoxicity tests should be completed before inclusion, in any clinical trial, of WOCBP not using highly effective birth control or whose pregnancy status is unknown.

Clinical Trial Facilitation Group
CTFG

Recommendations related to contraception and pregnancy testing in clinical trials

https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

London, 23 March 2006
EMEA/CHMP/203927/2005

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE

(CHMP)

GUIDELINE ON RISK ASSESSMENT OF MEDICINAL PRODUCTS ON HUMAN REPRODUCTION AND LACTATION: FROM DATA TO LABELLING

DRAFT AGREED BY MULTIDISCIPLINARY EXPERT GROUP	June 2005
DRAFT AGREED BY THE SAFETY WORKING PARTY/EFFICACY WORKING PARTY/ PHARMACO-VIGILANCE WORKING PARTY	November 2005
DISCUSSION AT THE HERBAL COMMITTEE FOR MEDICINAL PRODUCTS (HMPC) MEETING	March 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	March 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 September 2006

Clinical Trials: Original Research

DIA DEVELOP INNOVATE ADVANCE

Therapeutic Innovation & Regulatory Science
2016, Vol. 50(2) 155-168

DOI: 10.1177/2168479015608415
tirs.sagepub.com

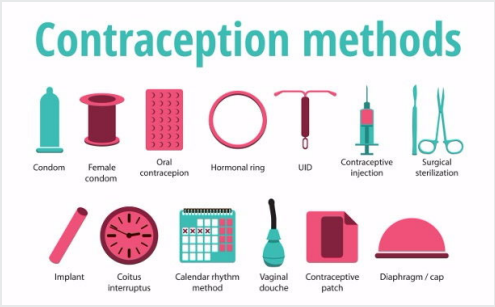
Birth Control in Clinical Trials: Industry Survey of Current Use Practices, Governance, and Monitoring

J. Stewart, PhD[1], W. J. Breslin, PhD[2], B. K. Beyer, PhD[3], K. Chadwick, PhD[4], L. De Schaepdrijver, PhD[5], M. Desai, MPH, MD[6], B. Enright, PhD[6], W. Foster, PhD[7], J. Y. Hui, PhD[8], G. J. Moffat, PhD[9], B. Tornesi, DVM, MS[6], K. Van Malderen, MSc[10], L. Wiesner, PhD[11], and C. L. Chen, PhD, MPH[12]

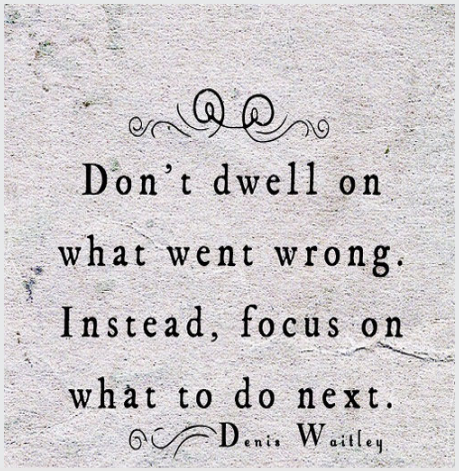
The guidance provides clear recommendations but does not rule out case-by-case deviations from the core recommendations where the sponsor can provide specific justification.

Information on the risks with exposure to the active substance before and during pregnancy and during lactation should be provided in the IB as well as recommendations on contraception and the management of risk in the clinical protocol.

The risk assessment is based on the results of non-clinical and any available clinical data.



Problem Areas and How to Resolve Them



Scientific Advice!!

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.

That's not what I expected when I asked for advice !

The MHRA used to prefer to meet face-to-face with companies but video-conferencing could be arranged.

Telephone and tele-conference meetings are now considered satisfactory to discuss complex scientific and regulatory issues and have been used exclusively over the last 24 months.

Pragmatic:

"dealing with things sensibly and realistically in a way that is based on practical rather than theoretical considerations"

The MHRA approach is actually simpler:

Adherence to sound science is more important than adherence to regulatory guidelines.

MHRA Clinical Trial Helpline

- 020 3080 6456
- clintrialhelpline@mhra.gov.uk

The Helpline is a useful tool (I actually use it extensively!!) for asking regulatory/broad issue questions.

You can also contact Assessors directly, especially for further information on GNAs.

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.

Note that there is a new section on the EMA web page devoted to scientific advice devoted to questions outside the scope of scientific advice.

https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance#questions-outside-the-scope-of-scientific-advice-(new)-section

Example of questions that the EMA considers now outside the scope of the SA includes “Are the non-clinical data adequate to support a first-in-human study?”

The EMA states that this would require a full review of the non-clinical data before they could respond.

The EMA states that such a question would belong to a clinical trial application under national competent authority remit.


AND THAT'S MY LAST SLIDE. ANY COMMENTS?
Dilbert.com DilbertCartoonist@gmail.com
YOU STOLE AN HOUR OF MY LIFE. SOMETHING INSIDE ME DIED. I WILL NEVER HAVE ANOTHER GOOD DAY.
zzzz
12-7-11 ©2011 Scott Adams, Inc./Dist. by Universal Uclick
I WENT IN WITH LOW EX-PECTA-TIONS.
AVOIDS THE DELUSION THEY WANT TO LISTEN TO YOU!

SIMBEC-ORION | Weatherden

Thank you!

For more information, or to submit an RFP

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