

Requirements for the First-In-Human Clinical Trials

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- Background
- Guidelines
- Achieving Harmonisation in the EU

Background

The pharmaceutical industry continues to look for ways to reduce drug candidate attrition throughout the drug discovery and development process.

A significant cause of attrition is due to safety issues arising either as a result of animal toxicity testing or in the initial clinical programme.

Background

The first trial in man is critical.

Current Guidelines

Current Guidelines

The main guidance document currently available for Clinical Trials is the ICH M3 document **"Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorisation for Pharmaceuticals"**.

(<http://www.emea.europa.eu/pdfs/human/ich/028695en draft.pdf>)

(Scheduled to be Finalised June 2009)

Current Guidelines

In 2003, the CHMP document "Position paper on Non-Clinical Studies to Support Clinical Trials with a Single Microdose" came into force.

This used a concept where the starting dose in man was $1/100^{\text{th}}$ of the dose calculated to yield a pharmacological response.

This Guideline will be withdrawn once ICH M3 is Finalised

Current Guidelines

Guidance for Industry, Investigators, and Reviewers Exploratory IND Studies

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
January 2006**

Pharmacology/Toxicology

This Guideline will be superseded by ICH M3

London, 19 July 2007
Doc. Ref. EMEA/CHMP/SWP/28367/07

**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

**GUIDELINE ON STRATEGIES TO IDENTIFY AND MITIGATE RISKS FOR FIRST-IN-
HUMAN CLINICAL TRIALS WITH INVESTIGATIONAL MEDICINAL PRODUCTS**

DRAFT AGREED BY CHMP EXPERT GROUP	6 March 2007
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	22 March 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	23 May 2007
AGREED BY CHMP EXPERT GROUP	4 July 2007
ADOPTION BY CHMP	19 July 2007
DATE FOR COMING INTO EFFECT	1 September 2007

Current Guidelines

Applies to all new chemical and biological investigational medicinal products **except** gene and cell therapy medicinal products.

Covers non-clinical issues for consideration prior to the first administration in humans and the design and conduct of such trials.

Current Guidelines

Should be read before ANY FTIM CTA, NOT
JUST "HIGHER RISK" COMPOUNDS!!

Revision of ICH M3

The general requirements for nonclinical support for human clinical trials in the EU, as set out in ICH M3 are:

Maximum Duration of Clinical Trial

Up to 2 weeks

Between 2 weeks
6 months

> 6 months

Minimum Duration of Repeated Dose Toxicity Studies to Support Clinical Trials

Rodents

2 weeks

Same as
clinical trial

6 months

Non-Rodents

2 weeks

Same as
clinical trial

6^a months

^aNote that in the USA, clinical trials > 6 months generally require 9 month studies in non-rodents.

However, these “absolute” requirements are “over the top” for early phase 1 studies in man.

In order to reduce the time and resources expended on candidate pharmaceutical products, new tools are needed to distinguish earlier in the drug development process those candidates that hold promise from those that do not.

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.

This section runs to about 6 pages - there were over 15 pages of consolidated comments received on it from Industry!!

Exploratory clinical studies for the purpose of this guidance are those intended to be conducted early in Phase 1, 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.

In all cases appropriate characterisation of pharmacology using *in vivo* and/or *in vitro* models is needed and should be used in support of human dose selection.

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.

Rationale

More screening work
in early Phase I



Better drug candidate
selection

Better drug candidate
selection



Less exposure to man;
less waste of animals
and resources

Less exposure to man;
less waste of animals
and resources



Happy Regulators,
Industry and Public!!

Obviously if only have one candidate compound then can't select best 😊.

However, these studies still allow earlier "readouts" to allow better informed decision making as to whether or not to progress with compound.

So what are the five clinical approaches outlined in ICH M3?

Microdosing Studies:

There are two different microdose approaches.

The first is limited to not more than a 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 per subject per administration up to a 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.

Achieving Harmonisation in the EU

There is a concern that the
Pharmaceutical Industry is worried about
a lack of harmonisation within the EU
(not generally a problem for Exploratory
Trials that are single sites)

Frequent teleconferences being held within framework of CTFG.

Regular meetings being set up for Assessors.

Revision of M3 discussed at SWP, Nonclinical Assessors Meeting and CTFG Assessors Meeting.

Voluntary Harmonisation Procedure (VHP) for the assessment of Multinational Clinical Trial Applications

Since the authorisation of a clinical trial is subject to National Legislations, the assessment of the same Clinical Trial Application might result in varying final decisions.

Country-specific modifications might occur due to changes requested by the different National Competent Authorities and Ethics Committees.

A CT might even be approved in one MS and rejected in another.

Such situations not only may jeopardise the scientific value of clinical trial results in the case of country-specific modifications but also are hardly understood by the public, since the levels of protection of clinical trials participants should be the same in all European countries.

The need to harmonise MN-CTs in Europe in order to ensure the protection of participants as well as the scientific value of clinical trials, by the means of harmonising processes and practices relating to MN-CTs (about 60% of CTs in EU), has become a priority for the CTFG.

The organisation of the coordinated assessment of multinational CTA applications through the Voluntary Harmonisation Procedure (VHP) is a major objective of the CTFG work plan for 2008-2009.

Due to the volume of MN-CTs to be assessed in the EU every year, and bearing in mind that CTA decisions remain a National Decision, an incremental process is proposed, with an initial pilot phase running from March 2009.

During the pilot phase, only MN-CTs involving an IMP without MA in the EU and any of the following criteria would undergo the VHP:

1. FIH MN-CTs and particularly with investigational medicinal products with known or anticipated risk factors as described in EMEA/CHMP/SWP/294648/2007.

During the pilot phase, only MN-CTs involving an IMP without MA in the EU and any of the following criteria would undergo the VHP:

2. MN-CTs with "Critical" investigational medicinal products (limited community expertise e.g. IMP with novel modes of action, links to a class of medicinal product with recognised safety concerns, or "Critical" MN-CTs (e.g. for limited trial populations e.g. orphan diseases)

During the pilot phase, only MN-CTs involving an IMP without MA in the EU and any of the following criteria would undergo the VHP:

3. MN-CTs with very large population and where the sponsor indicates a need for harmonisation (e.g. large phase III CTs and several 5-10 MS concerned)

The VHP will comprise three phases:

Phase 1: a "pre-procedural" or "Request for a VHP" step: inclusion of a request for review of a planned MN-CT CTA into the VHP system

Phase 2: an assessment step: review of a draft CTA by the NCAs of the participating MS

Phase 3: a national step, with formal CTA applications to all concerned NCAs.

More information on the VHP can be found in the Guidance document under:

http://www.hma.eu/uploads/media/VHP_public_CBB_22_Dec_08_hk_jan12.pdf

or on the CTFG website

<http://www.hma.eu/77.html>

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!!