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 parts to focus on. (4) List major documents, everything else is a regular citation.

**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.

Therefore, with all group members we will have at least 10 sections total.

# Abbreviations

EMA European Medicines Agency

EUDRALEX

ICH

3R reduce/refine/replace

MAA marketing authorization application

MFD maximum feasible dose

MTD maximum tolerated dose

PD pharmacodynamic

PK pharmacokinetics

PIP

SME small molecule

NOAEAL

STD10

HNSTD

MABEL

PAD

ATD

# Major reference documents

To do: find the rest, arrange these under 3 headings, add correct bibliography reference.

## Directives (mandatory)

## Regulations (mandatory)

## Guidelines (important suggestions)

ICH harmonised tripartite guideline***: 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>).

ICH ***Safety guideline*** (<https://www.ich.org/page/safety-guidelines>).

***EudraLex clinical trials guidelines***.

ICH harmonised tripartite guideline: ***Nonclinical evaluation for anticancer pharmaceuticals***

***S9 version step 4 2009***.

ICH harmonised guideline: ***Integrated addendum to ICH e6(r1): guideline for good clinical practice*** ***E6(r2)step 4 version 2016***.

EMA Committee for medicinal products for human use (chmp): ***Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials 2006***.

European Comission: ***Guidance documents containing the common provisions on the conduct of gcp inspections by competent authorities of the different member states, Guidance for the conduct of good clinical practice inspections 2008***.

# Executive summary.

# Advice to management.

# Market access.

Market access experts can be involved at the start to assess whether the product will be accessible in the market. e.g. will it be reimbursed such that patients can use it? Marketing authorization application (MAA) is typically after trials but understanding requirements early is a benefit.

# 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 recommended 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. Have we found all metabolites expected in animal/human?

## 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 to a mAb, a failure in safety [2].

The advent and rise of monoclonal antibodies [3].

The safety and side effects of monoclonal antibodies [4].

Monoclonal antibodies - versatile platforms for cancer immunotherapy [5].

Monoclonal Antibodies in Cancer Therapy [6] (same author).

FDA approves 100th monoclonal antibody product [7].

Pharmacokinetics of Monoclonal Antibodies [8].

# Other notes

The entire process can take over 10 years in most cases and cost over a billion CHF [9] (<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] K. Rajewsky, *The advent and rise of monoclonal antibodies*. Nature Publishing Group, 2019.

[4] T. T. Hansel, H. Kropshofer, T. Singer, J. A. Mitchell, and A. J. George, “The safety and side effects of monoclonal antibodies,” *Nature reviews Drug discovery*, vol. 9, no. 4, pp. 325–338, 2010.

[5] L. M. Weiner, R. Surana, and S. Wang, “Monoclonal antibodies: versatile platforms for cancer immunotherapy,” *Nature Reviews Immunology*, vol. 10, no. 5, pp. 317–327, 2010.

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[8] J. T. Ryman and B. Meibohm, “Pharmacokinetics of monoclonal antibodies,” *CPT: pharmacometrics & systems pharmacology*, vol. 6, no. 9, pp. 576–588, 2017.

[9] 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.