Non-Clinical Regulatory Considerations in Initiating Clinical Trials

David R Jones
Expert Scientific Assessor (Pharmacotoxicologist), Licensing Division, Medicines and Healthcare products Regulatory Agency (MHRA), UK
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- ICH M3R2 guidance on non-clinical safety studies
- ICH S9 non-clinical evaluation for anti-cancer pharmaceuticals
- ICH S6 guidance on non-clinical safety evaluation of biotechnology derived pharmaceuticals
- Understanding the ICH’s new areas of non-clinical data required for phase I applications
- Key components/areas for a successful CTA authorisation, level of detail, pitfalls
Regulatory non-clinical guidelines are like the modern map of the London Underground.

They’re not a completely accurate representation of the “real” world. They’re just intended to make it easier to navigate!

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

NEVER FOLLOW A REGULATORY GUIDELINE IF THERE’S A GOOD SCIENTIFIC RATIONALE NOT TO!!!
General points:
Guidelines are generally written in order to provide an element of flexibility and not to place undue legislative restraints on scientific progress.

All studies should be conducted according to acceptable current designs. Each study should be planned and designed taking into account the properties and indications of the drug concerned.
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.
Non-clinical Studies should be the basis of extrapolation to indicate possible risks to humans.

These studies are a means to an end, not an end in themselves!!
ICH M3R2

Guidance on non-clinical safety studies
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)

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What’s changed?

The Title!!

Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorisation for Pharmaceuticals

And the size! 2000 version had 6 pages of text. Revision has 27!!!
What’s changed?

The Scope.. especially...

... may provide general insight for biotechnology-derived products only with regard to timing of non-clinical studies relative to clinical development stage.
What’s changed?

Acute Toxicity Studies... no longer referred to as Single Dose Toxicity Studies

Two sentences in old... almost 2 pages in revised!! And we’re “removing” the requirement!!

“information on acute toxicity can be obtained from appropriately conducted dose escalation studies or short duration dose ranging studies that define a maximum tolerated dose in the general toxicity test species”.

EMA SME May 2010
What’s changed?

Duration of repeated dose toxicity studies to support clinical trial duration slightly changed.

Inclusion of reference to juvenile animal studies for paediatric clinical trials.

USA acceptance of 6 month non-rodent studies rather than 9 or 12 month duration under certain circumstances 😊
What’s changed?

New sections:

Estimation Of The First Dose In Human.

Exploratory Clinical Studies
What’s changed?

Local Tolerance section expanded.

Genotoxicity section amended to cover FTIM trials and equivocal findings.
Reproductive Toxicity Studies

**MAJOR REVISION** around inclusion of women of child bearing potential!!

“In all ICH regions, inclusion of women of childbearing potential in clinical trials may be acceptable **without** non-clinical reproductive/developmental toxicology studies in certain circumstances”
What’s changed?

Clinical Trials In Paediatric Populations – this section expanded.
What’s changed?

New Sections:

Immunotoxicology
Phototoxicity
Non-clinical abuse liability
Combination drug nonclinical testing
Limit Doses (i.e. Maximum Doses in Non-Clinical Studies added) Doses providing a 50-fold margin of exposure to the clinical systemic exposure generally are considered acceptable as the maximum dose for acute and repeated-dose toxicity studies in any species.
Limit Doses:
However, to support Phase III clinical trials for the United States, dose-limiting toxicity generally should be identified in at least one species when using the 50-fold margin of exposure as the limit dose.
While still in its early phases of the implementation, the complexity of the guidance, its broader scope, and numerous changes in recommendations from the M3R1 guidance have generated questions that will impact its successful implementation.

Several of these questions and issues can readily be addressed by Q & A.

The ICH website will have a section to which any of the parties or observers can submit questions about ICH M3 (R2)
The first questions to be answered surround:

Metabolites (especially unique human metabolites)

Limit Doses

Juvenile Animal Studies to support Paediatric Trials
Understanding the ICH’s new areas of Non-Clinical Data required for Phase I Applications
New Section added to revised M3:

EXPLORATORY CLINICAL STUDIES

It is recognised that in some cases insight on human physiology/pharmacology, knowledge of drug candidate characteristics and therapeutic target relevance to disease are benefited by earlier access to human data. Streamlined early exploratory approaches can accomplish this end.
Exploratory clinical studies for the purpose of this guidance are those intended to be conducted early in Phase I, involve limited human exposure, have no therapeutic or diagnostic intent, and are not intended to examine maximum tolerated dose.
Five clinical approaches that are described in the guidance can be supported by more limited non-clinical testing programs.
Remember, following Regulatory Guidance is only one way of achieving an objective. There might be a better way!
Other approaches not described in this guidance may be acceptable and should be discussed with the appropriate Regulatory Authorities.
The amount of nonclinical supporting data appropriate in these situations will be dependent on the extent of proposed human exposure, both with respect to the maximum clinical dose used and the duration of dosing.

However, in all cases, nonclinical requirements are reduced compared to those for non-exploratory trials.
So what are the five clinical approaches outlined in ICH M3?
Microdosing Studies:

There are two different microdose approaches.

The first is limited to \textit{not more} than a \textit{total} of 100 µg that can be divided among up to five doses in any subject.

The second microdose approach is limited to 100 µg \textit{per subject per administration} up to a \textit{total} of 500 µg
Single Dose Studies at Sub-Therapeutic or into anticipated Therapeutic Range.

Nonclinical toxicology support is extended single dose studies in rodents and non-rodents.

The maximum allowable dose should be derived from the available non-clinical data, but could be up to \( \frac{1}{2} \) NOAEL.
The fourth and fifth paradigms allow up to 14 days clinical dosing into the therapeutic range.

Allows determination of pharmacokinetics and pharmacodynamics but does not intended for examination of maximum tolerated doses.
Both approaches supported by 2 week studies in rodents and non-rodents. Differences depend on design of animal studies and doses used.

Both approaches need less compound than "traditional" 2 week studies.
ICH S9
Non-clinical evaluation for anti-cancer pharmaceuticals
**ICH Topic S9**
**Nonclinical Evaluation for Anticancer Pharmaceuticals**

**Step 4**

**NOTE FOR GUIDANCE ON NONCLINICAL EVALUATION FOR ANTICANCER PHARMACEUTICALS**
(EMEA/CHMP/ICH/646107/2008)

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In the development of anticancer drugs, clinical studies often involve cancer patients whose disease condition is progressive and fatal.

In addition, the dose levels in these clinical studies often are close to or at the adverse effect dose levels.
For these reasons, the type, timing and flexibility called for in the design of nonclinical studies of anticancer pharmaceuticals can differ from those elements in nonclinical studies for other pharmaceuticals.
This guideline provides information for pharmaceuticals that are intended to treat cancer in patients with serious and life-threatening malignancies (advanced cancer).

The guideline applies to both small molecule and biotechnology-derived pharmaceuticals (biopharmaceuticals), regardless of the route of administration.
The nonclinical data to support Phase I and the clinical Phase I data would normally be sufficient for moving to Phase II and into second or first line therapy in patients with advanced cancer.

The guideline also describes further non-clinical data to be collected during continued clinical development in patients with advanced cancer.
This guideline does not apply to drugs intended for cancer prevention, treatment of symptoms or side effects of chemotherapeutics, studies in healthy volunteers, vaccines, or cellular or gene therapy.

Radiopharmaceuticals are not covered in this guideline, but some of the principles could be adapted.
As well as listing the nonclinical requirements, the document also provides guidance on:

The ICH Guideline effectively replaces the existing CHMP Document: “Note for Guidance on the Pre-clinical Evaluation of Anticancer Medicinal Products”.

EMA SME May 2010
Addendum to ICH S6: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6(R1)

Current Step 2 version
Dated October 29 2009
The purpose of the addendum is to provide clarification on and an update of species selection, study design, immunogenicity, reproductive and developmental toxicity and assessment of carcinogenic potential.

This harmonised addendum will help to reduce the likelihood that substantial differences will exist among regions.
Species Selection
Study Design
Exploratory CTAs
Immunogenicity
Reproductive And Developmental Toxicity
Carcinogenicity
The flexible approaches to support exploratory clinical trials as outlined in ICH M3 (R2) can be applicable to biopharmaceuticals.

It is recommended that these approaches be discussed and agreed upon with the appropriate regulatory authority.
For biological products for which embryo-fetal exposure during organogenesis can be demonstrated to be low, the embryo-fetal development toxicity study can be conducted during Phase III.
Paediatric Trials
There is now a requirement under the new EU paediatric Regulation to obtain approval by the Paediatric Committee (PDCO) for either the development of a product still under patent protection for use in the paediatric population or alternatively approval for any proposed waiver(s) in either the entire paediatric population or subgroups.
The requirement to submit the results of such Paediatric Investigation Plans (PIPs) applies to applications for new medicines and to certain line extensions or variations.

Proposals for PIPs should be submitted to the PDCO secretariat at the European Medicines Agency and further information can be obtained from their website.
When paediatric patients are included in clinical trials, safety data from previous adult human experience would usually represent the most relevant information and should generally be available before initiation of paediatric clinical trials.
The appropriateness and extent of adult human data should be determined on a case-by-case basis. Extensive adult experience might not be available before paediatric exposures (e.g., for paediatric-specific indications).
The conduct of any juvenile animal toxicity studies should be considered only when previous animal data and human safety data, including effects from other drugs of the pharmacological class, are judged to be insufficient to support paediatric studies.
Key Components/Areas For a Successful CTA Authorisation, Level of Detail, Pitfalls
Case by case is good science, not a “cop out”.

Good Science is always better than blindly following guidelines.

Actually, Regulatory Affairs people do not ALWAYS know how Regulator’s think!

Don’t be afraid of standing up for yourselves if you’re certain you’re right! (just be careful how you tell us that we’re wrong).
MAAs have the nonclinical overview, written summaries, tabular summaries and all the primary reports.

CTAs have Investigator’s Brochures and/or IMPDs.

CTAs are not supported by primary reports – we are supposed to trust you not to tell fibs!
The clearer you set out your data, the easier to review, the happier the Reviewer!!!
Things to remember:

You know your drug and its history better than the Regulator does!!

Never assume that the Regulator knows more than you do (we do, but we’re very modest 😊)

No statements not supported by data!

No sweeping generalisations to “explain” away adverse findings!
Contraception advice (male and female) is very important, especially in Phase I/II.

Supply a justification for starting dose and maximum doses.

Ensure nonclinical “signals” are covered by inclusion/exclusion criteria and clinical monitoring.

Appropriateness of test species used.

Always discuss relevance of animal findings to human.
Problem Areas and How to Resolve Them
Scientific Advice!!
The MHRA has, for many years, provided scientific and regulatory advice to sponsors. Most of our EU colleagues also offer scientific advice.

In the UK, scientific advice can be requested during any stage of the initial development of the medicinal product (before submission of a marketing authorisation application).
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.
Scientific advice can also be obtained from the CHMP, but CTAs are a National Decision!!

It is the Scientific Advice Working Party (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.
Ultimate Goal
Risk assessment is a dual process, involving both the applicant and Regulatory Authorities.

Essentially, for all clinical trials, we’d all like to say to the subjects...
Thank You for Listening
Any Questions?

Don’t be shy!

There’s no such thing as a silly question to a Regulator!

And I promise I won’t take note of your names!!