In December 2009 the updated ICH M3 guideline on non-clinical development and safety testing came into operation ("ICH Topic M3 (R2), Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals"). I will address here the changes compared to the previous version and consequences for the design of a preclinical programme to support different phases of clinical development and marketing authorisation. For some parts of the development programme no major changes were made, such as for safety pharmacology, genotoxicity, carcinogenicity, immunotoxicity and local tolerance. The most obvious changes and additions are a complete set of predesigned preclinical packages for different kinds of exploratory clinical trial, the extended guidance to the support of paediatric clinical trials, the non-clinical assessment of abuse liability, and guidance for the development of combination drugs.

**Scope of the Guideline**

Basically, the scope didn’t change: the guidance applies to New Chemical Entities. Prior to and since the previous version, specific guidelines were developed for non-clinical safety of specific compounds and indications: biotechnology derived pharmaceuticals (ICH S6 guideline); advanced therapeutic products (e.g. gene therapy); anti-cancer products (ICH S9); paediatric indications. For these products and indications, ICH M3 only provides guidance to the timing of the necessary studies and in some cases guidance to the duration of repeated dose toxicity studies.

As it is an ICH guideline, non-clinical development according to this guideline will support clinical trials and registration in the 3 main regions, US, EU and Japan.

**General Toxicity Studies**

The guideline is extended with a helpful recommendation and scheme for dose selection for the general toxicity studies. High-dose selection applying maximum tolerated dose (MTD), exposure multiples and maximum feasible dose are discussed with the aim to “prevent the use of doses in animals that would not add value to predicting clinical safety”.

In general, single-dose (acute) toxicity studies can be replaced by dose-escalation / range-finding studies preceding the RDT studies. These studies do not necessarily need to be performed in compliance with Good Laboratory Practice (GLP).

The duration and timing for Repeated Dose Toxicity (RDT) to support the conduct of clinical trials is slightly adapted compared to the recommendations in the previous version. The included scheme in the guideline with recommended duration of RDT studies now indicates in most cases an RDT with the same duration as the anticipated clinical trial it supports, up to six months. For clinical trials >six months, in general a six-month rodent study and six-month (EU) or nine-month (US, Japan) non-rodent study is sufficient. And in some cases a six-month non-rodent study is also appropriate for Japan and the US.

For the duration of RDT studies to support marketing authorisation, there is one change: the duration of an RDT non-rodent study to support an indicated treatment of one to three months is elevated from three to six months.

**ADME**

In-vitro metabolism studies and protein binding should now be performed prior to the first human clinical trial. Although this was not a prerequisite in the past, NOTOX always raised the option of performing these studies early in development in our discussions with clients on this preclinical programme design. We favour this approach because it can provide valuable information that is very useful in early drug development. The information is useful to help estimate the predictability of animal data. Furthermore, it may help in species selection for general toxicity studies and dose selection for clinical safety studies. As such this change in the guidance is quite useful.

**Exploratory Clinical Trials**

A new chapter in the guideline describes a complete set of predesigned preclinical packages for different kinds of exploratory clinical trials. They are categorised as micro-dose trials, single-dose trial at (sub-)therapeutic dose and multiple-dose trials. Adapted toxicity studies and abbreviated preclinical programmes make it possible to shorten the time to clinical trial and can even reduce overall animal use in drug development. These exploratory clinical trials are used for an early investigation of PK profile, tissue distibution (PET study) pharmacodynamics (e.g. target receptor binding) or biomarkers in humans. Five different preclinical programmes are described supporting five different approaches for exploratory studies in human
volunteers. NOTOX has prepared standard study designs for these non-clinical studies and we offer the abbreviated programmes for all described exploratory trials.

Reproduction Toxicology

In general, the need for reproduction toxicity studies prior to clinical studies depends on the population to be exposed. These studies are described in the specific guideline for reproduction toxicity, ICH S5(R2). The inclusion of Women of Childbearing Potential (WOCBP) is the most critical consideration on this topic. In the former guideline, the requirements differed for each of the three regions, though they are more comparable for the EU, US and Japan in the updated version. In certain circumstances, WOCBP can now be included in early clinical trials without non-clinical, developmental studies, which applies to all regions. In most cases, fertility and embryo-foetal development should be assessed before large-scale or long-duration clinical trials (Phase II) and pre-postnatal development before marketing approval.

Juvenile Toxicity Studies / Paediatric Indications

Since the implementation of the Paediatric Regulation on 1st June 2007 in the EU, for all new medicines a “paediatric investigation plan” (PIP) has to be approved by the EMEA’s Paediatric Committee. The incentive in return is a half-year additional market exclusivity. For orphan drugs, the incentive is even a two year additional exclusivity above the ten years of regular market exclusivity in the EU. Besides the release of a new EMEA guidance for non-clinical development to support clinical trials in paediatric populations, this topic of growing interest and concern is also addressed extensively in this updated version of the general ICH M3 guideline.

Toxicology studies in juvenile animals to support the development of pharmaceuticals for paediatric patients are aimed at obtaining information on potential safety concerns that cannot be adequately addressed in human adults or in regular preclinical studies. These cases focus especially on effects on growth and development, and on immature systems such as the nervous system, the pulmonary system, the skeleton, kidneys, reproductive system and immune system. Additional differences in safety profile between paediatrics and adults can also be caused by metabolic, pharmacokinetic and pharmaco-dynamic differences.

The necessity and design of these studies will highly depend on the information on safety which might be available from experience in adults, and depends on results from clinical trials and general non-clinical studies. This information is generally available in cases where the pharmaceutical was originally developed for adults, and treatment is planned to be extended to treatment of paediatric patients. When this information indicates a cause for concern in paediatrics or when the safety profile in paediatrics cannot be predicted well enough with this information, toxicity studies in juvenile animals are warranted. NOTOX has adopted the development of pharmaco-dynamics for paediatric indications and offers these juvenile studies in rodents and non-rodents. The design of our studies is tailor-made and will depend on specific target population (age, gender), indication, duration of treatment, route of administration and concern for specific target organs. Our non-clinical programmes will be in line with the EMEA “guideline on the need for non-clinical testing in juvenile animals of pharmaco-dynamics for paediatric indications” and in line with the recently updated (R2) ICH M3 guideline. In general, when development for paediatric patients is an extension to use in adults and if additional testing is warranted, results from a juvenile toxicity study in one appropriate species is sufficient to support a paediatric clinical trial. In case paediatric patients are the primary patient population, a more extensive preclinical programme will be necessary.

Abuse Liability

Non-clinical abuse liability is a new chapter in the updated ICH M3 guideline. Until now, the topic was covered by regional guidelines, like the EMEA “Guideline on the non-clinical investigation of the dependence potential of medicinal products”. The necessity of non-clinical testing of abuse liability should be evaluated for all drugs that produce central nervous system activity, regardless of the therapeutic indication. Identification of early indicators of abuse potential can be obtained by PK/PD profiling and receptor binding, structure similarity with known drugs of abuse, in vivo pharmacology studies investigating CNS activity, and clinical signs in preclinical studies. When the results of these studies give rise for concern or in case the compound has a novel mechanism of action on the central nervous system, specific non-clinical studies are recommended to support large clinical studies (Phase III).

Combination Drug Toxicity Testing

In addition to the release of EMEA’s “Guideline on the non-clinical development of fixed combinations of medicinal products” in 2008, this topic is now covered in the ICH M3 document for the three main regions.

Three types of combinations are distinguished:

1. Two or more late stage entities. Defined as compounds with significant clinical experience (i.e. from Phase III studies and/or post-marketing). Non-clinical combination studies are only recommended to support large-scale or long-term combination trials as well as for marketing.

2. One or more late stage entities and one or more early stage entities (defined as compounds with limited clinical experience, i.e. Phase II studies or less). Non-clinical combination studies are only recommended to support large-scale or long-term combination trials as well as for marketing. The clinical study of the combination should not be longer than the clinical experience of each individual compound.

3. More than one early entity. In case a full preclinical programme has been performed with the individual components, an additional non-clinical combination study is recommended to support combination clinical trials. A 90-day combination toxicity study in one species generally covers for a marketing authorisation application.

Antoine Wellink, graduated in Chemical Engineering at the University of Groningen. He has been consultant and senior project manager for several preclinical development programs. Since 2002 Antoine has followed several international courses and workshops on Drug Development and Regulatory Affairs, in special those on the non-clinical testing of biotech products. Antoine Wellink joined NOTOX as Head of Regulatory Affairs in 2007. In this position he is responsible for 3 regulatory affairs sections: Pharmaceuticals; Agrochemicals & Biocides; Industrial Chemicals. Within the pharmaceuticals section he acts as external and internal consultant in designing and managing pre-clinical research projects for the global, innovative (bio-) pharmaceutical industry. Email: marketing@notox.nl