An EU Regulatory View on Non-Clinical Support for First in Human Trials in Rare Diseases

David R Jones  
*Expert Pharmaco-Toxicologist*  
MHRA  
[www.mhra.gov.uk](http://www.mhra.gov.uk)  
David.jones@mhra.gsi.gov.uk
ANY OPINIONS EXPRESSED IN THIS PRESENTATION ARE MY OWN,
ARE NOT NECESSARILY SHARED BY OTHER ASSESSORS AT THE MHRA,
AND CAN NOT BE CONSIDERED TO BE UK POLICY
ANY OPINIONS EXPRESSED IN THIS PRESENTATION ARE ALSO NOT NECESSARILY SHARED BY OTHER ASSESSORS FROM THE SWP, AND CAN NOT BE CONSIDERED TO BE EU POLICY.
The materials featured within this MHRA presentation are subject to Crown copyright protection for this event. Any other copy or use of Crown copyright materials features in this presentation, in any form or medium, is subject to prior approval of the MHRA which has Delegated Authority from Her Majesty’s Stationery Office (HMSO) to administer Crown copyright for MHRA originated material. Applications should be in writing, clearly stating the proposed use / reuse of the information, and should be sent to the MHRA at the following address: Conference and Education Function, MHRA, 151 Buckingham Palace Road, London SW1W 9SZ or e-mail speakers@mhra.gsi.gov.uk. You may not sell or resell any information reproduced to any third party without prior agreement. The permission to reproduce Crown copyright material does not extend to any material in this pack which is subject to a separate licence or is the copyright of a third party. Authorisation to reproduce such material must be obtained from the copyholders concerned.
Medicines and Healthcare products Regulatory Agency (MHRA)

An executive agency of the Department of Health
What is the MHRA?

- The MHRA is:
- an executive agency of the Department of Health
- regulates the safety, quality, effectiveness & performance of medicines and medical devices
- employs over 800 people
- is largely funded by fee income from provision of services to industry
- runs scientific committees which advise Ministers on safety of devices and medicines
- is mainly based in Central London
What are the MHRA Objectives?

- to protect public health
- to provide authoritative information
- to influence international regulation
- to support innovation and the development of medicines and medical devices
- to keep the cost of regulation as low as possible
- to make fact based, decisive judgements which are in the interests of patients and consumers
What does it do?

- ensures that medicines sold in the UK for human use are safe and effective
- ensures that medical devices – from heart valves to walking frames – are safe and meet performance standards
- promotes the safe use of medicines and medical devices
- promotes an understanding that there is an element of risk in all medicines and ensures that the benefits of licensed medicines outweigh the risks
- ensures that labelling and guidance are provided so patients are made aware of any risk and of proper usage
How does the MHRA Carry Out Its Responsibilities?

• operates a system of licensing, classification, monitoring and enforcement to ensure medicines for human use sold in the UK are safe, effective and of a high standard

• manages a system for monitoring suspected adverse reactions

• maintains processes to alert doctors and pharmacists if medicines or medical devices do not perform as they should

• takes enforcement action when things go wrong

• represents the UK on international bodies which work to set consistent standards for medicines and medical devices world wide
What Are Its Current Challenges?

• to be more accessible in order to meet increasing demands from patients and the public for more information

• to provide even more timely responses to health professionals and the industry

• to be more transparent, within the limits set by the need for confidentiality

• to be seen to be always acting in the best interests of patients and consumers
The Role of Toxicologists at the MHRA

- The MHRA Toxicologists evaluate non-clinical data submitted in support of applications for product licenses or clinical trials.
- The UK Good Laboratory Practice monitoring unit is part of the MHRA and is involved in the inspection of GLP compliance.
The Role of Toxicologists at the MHRA

• The MHRA has the protection of humans and their environment as its Primary Duty

• The MHRA believes that some animal use will remain necessary for Safety Evaluation purposes for the foreseeable future.

• The MHRA is committed to the principles in line with the Animals (Scientific Procedures) Act of 1986
The MHRA fully supports the NC3Rs. MHRA staff attend the workshops and contribute to many projects.

The MHRA has direct and indirect links with other organisations working in the field of predictive toxicology.

The MHRA welcomes discussions with parties seeking to improve drug development/drug safety procedures.
Working to reduce the use of animals in scientific research
In Pharmaceutical industry

Pharmaceutical industry: A one-stop resource

Welcome to the pharmaceutical industry area of the MHRA website. This section, which has been developed following feedback from users, provides targeted links to information throughout the site, as well as content relevant to the industry.

If you have any feedback on this section and how we can improve it please fill out our feedback form.

There is a link at the top of every page of the MHRA website which links directly to the new section.

News and hot topics

17 Feb 2011 | Best Practice in Reporting of Individual Case Safety Reports (ICSRs)

We have today published guidance for industry that sets the MHRA’s position on how to code adverse drug reactions (ADRs) to a high-quality standard for entry into our Sentinel database. This ‘Best Practice’ guide has been developed combining ideas from both industry trade associations and the MHRA.

16 Feb 2011 | Department of Health announcement about the regulation of herbal practitioners

Contacting the MHRA

This page provides links to information about how to contact the MHRA. It also includes an escalation procedure for industry to resolve any issues informally.

Go to the contacting the MHRA page

Legislation, guidance and policy
The Role of the Regulator
The Drug Regulator’s Tightrope Walk

Protect public health …

... against negative consequences from unsafe or ineffective medicines.

When in doubt, be negative, “we need more information”

Worry about false-positive decisions “Type-1 error”

Experts Say that FDA Cannot Ensure Drug Safety

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

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

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?

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

What are the consequences?

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

What are the consequences?
or put another way.....
"C'mon, c'mon — it's either one or the other."
Enough of my problems....

Let’s turn to yours 😊
Regulatory Guidelines
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!

**NEVER FOLLOW A REGULATORY GUIDELINE IF THERE IS A GOOD SCIENTIFIC RATIONALE NOT TO! GOOD SCIENCE IS FAR MORE IMPORTANT THAN A RIGOROUS ADHERENCE TO A GUIDELINE.**
• 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 protocols. Each study should be planned and designed taking into account the properties and indications of the drug concerned.

  • Requirements of OECD GLP guidelines should be met.
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)
### ICH Topic S 6

Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

---

**Step 5**

---

**NOTE FOR GUIDANCE ON**

**PRECLINICAL SAFETY EVALUATION OF BIOTECHNOLOGY- DERIVED PHARMACEUTICALS**

(CPMP/ICH/302/95)

---

<table>
<thead>
<tr>
<th>TRANSMISSION TO CPMP</th>
<th>November 1996</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRANSMISSION TO INTERESTED PARTIES</td>
<td>November 1996</td>
</tr>
<tr>
<td>COMMENTS REQUESTED BEFORE</td>
<td>May 1997</td>
</tr>
<tr>
<td>FINAL APPROVAL BY CPMP</td>
<td>September 1997</td>
</tr>
<tr>
<td>DATE FOR COMING INTO OPERATION</td>
<td>March 1998</td>
</tr>
</tbody>
</table>
ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals
Step 5

<table>
<thead>
<tr>
<th>Part II (Addendum)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission to CHMP</td>
<td>November 2009</td>
</tr>
<tr>
<td>Release for consultation</td>
<td>November 2009</td>
</tr>
<tr>
<td>Deadline for comments</td>
<td>February 2010</td>
</tr>
<tr>
<td>Final approval by CHMP</td>
<td>July 2011</td>
</tr>
<tr>
<td>Date for coming into operation</td>
<td>December 2011</td>
</tr>
</tbody>
</table>
The addendum should be read in close conjunction with the original ICH S6 Guideline.

In general the addendum is complementary to the guideline, and where the addendum differs from the original guideline, the guidance in the addendum prevails.
This harmonised addendum should help to define the current recommendations and reduce the likelihood that substantial differences will exist among regions.

This guidance should facilitate the timely conduct of clinical trials, reduce the use of animals in accordance with the 3Rs (reduce/refine/replace) principles and reduce the use of other drug development resources.

Although not discussed in this guidance, consideration should be given to the use of appropriate *in vitro* alternative methods for safety evaluation.
For biotechnology-derived products intended to be used in oncology the Guidance on Nonclinical Evaluation for Anticancer Pharmaceuticals (ICH S9 Guideline) should be consulted.

November 2009
EMEA/CHMP/ICH/646107/2008

ICH Topic S9
Nonclinical Evaluation for Anticancer Pharmaceuticals

Step 4

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

<table>
<thead>
<tr>
<th>TRANSMISSION TO CHMP</th>
<th>December 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRANSMISSION TO INTERESTED PARTIES</td>
<td>December 2008</td>
</tr>
<tr>
<td>DEADLINE FOR COMMENTS</td>
<td>March 2009</td>
</tr>
<tr>
<td>FINAL APPROVAL BY CHMP</td>
<td>November 2009</td>
</tr>
<tr>
<td>DATE FOR COMING INTO OPERATION</td>
<td>May 2010</td>
</tr>
</tbody>
</table>
GOALS OF NON-CLINICAL STUDIES
The development of a new medicinal product is a stepwise process involving an evaluation of both animal and human efficacy and safety information.

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.
General Goals of Non-Clinical Studies

Identification of potential target organs
Characterisation of toxic effects with respect to target organs
Dose response relations
Relationship to duration and extent of systemic exposure
Potential reversibility of toxic effects
Identification of parameters for clinical monitoring (for human medicines)
Estimation of safe starting dose for clinical trials (for human medicines)
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.
Non-Clinical Study Requirements
# Table 1  
**Recommended Duration of Repeated-Dose Toxicity Studies to Support the Conduct of Clinical Trials**

<table>
<thead>
<tr>
<th>Maximum Duration of Clinical Trial</th>
<th>Recommended Minimum Duration of Repeated-Dose Toxicity Studies to Support Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rodents</td>
</tr>
<tr>
<td>Up to 2 weeks</td>
<td>2 weeks&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Between 2 weeks and 6 months</td>
<td>Same as clinical trial&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>&gt; 6 months</td>
<td>6 months&lt;sup&gt;b, c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

---

<sup>a</sup> In the United States, as an alternative to 2 week studies, extended single-dose toxicity studies (see footnote c in Table 3) can support *single-dose human trials*. Clinical studies of less than 14 days can be supported with toxicity studies of the same duration as the proposed *clinical study*.

<sup>b</sup> In some circumstances clinical trials of longer duration than 3 months can be initiated, provided that the data are available from a 3-month rodent and a 3-month non-rodent study, and that complete data from the chronic rodent and non-rodent study are made available, consistent with local clinical trial regulatory procedures, before extending dosing beyond 3 months in the *clinical trial*. For serious or life-threatening indications or on a case-by-case basis, this extension can be supported by complete chronic rodent data and *in-life* and necropsy data for the non-rodent study. Complete histopathology data from the non-rodent should be available within an additional 3 months.
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).
Results from repeated-dose toxicity studies of appropriate duration in adult animals, the core safety pharmacology package, and the standard battery of genotoxicity tests should normally be available before initiation of trials in paediatric populations.

Reproduction toxicity studies relevant to the age and gender of the paediatric patient populations under study can also be important to provide information on direct toxic or developmental risks (e.g., fertility and pre-postnatal developmental studies).

Embryo-fetal developmental studies are not critical to support clinical studies for males or prepubescent females.
The conduct of any juvenile animal toxicity studies should be considered **only** when previous animal data and human safety data, including effects from other similar medicinal products, are judged to be insufficient to support pediatric studies.

If a study is warranted, one relevant species, preferably rodent, is generally considered adequate. A study in a non-rodent species can be appropriate when scientifically justified.

Guidelines on Juvenile animal studies exist in the EU, USA and Japan and the topic is also discussed in ICH M3(R2). There are inconsistencies and this is now an ICH topic.
SPECIES SELECTION
Repeated-dose toxicity studies in two species (one a non-rodent) are generally required to support any clinical development trial.

Within the usual spectrum of laboratory animals used for toxicity testing, the species should be chosen based on their similarity to humans with regard to pharmacokinetic profile and/or pharmacological responsiveness.

Studies in animal models of disease can be considered if there are no other appropriate species.
FIRST IN HUMAN TRIALS
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 ICH M3R2:

**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 are necessary to accomplish this end.
The MHRA authorises approximately 1000 clinical trials per year – more than any other Competent Authority in the EU.

Approximately 40% of all FTIM trials conducted in EU are performed in the UK.
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.
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 400 Scientific Advice meetings with Companies in 2013.

The MHRA Clinical Trials Unit has held almost 110 meetings with companies, academic institutes or hospital groups over the last 9 months!

The CTU’s email helpline also 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.

I WENT IN WITH LOW EXPECTATIONS.

AVOIDS THE DELUSION THEY WANT TO LISTEN TO YOU!
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!!
Any Further Questions?

Please Feel Free to Contact the MHRA If You Have Any Further Queries:

Telephone: 020 3080 6000
Address: 151 Buckingham Palace Road
         London SW1W 9SZ
Home Page: www.mhra.gov.uk
Any Further Questions?

Please Feel Free to Contact the MHRA If You Have Any Further Queries:

Telephone: 020 3080 6000
Address: 151 Buckingham Palace Road
          London SW1W 9SZ
Home Page: www.mhra.gov.uk