Regulatory compliance in Non-Clinical development

SME Workshop

Presented by Milton Bonelli on 3 October 2016
Clinical Pharmacology and Non-Clinical Office - Human Medicines R & D Support Division
Contents

1) How to shape a Non-clinical development program
2) Regulatory interactions
3) Our experience so far from non-clinical Scientific Advice and Marketing Authorisation applications
Non-clinical development – overarching goals

- Guide early go/no-go decisions on whether a new potential drug should further progress in development

- Support adequately the design of first-in-human (FIH) administration (and subsequent CTs)
  1. Identify a correct dose range
  2. Inform planning of clinical monitoring
  3. HV/patients and inclusion/exclusion cr.

- Contribute to benefit-risk assessment at stage of MAA

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Non-clinical testing to support First-in-Human

Usually in-vivo studies:

• Biological/Pharmacologic activity
• Pharmacokinetic Profile
• Toxicology testing

Principles:
• Not a “one size fits all”
• Experimental approaches science-based
• Decisions justified and explained in Reg. Submissions
Non-clinical testing to support First-in-Human Starting Points

• Primary and secondary pharmacodynamic properties of the substance can contribute to the safety evaluation (e.g. mode of action, nature of the target, selectivity to targets related/non to intended target).

• Appropriate characterization of primary pharmacology (mode of action and/or effects) in a pharmacodynamically relevant model should be available to support human dosing (e.g. frequency of administration, therapeutic dose range).

• In vitro metabolic and plasma protein binding data – for animals and humans – and systemic exposure data in the NC species.
Non-clinical testing to support First-in-Human Relevant guidance

- **ICH M3 (R2)**
  NC Safety Studies for Human CTs and MA for Pharmaceuticals

- **ICH S6 (R1)**
  Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

- **ICH S9**
  NC Evaluation for Anticancer Pharmaceuticals (for advanced cancer)

- **EMA Guideline on Strategies to Identify and Mitigate Risks for FIH Clinical Trials with IMPs**
### Non-clinical safety testing to support FIH CTs

<table>
<thead>
<tr>
<th>Safety Pharmacology</th>
<th>ICH M3 (R2) – NCEs and Biotech</th>
<th>ICH S6(R1) - Biotech</th>
<th>ICH S9 – Advanced Cancers</th>
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<tr>
<td>Study of CNS, CV and Respiratory functions  “Core battery” – possibly in RDT</td>
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<td>Information on impact on CNS, CV and Respiratory functions - possibly in RDT</td>
<td></td>
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<tr>
<td>Repeated-dose Toxicity (w Toxicokinetics)</td>
<td>Two species (rodent + non-rodent) Study duration equal to dosing in CTs</td>
<td>Depending on availability of relevant species – one or two species Study duration equal to dosing in CTs</td>
<td>Two species (except genotoxic drugs vs rapidly dividing cells – only rodent) Should support Clinical admin. Schedule/exposures</td>
</tr>
<tr>
<td>Genotoxicity</td>
<td>• Gene mutation assay (Single dose trials)  • Chromosomal damage assay (Multiple dose trials)</td>
<td>Not warranted</td>
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</tr>
<tr>
<td>Reproductive Toxicity</td>
<td>As appropriate to the CT population:  • Men and WOCBP – Histopathology in RDT  • Pregnant Women – full ICH S5(R2) battery</td>
<td>As appropriate to the CT population Men and WOCBP – Histopath. in RDT See ICH S6(R1)</td>
<td>Not warranted</td>
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GLP Compliant!
## Non-clinical studies to support Clinical Development

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</table>
| **Repeated-dose Toxicity (w Toxicokinetics)** | Two species (rodent + non-rodent) Study duration equal to dosing in CTs | Study duration based on CTs to support (usually 1-3 months sufficient). Depending availability of relevant species: one or two species. One species justifiable for long-term studies (6-months) | Two species (rodent + non-rodent) 3 month studies before Phase III  
*See ICH S6(R1) for biotech* |
| **Reproductive Toxicity**      | Depending on population and size of trial:  
• M/F fertility before Phase III  
• Preliminary EFD – Up to 150 WOCBP for 3 months  
• Definitive EFD – Inclusion WOCBP | As ICHM3(R2), however if NHP only relevant species:  
• If PP insufficient during Phase III - EFD study or an interim report of an ePPND study during phase III  
• If PP effective – EFD/ePPND study during Phase III | • For NCEs, EFD in 2 species. One study in cases where an EFD study is positive.  
• For Biotech – see ICH S6(R1)  
• NO STUDIES based on Weight-of-evidence approach |
| **Genotoxicity**               | Full Battery as ICH S2(R1) – 2 options:  
Both include bacterial mutation assay + one in vivo mammalian assay | Not warranted | Full Battery (ICH S2(R1)) ahead of Phase II |
| **Carcinogenicity**            | Needed only if cause for concern | Not warranted | Not warranted |

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## NC studies to support Marketing (Applications)

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### Repeated-dose Toxicity (w Toxicokinetics)

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<tr>
<th>Study Type</th>
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| Two species studies (rodent + non-rodent) | a. Use up to 2 weeks - 1 month studies  
   b. >2 weeks to 1 month - 3 months studies  
   c. Chronic admin. - 6 month studies | Depending on avail. of relevant species | Two species (rodent + non-rodent) 3 month studies  
   **See ICH S6(R1) for biotech** |

### Reproductive Toxicity

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| 1 Study for fertility and early development | 2 Embryo-fetal dev. (rodent + non-rodent)  
   1 pre-post natal dev. Study (as ICH S5(R2)) | Depending on availability of relevant species  
   • See ICH S5(R2) if rodents are relevant  
   • If NHP is only relevant: ePPND study + histology evaluation of reproductive organs in RDT | Fertility (M/F) – Histopath. of Reproductive organs in RDT  
   EFD - Two species, one only if positive, or  
   NO STUDIES based on Weight-of-evidence approach |

### Genotoxicity

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| Full Battery as ICH S2(R1) – 2 options: | Both include bacterial mutation assay + one in vivo mammalian assay | Not warranted | Full Battery as ICH S2(R1) – 2 options:  
   Both include bacterial mutation assay + one in vivo mammalian assay |

### Carcinogenicity

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<td>1 Two-year study (rat) + 1 Two-year study in mice or a 6-m study in transgenic mice</td>
<td>Not warranted</td>
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NC studies to support Marketing (Applications)

Also consider (see ICH M3R2):

• Local tolerance
• Juvenile animal toxicity studies
• Immunotoxicity
• Photosafety testing
• Evaluation of abuse liability
• Qualifying impurities and degradants
• Combinations

• Environmental Risk Assessment – as per EMA Guideline
  (EMEA/CHMP/SWP/4447/00 corr 2¹*)

Think 3Rs!
NC development in support of FIH studies

Changes/integrations to relevant guidance

- ICH M3 (R2) - NC Safety Studies for Human CTs and MA for Pharmaceuticals
  Q&A Document present

- ICH S9 - NC Evaluation for Anticancer Pharmaceuticals (for advanced cancer)
  Draft Q&A Document undergoing consultation

- EMA Guideline on Strategies to Identify and Mitigate Risks for FIH Clinical Trials with IMPs
  Currently under revision
European regulatory/scientific guidelines

Clinical development

Pharm  Non-clinical  I  II  III  MAA  Post-mkt

ICH Guidelines

- Stability
- Impurities testing
- GMP
- Carcinogenicity
- Genotoxicity
- Reprotoxicity
- Clinical trials
- Pharmacogenomics

- MedDRA
- CTD
- Electronic Standards

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European regulatory input along drug life cycle

Clinical development
- Pharm
- Non-clinical
- I
- II
- III

Post-mkt
- MAA
- PhV & PSE

MAA

Pharm

Orphan Drug Designation

Innovation Task Force (ITF)

ATMP Certification & Classification procedures

Scientific Advice/Protocol Assistance

PRIME

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SA/PA - Practical considerations

- Have a clear regulatory strategy (MAA type, therapeutic indication)
- Be prepared to disclose and discuss details of your planned pharmaceutical development (e.g. details on planned clinical trials)
- Ask concrete questions and give the company position including detailed plans
- The quality and detail of the answer will depend on the detail of your presentation
- Pre-submission meeting with EMA co-ordinator and EMA experts
SA/PA - Practical considerations

Question x: Does the CHMP agree that/with ...?"

- Conform to scope of the Scientific Advice/Protocol Assistance procedure
- Unambiguous understanding of the question.
- No pre-assessment

Applicant’s position

- Comprehensive justification of the chosen approach.
- ‘Stand alone’ argument.
- Critical discussion on the relative merits and drawbacks of various approaches, possible consequences and eventual measures to ameliorate these.
SA/PA – Non-clinical topics (2015)

- Pre-Clinical Development: 51%
- Carcinogenicity: 4%
- Genotoxicity: 3%
- Chronic toxicity: 7%
- Acute toxicity: 7%
- Repro foetal toxicity: 6%
- Bridging programme: 2%
- Choice of animal model: 4%
- Immunotoxicity: 4%
- Immunotoxicity: 3%
- QT assessment: 1%
- Comparability: 1%

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SA/PA – Non-clinical FAQs

“Does the CHMP agree that the scope of the non-clinical data package is acceptable to support the clinical development and that, if the assessment of these studies is satisfactory, no additional non-clinical studies should be required to support a marketing authorisation application in the EU?”

Consider:

- Requirements for CTs vs MAA
- Proof-of-concept vs Non-clinical Safety package
- Single out specific types of NC studies – Reproductive Toxicology, Carcinogenicity,
- Address directly (by standalone Q) overarching issues in NC development – Species selection, choice of dose levels, RDT study duration, need for combination studies
SA/PA – Further requests for clarification/studies in FAL

SA/PAs in Oncology – 2010-2013

NCEs

- Phototoxicity: 21%
- RDT Design: 20%
- Applicability ICHS9: 10%
- Bridging: 8%
- Combination Study: 6%
- Metabolite: 7%
- Genotoxicity: 7%
- Other: 15%
- Reproductive Toxicity: 6%

Biotechnology-derived

- Reproductive Toxicity: 25%
- RDT Design: 25%
- Species relevance: 19%
- Duration RDT: 13%
- GLP: 6%
- Phototoxicity: 6%
- Immunotoxicity: 6%
- Reproductive Toxicity: 6%

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Marketing Authorisation Applications – Frequent NC issues

Carcinogenicity

Reproductive Toxicity

Teratogenicity

Impurities

Mechanism of action

PK/ADME
Thank you for your attention

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