

Non-clinical Assessment Requirements

Perspectives from a Member State

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Requirements: Guidelines ?

Interpretation of requirements: Ongoing issues.

Future challenges with respect to non-clinical requirements.



Goals/ Requirements of Nonclinical Studies

- To characterize beneficial pharmacodynamic effects
 - Proof of principle
- To characterize pharmacokinetic profile
- To characterize potential adverse drug effects Guidelines are guides to achieve these goals not strict requirements.
- To guide safe use in human clinical studies
 - To determine a safe & reasonable starting dose
 - Provide monitoring guidelines for the clinical study
- Provide sufficient data to conclude that patients are not exposed to unreasonable risks

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Potential for benefit must also exist

Purpose of the Guidelines

Achieve the goals not simply satisfy the Guideline

Guidelines provide an outline of the path to take



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Purpose is not always achieved (Ongoing Additions/ Revisions)

Overview of the Guidelines

Deliberately not specifically detailed documents:

Advantages and Disadvantages

- •Open to interpretation
- •Flexibility/ Rigidity

ICH S6: All regions have adopted a flexible, case-by-case, science-based approach to preclinical safety evaluation needed to support clinical development and marketing authorisation.



Crossing the Guideline



- Good scientific reasons not to follow a guideline, do it but justify it explicitly
- Advocate: In case of doubt seek scientific advice



Clinical Trials 2010 Ireland



Referenced Guidelines

AR: Type of Application and aspects on development/ GLP

Primarily Consult: ICH M3: <u>Timing</u> of studies (NCE's and Biologicals)

ICH S6: Biological ICH S9: Anti-cancer medicinal products

Genotoxic Impurities Guideline

"nonclinical studies to support the development of anticancer pharmaceuticals in patients with <u>advanced disease</u> and <u>limited therapeutic options</u>."

"This guideline does not apply to pharmaceuticals intended for patients with long life expectancy, cancer prevention, treatment of symptoms or side effects of chemotherapeutics, studies in healthy volunteers, vaccines, or cellular or MEDICINES BOARD gene therapy. "

Pharmacology:

Primary Pharmacodynamics:

AR: Salient results Relevance of the models Species Selection (Biologicals) Mechanism of Action Proof of Concept Therapeutic Indication

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SA/CT Experiences:

- ICH M3/ S9: Combinations appropriate rational and MOA not always discussed.
- ICH S6: Appropriate discussion of relevant species, need for one species or two

Pharmacology:

Secondary Pharmacology/ Safety Pharmacology

AR: Salient results regarding off target effects to predict adverse event

SA/ CT Experiences:

- ICH M3: Failure to investigate/ discuss secondary pharmacological targets Adequate exposure in the Safety Pharmacology studies
- ICH S6: Incorporation of safety pharmacology endpoints into general toxicology studies.
- ICH S9: Incorporation of safety pharmacology endpoints into general toxicology studies. Concern identified, perform stand-alone studies.

Pharmacokinetics/ Toxicokinetics

AR: Discuss relevant animals species considering metabolic pattern Differences in ADME, interspecies variability Impact on safety assessment, protein binding, distribution target organs excretion route pharmacologically active metabolite

SA/ CT Experiences:

ICH M3/ S9: Metabolite: Significantly greater levels?

ICH S6: Difficult to establish uniform guidelines Issues related to immune-mediated clearance mechanisms

SA questions; Addendum to ICH S6 has provided clarity

Recent Examples:

Example 1: Late stage identification of a major human specific metabolite.

> Identified in animals as a minor metabolite. No exposure/ quantitative data from original studies Unknown if there was sufficient exposure

Implications for the Safety Pharmacology Studies Toxicology Studies Genotoxicity Studies Carcinogenicity Reproductive Studies

Example:

ICH S6 Addendum Immunogenicity: *"Measurement of anti-drug antibodies (ADA) in nonclinical studies is not routinely warranted if there is evidence of sustained pharmacodynamic activity, no unexpected changes in the pharmaco/toxicokinetics of the test article during the dosing or recovery phase, and/or no evidence of immune-mediated reactions (immune complex-related, vasculitis, anaphylaxis, etc.). "*

Example:

SA 1: No requirement in the absence of toxicity findings and no observed effect on the pharmacodynamic response

SA 2: Even if adverse findings are not detected and PD properties remained intact throughout the study, preclinical immunogenicity data was requested.

Toxicology Studies (Single/ Repeat dose)

- <u>New Chemical Entities</u>
 - Two Species Rodent & Non-rodent
 - Clinical Route & Schedule
 - Pharmacokinetics





- BIOLOGICALS
 - Most Relevant Species
 - Clinical Route & Schedule



Toxicology Studies (Single/ Repeat dose)

AR: Appropriate ; Species, Route of Administration, Dose Groups, No. of Animals Gender, Rational for schedule, Recovery groups (reversibility?).

Main findings: Parameters to be examined outlined in the guidelines

Identification of the No Observed Adverse Effect Level in different species:

Establish Safety Margins wither respect to Maximum intended dose.

ICH S6:

Use of only one species? Relevant species?

Dose (Stop at 10-fold?)?

Use of homologus molecules? Relevance of the finding to humans.

Animal models of the disease?

Administration schedule and dose mimicking the human situation?

Recovery: limited to one study at one dose level



ICH M3; S6; S9 Recovery Groups:

Complete recovery is not required a trend toward reversibility and a scientific assessment that this would lead to eventual recovery are generally sufficient.

In certain circumstances where significant therapeutic gain has been shown, trials can be extended beyond the duration of supportive repeat dose toxicity studies on a <u>case-by-case basis</u>.

Signs in the non-clinical studies not sufficiently explored/ discussed:

•Requirement for additional studies? Hepatotoxicity

•Can they be clarified within the clinical setting?



Impurities testing/ qualification: Batch Analysis: Impurity/ies tested sufficiently?

ICH M3: ICH Q3A and Q3B (not applicable during clinical research stage

ICH S6: Preferable to rely on purification than qualification Changes in development program should be considered for their impact

ICH S9: Limits of impurities might be exceeded case-by-case



Toxicology Issues (Single/ Repeat Dose Studies)

Metabolites:

ICH M3:

Characterisation of human metabolite required when exposure > <u>10%</u> of total drug-related exposure and metabolite is observed at <u>significantly</u> greater levels in humans than the maximum exposure observed in the toxicological studies. Some confusion with these terms.

Issues in later stage clinical trials: Species metabolite profile is qualitatively similar to the humans metabolic profile.

ICH S9: Human specific metabolite: might not be warranted safety assessed in Phase I ? Unless there is a specific concern?

Toxicology Issues (Single/ Repeat Dose Studies)

ICH M3/ S9

Combinations: When are studies required? Adequacy of the clinical experience? Discussion of the pharmacological rational for the combination? (Clinical Trials, ICH S9)

What is meant by <u>significant</u> clinical experience?

Does this only apply to marketed products (clinical experience)?



AR: No remarkable findings, present as a table.

Established a long time and more consistent approach/ understanding of requirements.

Revision of S2R1 : NO in vitro assay in mammalian cells! In vivo micronucleus test + 2nd in vivo endpoint/tissue (Liver comet assay: preferably as combined study)

SA/ CT Experiences:

Testing of metabolites at sufficient levels/ species. Relevance of any positive findings Justification for any deviations. Testing of impurities at sufficient levels.

ICH S9/ ICH S6: In general not considered to be required

Genotoxic Impurities

Topic under discussion at ICH: ICH M7 Guideline on Genotoxic Impurities

Regular Issues regarding evaluation of GTI's

Application of Threshold of toxicological concern (Single or multiple impurities, Staged TTC) Structure Activity Relationships: In adequate consideration/ discussion Inadequate testing: present in batches, spiked, isolated impurity

Is there a need to revise ICH Q3A and Q3B?



Carcinogenicity Testing:

Guidelines ICH S1 : Established a longtime and considered clear.

Flexibility: ICH S6/ ICH S9 : Not required?

Some issues identified: Need for carcinogenicity studies? ICH S1A Significance of the findings? Adequate testing of metabolites? Relevance to humans? Use of transgenic animals? Timing of submission?

Ongoing Initiatives: Carcinogenicity Testing changing the old paradigm?

•Life time studies?

•Carcinogenicity studies always required predictability from other studies

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•Revision of ICH S1?

Example 1: ICH S1A Note for Guidance on the Need for Carcinogenicity Studies of Pharmaceuticals, states that it is important that the <u>relevant organs</u> for the clinical route be adequately exposed to the test material.

SA: Proposed dermal administration

Available Data: 6-month dermal repeat dose Oral carcinogenicity studies (2 species)

Q : Need for a dermal carcinogenicity study?



Well established for New Chemical Entities and MAA.

Interpretation of the findings/ level of concern. Wording required in the SPC and PIL.

ICH M3: Clinical Trials Inclusion of Women of Childbearing Potential (timing ICH M3).

Why?/ When?/ How?

Pregnancy testing/ reliable use of contraception/ short exposure



Example:

Small molecule, specific immunological target Intended for treatment of Chron's Disease

Q : Given relevant contraception measures advised and supervised: Include WOCBP?

Reproductive Testing: Single embryofetal study in rabbits: No teratogenicity Abortion at all doses (1 LD, 7 MD, 8 HD) PK, TK data

Clinical Experience: FIM multiple ascending dose study Appears to be an inducer of CYP3A4

Proposed: Phase II study: Several dose groups, 8-weeks treatment Inclusion of WOCB potential: Slightly more prevalent in women Develops at young ages



ICH S6: Timing of the Non-human primate developmental studies:

Prior to Phase III or Parallel to Phase III with contraception?

Addendum to ICH S6:

For monoclonal antibodies for which embryo-fetal exposure during organogenesis is understood to be low in humans based on current scientific knowledge, the embryo-fetal development toxicity study can be conducted during Phase III (see ICH M3 (R2)). The completed reports should be available to support submission of a marketing application.

For other biological products where embryo-fetal exposure is demonstrated to be low during organogenesis, the same timing for testing can be applicable.

Where there is embryo-fetal exposure during organogenesis and the product is pharmacologically active only in NHPs and a sponsor elects to use the ePPND study design, an interim report (see note 2) for data to day 7 post-partum for all animals is called for to support Phase III.

This position was being reflected in SA applications prior to the inclusion in ICH S6 R1

Other toxicity studies

Juvenile:

ICH M3/ ICH S6: Identified cause for concern (previous animal or humans data). Area of concern not addressed by the available data on molecule, known class effect.

One relevant species is appropriate: Regional differences.

ICH S9: Not usually conducted to support inclusion of paediatric populations for the treatment of cancer.

If a juvenile study is required:

The primary factors to consider when designing a targeted juvenile animal study in one relevant species, preferably rodent, are: ensure that the organ system of concern is undergoing similar developmental processes during the postnatal period as in the intended paediatric population; define the age of exposure in the experimental species to ensure that the organ systems of concern are at the same stage of paediatric population; and ensure that the appropriate endpoints to enable an in-depth investigation of the organ system of concern are selected. The report should be sufficiently detailed to allow for secondary assessment by other experts.

The report should describe salient findings and especially those deficiencies that justify the questions intended for the applicant. These questions will also be listed in the "overview module" of the assessment.

Critical assessment (e.g. comments on the validity and interpretation of the data, conclusions) should be described in the "Assessor's comments" sub-sections that follow each chapter.

Assessment Report: Generation of Questions: NICE TO KNOW? NEED TO KNOW?



Challenges/ Improving Predictions:

Increased Role of Pharmacogenetics/ Omics Technologies

Data Rich Specialist Expertise Access Agency Resources Interpretations/ Implications

New Approaches:

Increased use of Pharmacokinetic/ Pharmacodynamic Modelling

Non-clinical Biomarkers:

Identification/ Qualification/ Validation/ Translation Use by industry/ Regultors Troponins KIM-1, Urinary Clusterin, b2 Microglobulin

Initiatives; C-Path MARCAR IMI EU FP7 Non-genotoxic carcinogen Biomarkers



Challenges

Animal models of disease New Therapies: Cell, Gene Therapies and Nanotechnologies Reflection paper on non-clinical studies for generic nanoparticle iron medicinal product applications EMA/CHMP/SWP/100094/2011

Excipients: Looking again at the guidelines issues associated with Paediatric formulations

Biosimilars: Testing Requirements in vitro comparability and in vivo PK: Is this sufficient?

•Level of testing required: In vitro/ In vivo (PK/ PD/ Toxicity)

•Presence of an alternative excipient?



Thank you for your attention



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