Rough personal notes Dylan

Table of Contents

[2 Assignment 1](#_Toc112271098)

[3 Abbreviations 1](#_Toc112271099)

[4 Executive summary. 2](#_Toc112271100)

[5 Advice to management. 2](#_Toc112271101)

[6 Part A. Preclinical Plan. 2](#_Toc112271102)

[6.1 Aims 2](#_Toc112271103)

[6.2 Pharmacology studies 2](#_Toc112271104)

[6.3 Toxicokinetic and pharmacokinetic studies 3](#_Toc112271105)

[6.4 Acute toxicity studies 3](#_Toc112271106)

[7 Part B. Clinical Plan. 3](#_Toc112271107)

[8 Part C. Chemistry, Manufacturing and Controls. 3](#_Toc112271108)

[9 Part D: Pre-IND Meeting / Scientific Advice. 4](#_Toc112271109)

[10 Part E: Inspection Readiness. 4](#_Toc112271110)

[11 Technology review 4](#_Toc112271111)

[12 Other notes 4](#_Toc112271112)

[13 References 4](#_Toc112271113)

**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.

# Market access.

This is new but now market access experts are involved at the start so that something is not produced which is in accessible in market. e.g. will it be reimbursed.

# 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.