Rough personal notes Dylan

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**Aim**: (1) summarise source material relevant to parts A-E. (2) Build citation list. (3) Then decide which part to choose for focus.

**Note**: These notes contain snippets from reference material and are not sufficiently re-written for final quoting.

# Assignment

For each part A-E, each individual takes at least 2 points.

# Abbreviations

EMA - European Medicines Agency

EUDRALEX -

ICH -

3R - reduce/refine/replace

MFD - maximum feasible dose

MTD - maximum tolerated dose

PD - pharmacodynamic

PK - pharmacokinetics

# Executive summary.

# Advice to management.

# Part A. Preclinical Plan.

The guidelines can be found in: ***Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals M3(R2) version step 4 2009*** [1] (<https://database.ich.org/sites/default/files/M3_R2__Guideline.pdf>).

You may also choose from S guidance ICH <https://www.ich.org/page/safety-guidelines>

This document provides the recommend international standards for nonclinical safety studies. This process is aimed at satisfying requirements for marketing approval. Typical applications include:

• pharmacology studies,

• general toxicity studies,

• toxicokinetic and nonclinical pharmacokinetic studies,

• reproduction toxicity studies,

• genotoxicity studies and,

• for drugs that have special cause for concern or are intended for a long duration of use, an assessment of carcinogenic potential.

• Several examples are provided where instead a case-by-case approach is more appropriate.

## Aims

• estimate an initial safe starting dose and dose range for the human trials and

• to identify parameters for clinical monitoring for potential adverse effects

• Limited but adequate to characterise potential adverse effects

• The MTD might be tested in a toxicity study but is not necessarily required.

• Limit doses such as MFD or saturation of exposure are discussed.

## Pharmacology studies

The main safety pharmacology studies include assessment of effects on:

• cardiovascular,

• central nervous,

• respiratory systems.

Generally required before human exposure, in accordance with ICH S7A and S7B (Refs. 5 and 6). Additional testing during clinical development. The 3Rs should be respected particularly the use of in vivo testing.

## Toxicokinetic and pharmacokinetic studies

Metabolic and plasma protein binding effects should be assessed In vitro before animal/human studies, for repeated-dose toxicity studies.

Pharmacokinetics (PK) includes:

• absorption,

• distribution,

• metabolism and excretion, etc.

PK should be performed in in test species before large-scale human clinical studies.

As should in vitro testing for potential drug interactions.

Characterise metabolite only with >10% total drug-related exposure and significantly higher than seen during maximum exposure in toxicity studies. Benign metabolites do not require additional testing.

## Acute toxicity studies

Traditionally performed:

• single-dose toxicity studies in two mammalian species

* using both the clinical and
* a parenteral route of administration.

Instead, you may perform:

• dose-escalation studies or

• short-duration dose-ranging studies

with an MTD in the general toxicity test species (Refs. 8 and 9).

If this is done, single-dose testing is not required.

• Can be limited to the clinical route only.

• Allows non-GLP studies if clinical administration is supported by appropriate GLP repeated-dose toxicity studies.

• Lethality should not be an intended endpoint.

• Outcomes of acute tocxicity testing may be used to predict human overdose or risk support for Phase III.

# Part B. Clinical Plan.

For Part B, ICH <https://www.ich.org/page/efficacy-guidelines>

# Part C. Chemistry, Manufacturing and Controls.

For Part C, the EUDRALEX Vol 10:

Requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials - Rev. 2. https://health.ec.europa.eu/system/files/2022-02/mp\_eudralex\_guideline-chemical\_en\_1.pdf

# Part D: Pre-IND Meeting / Scientific Advice.

For Part D, the EMA guidance: Scientific advice and protocol assistance.

https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance

# Part E: Inspection Readiness.

For Part E, the EUDRALEX Vol 10: ANNEX I - Investigator site. https://health.ec.europa.eu/system/files/2018-03/eudralex\_vol10\_chapter4\_guidance-conduct\_annex1\_0.pdf

# Technology review

Lessons learned – an unavoidable biological response, a failure in safety [2].

# Other notes

The entire process can take over 10 years in most cases and cost over a billion CHF [3] (<https://pubmed.ncbi.nlm.nih.gov/32125404/>).

Discussion in CYP screening for drug metabolism.

Discussion on population genetics and ancestry cohort selection.

How to cite guidelines in APA style:

Reference list: Organization That Made the Standard. (year). Title of the standard (Standard No. 1234). Retrieved from http://xxxxx

In text: (Organization That Made the Standard, year).

# References

[1] I. H. T. Guideline, “Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals M3 (R2),” 2009.

[2] G. Suntharalingam *et al.*, “Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412.,” *N Engl J Med*, vol. 355, no. 10, pp. 1018–1028, Sep. 2006, doi: 10.1056/NEJMoa063842.

[3] O. J. Wouters, M. McKee, and J. Luyten, “Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018.,” *JAMA*, vol. 323, no. 9, pp. 844–853, Mar. 2020, doi: 10.1001/jama.2020.1166.