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Getting a molecule into the clinic: Nonclinical testing and starting dose considerations

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ABSTRACT

Examination of content of 35 Investigator Brochures (IBs) for small molecules (including some for oncology) used to support First-In-Human studies over a 2 year period (2014–2016) showed that a mean of 37 nonclinical studies were performed per molecule with pharmacology, ADME and toxicology testing contributing 43%, 32% and 24% of the studies, respectively. Examination of 11 IBs for biopharmaceuticals (monoclonal antibodies) over the same time frame showed that the mean number of nonclinical studies was 17 studies per molecule with pharmacology, ADME and toxicology testing contributing 82%, 6% and 12% of the studies, respectively. For both types of molecule, similar numbers of pharmacology studies were performed but the approximately 50% fewer studies for biopharmaceuticals was due to considerably limited ADME and toxicology testing. Despite available regulatory guidance to allow calculation of a safe clinical starting dose, examination of how this occurred in the examined IBs showed that a variety of approaches are in practice, although reference to the NOAEL in toxicology testing is still key, whether in calculation of a Maximum Recommended Starting Dose (small molecules), or after use of pharmacology and/or PK data (especially for biopharmaceuticals) to show acceptable safety margins over doses used/exposure seen in toxicology studies.

1. Introduction

That nonclinical testing needs to support the proposed efficacy and safety of new drug candidates to allow dosing in first-in-human (FIH) clinical trials is well established and confirmed in a number of international guidelines. However, the actual extent of testing can vary with the class of molecule being investigated, which is reflected in guidelines for chemically synthesised small (including non-advanced state oncology) molecules (ICH M3(R2), 2009), life-threatening state oncology drugs (ICH S9, 2010) and biopharmaceuticals (ICH S6(R1), 2011). Key nonclinical data for these categories are primary pharmacology/biological activity (examining the mode of action of a drug in relation to its desired therapeutic effect) and toxicology evaluation (for example, examining for systemic or organ toxicity) but differences in further testing needs can occur as shown in Table 1. Thus, for biological drugs, genotoxicity studies (tests designed to detect genetic damage) are not required, safety pharmacology evaluation (to investigate potential undesirable pharmacological effects) is usually incorporated into toxicology studies and absorption, distribution, metabolism and excretion (ADME) testing (looking at entry of drug into body and what happens to it) is limited (in line with ICH S6(R1), 2011). More detailed examination for immunogenicity/immunotoxicity (for example, antibody formation, immune system cell population effects or induced antibody response) may be included in the toxicology studies. For all the drug categories, whether or not secondary pharmacology evaluation (examining the mode of action and/or effects of a drug not related to its desired therapeutic effect) occurs can be drug-specific. In order to investigate what types of nonclinical testing is currently being performed by companies developing small and biopharmaceutical molecules, the study content was examined from 46 Investigator's Brochures (IBs) used to support FIH studies over a 2 year period (2014–2016). Furthermore, how this information was used to generate the proposed clinical starting dose was evaluated.

It should be noted that until fairly recently, there was no set process in using nonclinical study data to help select a safe clinical starting dose. In the past, companies sometimes used, for example, 1/100 of the No Observed Adverse Effect Level (NOAEL), usually in

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Table 1
General overview of types of nonclinical testing across drug categories to support FIH clinical trials.

Study type	Small molecule	Small molecule oncology	Biological
Primary pharmacology/biological activity *in vitro*	Y	Y	Y
Primary pharmacology/biological activity *in vivo*	Y	Y	Y
Secondary pharmacology	N/Y[a]	N/Y[a]	Y
Safety pharmacology	Y	Y or N[b]	N
ADME *in vitro*	Y	Y	N
ADME *in vivo*	Y	Y	Y
General toxicology	Y	Y	Y
Genotoxicity	Y	Y or N[b]	N
Other toxicology	N/Y[a]	N/Y[a]	N

ADME absorption, distribution, metabolism and excretion; Y Yes to study type; N No to study type.
[a] N/Y indicates less likely to be performed.
[b] Y or N indicates studies performed if molecule tested as "standard" small molecule (ICH M3(R2), 2009) but not performed if molecule tested as life-threatening state oncology drug (ICH S9, 2010); Other toxicology includes additional evaluation such as phototoxicity or reproduction toxicology.

mg/kg derived from toxicology work involving repeated administration of different dose levels of the molecule to rodents and non-rodents. A number of definitions of the NOAEL exist but it is "the highest dose level that does not produce a significant increase in adverse effects in comparison to the control group" (FDA, 2005). It is up to the toxicologist to determine what is adverse or not. Other ways to assist clinical starting dose calculation in the past involved using allometric scaling (for example, extrapolation from clearance/volume of distribution/protein binding measurements in ADME studies) or use of pharmacodynamics (PD) findings from the animal efficacy model and pharmacokinetic (PK) data (PD/PK modelling) to estimate dose.

In 2005, regulatory guidance became available outlining a standardised algorithmic process for deriving the Maximum Recommended Starting Dose (MRSD) for FIH clinical trials in healthy volunteers, which can involve a 5 step process (FDA, 2005) as follows:

- Step 1: Determine the NOAELs (mg/kg) in toxicity studies
- Step 2: Using the assumption that doses scale by body surface area, divide the NOAEL in each animal species by an appropriate body surface area conversion factor (BSA-CF) = the Human Equivalent Dose (HED)
- Step 3: Pick the appropriate species HED (lowest species HED is the most sensitive)
- Step 4: Choose a Safety Factor (10 is recommended) and divide the HED by this = the MRSD
- Step 5: Consider lowering the MRSD based on other factors such as a Pharmacological Active Dose (PAD)

In 2007, further regulatory guidance was produced around risk assessment to "assist sponsors in the transition from non-clinical to early clinical development" and included information to help in the calculation of the initial dose to be used in humans with application "to all new chemical and biological investigational medicinal products except gene and cell therapy medicinal products", ie, both small and biopharmaceutical molecules (EMEA, 2007). This guideline has been updated (draft issued November 2016) and indicates that the clinical starting dose needs to use a combination of the NOAEL and/or pharmacology and PK data (EMA, 2016). It mentions that exposures achieved at the NOAEL in the most relevant and sensitive species should be used for the estimation of the equivalent dose for humans with reference to, for example, PK/PD modelling. Other data including *in vitro* and *in vivo* pharmacology studies should be used to determine a minimal anticipated biological effect level (MABEL) and estimation of a PAD and/or an anticipated therapeutic dose range (ATD) in humans. It is stated that a safety factor/s generally needs to be applied in calculation of the human starting dose. Although not seen for the molecules examined in this investigation, exploratory clinical trials (for example, a microdose approach) can be performed in cases involving limited human exposure, having no therapeutic intent and without intention to examine clinical tolerability (ICH M3(R2), 2009). Reduced nonclinical testing to support such trials includes, minimally, some pharmacology and an extended single dose toxicology study or, maximally, pharmacology, safety pharmacology, repeat dose toxicology and genotoxicity studies. The recommended starting dose can involve using a maximal dose of 100 μg or a value based around exposure at the NOAEL compared to what is predicted in humans.

Help in the calculation of the clinical starting dose for small molecule oncology molecules became formalised in guidance in 2010, especially for cytotoxic drug development in the treatment of patients with advanced disease and limited therapeutic options (ICH S9, 2010). For many oncology molecules, toxicity can be expected in animal studies and as a NOAEL may not be determined, it is possible to set a clinical starting dose at 1/10 the Severely Toxic Dose [STD] in 10% of animals for rodents. If the non-rodent is more sensitive, then 1/6 the Highest Non-Severely Toxic Dose [HNSTD] (defined as dose level that does not produce evidence of lethality, life-threatening toxicities or irreversible findings) can be used.

2. Materials and methods

Nonclinical data presented in IBs tends to follow the requirements specified in the Guideline for Good Clinical Practice (ICH E6(R1), 2016). For nonclinical studies, it is stated in the "Contents of the Investigator's Brochure" section within this document that "The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in humans". From this basis, a total of 46 IBs available internally to the author were examined for the following study types:

- Pharmacology studies (primary pharmacology/biological activity *in vitro* and *in vivo*, secondary pharmacology and safety pharmacology)
- ADME studies (*in vitro* and *in vivo*)
- Toxicology studies (general toxicology, genotoxicity and other toxicology [usually *in vitro* phototoxicity or reproduction toxicology])

Drug categories covered in the examined IBs comprised chemically synthesised small molecules (n = 29), small molecule oncology molecules (n = 6) and biopharmaceuticals (n = 11). The