Lessons learned from pilot CTR:

Tips for applicants

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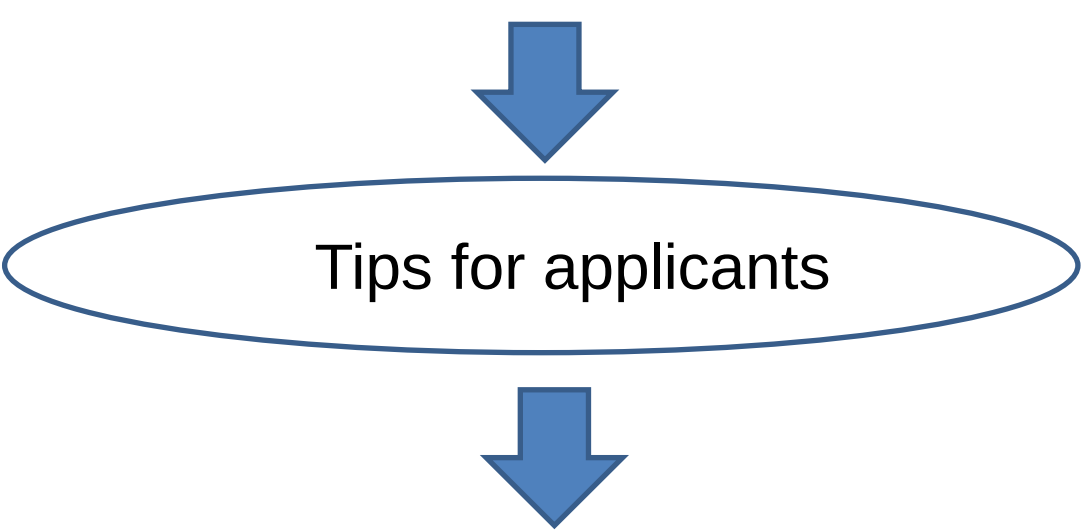
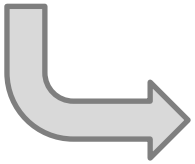
Objective

Based on experience of assessment of CTR pilots (quality, non-clinical, clinical, safety)





Process optimisation within agency

Contribute to a fluent handling of the clinical trial appications

Objective

Based on experience of assessment of CTR pilots (quality, non-clinical, clinical, safety)

- Very little experience with refusal of applications:
  - ✓ Only 4 out of approx. 450 pilots were refused by agency
  - ✓ The reasons for refusal were very specific and different for those 4 cases.
- Experience with:
  - ✓ (avoidable) GNAs/RFIs that come back in different dossiers
  - ✓ Input from collaborators on how assessment could be facilitated

Objective

Tips for applicants

- No detailed guidance
- Based on existing EU / ICH guidelines
- Not an exhaustive list
- Potentially, some may be obvious points for you

General tips

- **Cover letter:** please also indicate the NIMP that are used in the study.

- **Application form**:
  Please ensure that the following sections are accurately completed:
  - D.3.8-3.10 (name substance, strength, etc.)
  - D.9.1-9.2 (QP for batch release)

- Provide a Manufacturing and Importation Authorisation (**MIA**), not a GMP certificate

- For **substantial modifications**, please provide:
  - ✓ Track-changes versions of the amended documents
  - ✓ A summary / list of the changes

Quality

General considerations:

- Please complete all chapters of the IMPD, even if only with "not applicable". This confirms that this chapter was taken into consideration.
- A good summary can be more valuable than a series of complete reports.
- For the Drug Substance part, a simple reference to an ASMF can be sufficient if this ASMF has already been accepted by the Agency as part of another authorized file.

Quality

Other tips:

- In all cases, define a shelf life (or a retest date) for the Drug Substances and the Drug Products.
- Avoid referring to "exotic" pharmacopoeias. If this is not possible, provide a copy of the monograph (in English).
- A discussion of mutagenic (potential) impurities according to ICH M7 is expected (structure, origin, justification for limit).
- A discussion of the potential formation of nitrosamine impurities or their level of presence is expected.

Quality

Please ensure that the following is included in the documentation for ATMPs:

2.1.S.2.2 Description of Manufacturing Process and Process Controls

- A clear description of the manufacturing process (including information on process parameter, IPCs and QC tests including acceptance criteria),
- The manufacturing flow chart

2.1.S.2.3 Control of Material

- Acceptance release testing for starting materials for downstream manufacturing,
- Declaration with respect to compliance with the the guidance on minimizing the risk of transmitting TSE agents is presented for biological raw or a declaration that no biological materials has been used during their manufacturing process,

2.1.S.2.4 Control of Critical Steps and Intermediates

- Specification criteria for IPCs

2.1.S.2.5 Process Validation and/or Evaluation

- Results media fill test and validation of aseptic processing,

Quality

Please ensure that the following is included in the documentation for ATMPs:

2.1.S.3 Characterisation:

- *in vitro* characterization data and summary of methods used during the characterisation studies,
- description of MCB/WCB characterization studies according to Ph. Eur. monograph 5.2.3,
- product-related impurities,

2.1.S.4 Control of the Drug Substance

- justification on the release testing performed on cryopreserved products after their thawing and not before their cryopreservation,
- justification of proposed upper limits for product/process impurities,
- justification for the use of alternative sterility testing methods for cryopreserved drug product instead of the required Ph. Eur. 2.6.1. general chapter,

2.1.P.5.3 Validation of Analytical Procedures

- information on alternative microbiological methods validation,

2.1.A.2 Adventitious Agents Safety Evaluation

- information on the risk assessment performed to evaluate the risk of viral contamination of the drug product,

Non-clinical

General considerations:

Please ensure that **clinical trial protocol** is in compliance with current standards:

- GCP guidance (ICH E6R2), section 6
- EU regulation No 536/2014 (CTR), Annex I, section D
- CTFG guidance (specifically “Recommendations related to contraception and pregnancy testing in clinical trials”).

Please ensure that **investigators brochure** is in compliance with current standards:

- EU Regulation No 536/2014 (CTR): IB prepared in accordance with international guidance
- Structure of Module 4 of the ICH Common Technical Document format recommended

Non-clinical

General considerations:

Regarding **Good laboratory practice (GLP)**, the following is expected:

- A statement on the GLP status of the studies within the IMPD, unless justified
- A summary table with indication if in that period the facility was part of an accepted GLP monitoring programme

References:

- ✓ *CTFG question & answers on GLP*
- ✓ *Eudralex, volume 10, questions & answers*

Non-clinical

General considerations:

Pivotal non-clinical studies conducted in a country which has not joined the **OECD MAD** system may be accepted under the following conditions:

- The test facility was included in the compliance monitoring programme of an EU monitoring authority at the time of the conduct of the study(ies), or,

  has been inspected and acknowledged as being GLP compliant by an EU GLP monitoring authority within 3 years after the completion of the study(ies);

- In both cases, the test facility has been found to be operating in compliance with GLP principles in the concerned area of expertise.

Non-clinical Pharmacology

Primary pharmacodynamics – key questions

- What are the reasons to believe that the product will have therapeutic effects?
- How is the pharmacology of your product translatable to human?
- What are interspecies differences and what is impact on clinical dose?
- Are the in vitro/in vivo PD studies a valid POC for the intended indication/population?

Secondary pharmacodynamics – key questions

- What is the potential for off-target effects?
- What are the consequences in relationship with the planned clinical exposure?
- What are the risk mitigation measures, and specific safety monitoring, if necessary?

Non-clinical: Pharmacokinetics

Reference is made to ICH M3(R2):

In vitro metabolic *and* ***plasma protein binding*** *data* ***for animals and humans*** *and* ***systemic exposure data*** *(ICH S3A, Ref. 7)* ***in the species used for repeated-dose toxicity*** *studies generally should be evaluated* ***before initiating human clinical trials****. Further information on PK (e.g., ADME), in test species and in vitro biochemical information relevant to potential drug interactions should be available before exposing large numbers of human subjects or treating for long duration (generally before Phase III)*.

Points for attention:

- Information on the methods of analysis of the IMP (and/or its metabolites) in animal blood/plasma (validation and sensitivity).
- (For further clinical development) A detailed qualitative and quantitative overview of human metabolites and metabolites formed in test species, preferably in a tabulated format.

Pharmacokinetic drug-drug interactions

Potential for drug-drug interactions

Not fully elucidated at early stage but *in vitro* data (metabolism, inhibition/induction of CYPs, interaction with drug transporters) may be of high relevance

e.g., trial in patients (possible interaction with concomitant medications, background therapies…)

e.g., early phase trial with a combination of new IMPs

If uncertainties:
include appropriate restrictions/recommendations in the protocol

Toxicology

Toxicity studies to support clinical trials

Justification of the relevance the animal species selected for the toxicity studies

General toxicity studies

- NOAEL scientifically justified based on all the toxicological data
- The exposure data (Cmax, AUC) of all the doses tested in the toxicity studies (incl. NOAEL) clearly identified and provided (preferably as tabulated format)
- Exposure multiples (at the NOAEL) in relation with the planned human exposure range (starting - max dose) are expected be addressed
- Thorough justification of starting dose, dose escalation range, maximal dose
- Impact of non-clinical findings on safety monitoring plan

Toxicology

Point of attenton:

Phototoxicity testing

- Initial assessment of the phototoxic potential expected before phase 1
- If assessment of all available data and the proposed clinical plan indicates a potential for a significant human phototoxicity risk: appropriate protective measures should be taken during outpatient clinical studies.
- Before exposure of large numbers of subjects (Phase III), if appropriate, an experimental evaluation (nonclinical, in vitro or in vivo, or clinical) of phototoxic potential should be undertaken.

References:

- ✓ *ICH M3*
- ✓ *ICH S10*

Clinical: Design and plan

- Please provide a **graphical representation** of the overall scheme of the proposed trial
- Ensure that **reference arm** is standard of care, validated by the appropriate guidelines/recommendations or placebo. If medicine has a MA, take into consideration SmPC
- Ensure that **duration** of the study is long enough to have a measurable effect
- **First In Human** (FIH) trials
  - ✓ Sentinel dosing expected
  - ✓ Clear scientific rationale when this approach is not followed
- **Complex integrated trials**

  Criteria to move from one part to another, should be predefined

Reference:
Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products

Clinical: Contraception measures

Reference is made to the CFTG guideline

Recommendations related to contraception and pregnancy testing in clinical trials, version 1.1, adopted 21/09/2020

Please note that a new version (1.1) was published in 2020:

- after the relevant systemic exposure to the medicinal product has ended for **exposure to other types of genotoxicants than aneugenic compounds**, the duration for applying **highly effective contraception** measures for **women of childbearing potential**, has been **extended from 1 month to 6 months** (one folliculogenesis cycle).
- the need for informing participants to seek advice about **donation and cryopreservation of germ cells** in line with this guidance **prior treatment** if applicable, has been added to the section on the need for sexual counseling of study subjects, e.g. in adolescents, which should be reflected in the protocol

Clinical: Data Safety Monitoring Committee

Reference is made to
CHMP guideline on data monitoring committees

Points of attention:

- A justification is expected when no DSMC is set
- Document the responsibilities of DSMC in the specific study
- Document the Members, to assure that they have appropriate qualifications and they have no conflict of interest

Clinical

Other points for attention

Selected dose

- Justification in relation with the previous non-clinical or clinical studies
- Clear description of the dose, frequency of administration, mode of administration
- Clarification dose modification(s) in case of AE/SAE

Please pay attention to:

- Drug-drug interactions
- PK characteristics of specific populations, where relevant

Clear stopping rules should be defined

If **AE** were observed with the IMP in **non-clinical/previous clinical trials**, please describe how they are managed

Safety: Reference Safety Information (RSI)

- Please ensure that the **total number of patients/participants** is given in the reference safety information (RSI)
- Where the IMP is not expected to cause any SARs, e.g. early in the clinical development, a clearly defined section of the IB called RSI should still be present *(see CTR Q&A 7.14).*
- Please use the SmPC guideline to calculate the **frequency of SARs** (Serious adverse reactions) from postmarketing.

Safety: RSI

- Avoid unspecific terms (e.g.“Rash or “Infections”. Please use MedDRA **Preferred Terms**. If there are multiple lower level terms (LLTs) within a single PT, they are all expected *(see CTR Q&A 7.10).*
- Please provide a justification when for including life-threatening SARs, postmarketing SARs and for SARs with n=1,
- Expected **fatal SARs** are not considered acceptable for IMPs with no MA.

Safety

- When an **updated** IB/RSI with **new SARs** is submitted, ensure that:
  - ✓ An updated protocol is submitted which includes risk mitigation measures (RMM) that cover new expected SAR, or
  - ✓ A justification of why such update of the protocol is not necessary (with reference to RMM that are already in place to cover these new expected SARs)

Safety: Major changes to the RSI

Is RSI clearly identified? (cover letter?)

new SARs (risk mitigation measures, B/R update)→check→ protocol needs update?→ if not→ state in the cover letter or in the section close to the RSI

Classification by SOC? SARs presented with PTs?

Frequency-present? Is it based on SARs as assessed by the investigator?

Does it include expected SARs only?Do any SARs=1? Fatal (only for MA in EU)? life-threatening? SARs from postmarketing? Justification provided?

Thank you
for your attention

Contact

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