eatris

European infrastructure
for translational medicine

# Translational Research Management Manual

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Table of Contents

## 1. List of abbreviations

| | |
|---|---|
| CTA | Clinical trial Application |
| ECTD | Electronic Common Technical Document |
| FTO | Freedom-to-Operate |
| FMEA | Failure Mode and Effect Analysis |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| GSP | Good Scientific Practice |
| IB | Investigator Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IMPD | Investigational Medicinal Product Dossier |
| IMP | Investigational Medicinal Product |
| IP | Intellectual Property |
| OECD | Organization for Economic Cooperation and Development |
| PIs | Principal Investigators |
| PD | Pharmacodynamics |
| PDP | Project Development Plan |
| PDT | Project Development Team |
| PM | Project Manager |
| RM Team | Research Management Team |
| RPM | Research Project Manager |
| SC | Steering Committee |
| SMEs | Small and Medium sized Enterprises |
| SWOT | Strength/ Weaknesses/ Opportunities/ Threats |
| TDD | Toll-Gate-Decision Document |
| TTO | Technology Transfer Organization |
| TPP | Target Product Profile |
| QA | Quality Assurance |
| RA | Regulatory Affairs |
| WBS | Work Breakdown Structure |
| WP | Working Package |

## 2. Introduction and How-To

The aim of the EATRIS Research Management Manual is to provide general guidance on how to structure and run a translational research project, from project initiation to project closure, to optimize the translational feasibility of your project. It also provides the necessary tools and templates, based on best practice experience and established project management methodologies. More in-depth guidance on project management can be found at the Project Management Institute (https://www.pmi.org). You can also refer to the PRINCE2® which is a process-based method for effective project management which provides qualification that will equip you with the fundamental skills needed to be a successful project manager (https://www.prince2.com).

This Research management manual describes the rules and procedures that are required to successfully conduct translational research projects. Depending on the nature and the complexity of a given project, an increasingly complex and thorough project planning is required.

### How to use this manual:

This research management manual is intended to serve as a:

1. Glossary of terms to define a common understanding for the rules and responsibilities of different project roles and functions
2. Guideline on how to successfully initiate, plan, conduct, and finalise translational research projects
3. Toolbox for a set of templates and procedures to be used when setting-up and while a research project develops. Here, not all tools are mandatory for all types of projects but it is recommended to make use of the suggested templates when required
4. Reference guide for the minimally required quality standards as defined by European and international guidelines

## 3. Research Project Management

The Research Management manual is made for Users from academia, start-ups, Small and Medium sized Enterprises (SMEs) or non-profit organizations and who are active in research and development of innovative pharmaceutical products with projects starting in basic research and developing it up to clinical proof of concept. The research & development projects can be at different stages of development. To highlight this, the following scenarios of projects are given in Table 1 with recommended steps, quality standards and templates to follow according to the different project phases:

1. Scenario 1: Full scale development of a medicinal product covering late basic research stage up to clinical phase II testing, 4-6 years duration, academic research centre as User.
2. Scenario 2: Complete nonclinical development program for a small molecule, 2 years duration, SME company as User.
3. Scenario 3: Performance of a preclinical model as pharmacodynamic assay as part of the development of a gene therapy, 1 year duration, academia as User.

The following table gives the aspects and templates described in the manual used for the respective project:

**Table 1: Project Development Scenarios**

| RM-Manual Item | | Scenario 1 Full scale dev. | Scenario 2 Nonclinical development. | Scenario 3 Preclinical study |
|---|---|---|---|---|
| **Applicable Quality Standards** | | GSP, GMP, GLP, GCP | GSP, GLP | GSP |
| **Project Preparatory Phase** | Project Proposal | X | X | X |
| | Project Decision | X | X | X |
| **Project Initiation** | Development Plan | X | X | |
| | TPP | X | | |
| | Kick-off | X | X | |
| **Project Implementation** | Contracts | X | X | X |
| | Workshop | X | X | |
| | Work structure | X | X | |
| **Project Realization/ Conduct** | Team meetings | X | X | X |
| | Work packages | X | X | |
| | Milestones | X | X | |
| | Toll Gates | X | | |
| | QA-Audits | X | X | |
| | Project Reports | X | X | X |

| | | | | |
|---|---|---|---|---|
| **Project Close-out** | Close-out Meeting | X | X | |
| | Final Report | X | X | X |
| | Archiving | X | | |
| | Hand-over | X | | |

GCP: Good Clinical Practice, GLP: Good Laboratory Practice, GMP: Good Manufacturing Practice, GSP: Good Scientific Practice, QA: Quality assurance, TPP: Target Product Profile.

## 3.1. Aim and Objectives of the Research Management Team

In order to manage the development project cost- and time efficiently and with pre-defined quality standards the Research Management Team (RM Team) has to:

1. Ensure that translational R&D programmes enter the clinical phase timely, cost efficiently and with a higher probability of success.

2. Provide procedures and tools to support the development process in a quality-driven manner.

3. Perform multi-project management: Provide procedures and tools to enable decision makers to prioritize the project portfolio and to make decisions concerning conflicting resource allocation.

## 3.2. Critical Success Factors for Successful Research Management

In order to establish the RM Team as cross-functional team that enhances the development process, it is crucial to obtain the commitment by the line functions (centre managers or Principal Investigators (PI)) to abide to the target-oriented, milestone-driven project planning. Furthermore, a clear understanding of the goals of each development program and an open and goal-oriented communication within and between development teams is crucial for the success of development projects. Also, it is required that the parties involved adhere to documented decisions and follow the rules that were agreed upon.

## 3.3. Definitions

Below you will find a list of commonly used definitions and terms that you may encounter when managing a project. These terms will help you and your project team to standardize the running of your project, be more organized, have a clearer vision on how to achieve your goals and have a stronger sense of what needs to be done by

whom and when. Be mindful of the fact that some people or organisations may use different wording for organising their project plan, according to their needs.

**Deliverable:** Deliverables are additional outputs (e.g. information, special report, a technical diagram brochure, list, a software milestone or other building block of the project) that must be produced at a given moment during the action (Milestones are, by contrast, control points in the project that help to chart progress).

**Failure Mode and Effect Analysis – FMEA**: The failure mode and effect analysis (FMEA) are an *ad hoc* risk analysis tool wherein all project-related risks are listed and reviewed in terms of their severity, probability of occurrence and probability of detection. When assigning arbitrary numbers to these parameters, the product resulting from them gives a *risk prioritization number* that in turn allows the classification of risk. Early risk mitigating actions will lower this number and therefore minimize the associated risk.

**Milestone:** A milestone is an event of special importance. Milestones are predefined, important incidents during project conduct with special interest to the project, the user or the project organization. Milestones represent the project situation and mark a key development stage at a given time point.

**Project:** A Research project is an undertaking defined by a unique goal and it is limited concerning resources, budget, time, etc. A research project always allows differentiation against other undertakings and is characterized by a specific project organisation.

**Technology Transfer Organisation – TTO:** A technology transfer organization (TTO) is associated to an academic institution and dedicated towards the identification, securing Intellectual Property (IP), and commercialization of academic research results. TTOs act as information brokers between academic research groups, patent attorneys, and commercially focused parties (e.g., venture capital, biotech, Pharma companies, etc.).

**Toll-Gate:** Toll-gates are similar to milestones since they reflect an important event during the course of the project. Toll-gates, however, are critical events that need special attention of and go/no-go decision-making by the User, the Steering Committee (SC) and other stakeholders because the fulfilment and approval to continue the project has significant impact on time and resource allocation for the next project phase. It is therefore required to prepare a Toll-Gate-Decision Document (TDD), summarizing the work performed to date and describing the planned work (incl. budget, resources, risk, and deliverables) until the next toll-gate. Examples for toll-gates in pharmaceutical development are:

- Progress a lead candidate to in vivo preclinical studies
- Initiate the nonclinical development programme, incl. GMP-production

- Initiate clinical phase I (first-in-man) studies
- Initiate clinical phase II (efficacy in target population) studies
- Initiate clinical phase III (pivotal) studies, incl. full GMP-process validation and manufacturing of GMP-validation batches

**Work Breakdown Structure – WBS:** The work breakdown structure (WBS) is an overview of the major project activities in a structured manner. Depending on the nature of the project the WBS may be based on organisational, process, or other procedural parameters. The WBS structures shall describe the time-, and organizational aspects of the overall project. The WBS is therefore structured into and is described by sub-projects and working packages. Sub-projects are broken down further to result in WPs with clearly assigned responsibilities are defined.

**Working Package - WP:** A working package (WP) is a defined unit for assigning work to a responsible party. During project planning and project implementation, it is the RP manager's task to break down the project plan and assign responsibilities to the single WPs. This breakdown process is documented in the work breakdown structure. This term could be aligned or overlap with the Work Package definition used in large EU projects and consortia.

## 3.4. Governance and Responsibilities

Good project management relies on a clear governance structure, identifying the responsible parties for the advancement of the project. Below you will find a list of entities that can be part of such a governance structure, describing the roles and responsibilities in the decision making process, which can be tailored to the needs of a project.

**Sponsor:** The Sponsor provides the necessary (financial) resources to the project and therefore makes the ultimate decisions based on the project-related reporting by the research project manager. In large EU funded projects, this person or entity is often called the Project Coordinator who is executing the project on behalf of the European Commission. The Sponsor approves the research project manager and decides on relevant centres involved in a project. In the context of clinical trials, a sponsor is an individual, company, institution or organization which takes responsibility for the initiation, management and/ or financing of a clinical trial. In regulatory terms, the sponsor is defined as the party who submits a marketing application to the regulatory authorities for approval of a medicinal product or device.

**Research Project Manager – RPM**: The research project manager (RPM) is empowered by the Sponsor to act on its behalf. The role of the RPM is to coordinate and lead the project. Therefore, the RPM's tasks are mainly:

- Management of the overall project coordination
- Clarify the project infrastructure
- Responsibility for the project definition and initial project planning
- Responsibility for the detailed project development plan (PDP)
- Responsibility for the toll-gate decision document (TDD)
- Responsibility for the final report
- Continuous project controlling during project conduct
- Supporting the steering committee, and key project members (Project managers, experts, etc.) to enable
    - Change management and control
    - Budget and resource controlling
    - Continuous reporting to stakeholders

NOTE: The RPM has the responsibility to report to key project members when projects fail to meet scientific and/or operational criteria to warrant continuation or to stop the projects early. This will allow to reposition the projects and the resources early on.

**Project Manager:** If required, a project may be subdivided into less complex sub-projects or tasks. The Project Manager (PM) is a dedicated expert, located in one of the centres in case of a multicentre research project, where a sub-project is conducted, and the PM reports on a project-basis to the RPM.

**Team Member:** A team member is an expert who is assigned to work and complete a dedicated WP. Team members are located in the centres that shall have the capability to operationally work on an assigned WP. The main tasks are:

- Operational execution of project activities
- Participation on project team meetings and pro-active information to the RPM
- Participation on the project reporting (giving content)
- Participation on other project-related activities, e.g., workplan monitoring, risk analyses, budgets, etc.

**Project Development Team – PDT:** The project development team (PDT) is a condensed group of experts (approx. 5 – 7 team members) mainly dealing with the establishment of the PDP. The PDT consists of

- The responsible RPM

- Experts playing a key role in the project-to-be-planned. Here, at least one nonclinical expert and one clinician shall be part of that team.
- Quality assurance (QA) and Regulatory Affairs (RA) experts may be of importance to the project

**Steering Committee – SC:** Complex development projects may involve many participants and stakeholders. To coordinate the numerous and sometimes diverging interests all projects might need a steering committee (SC).
A steering committee may be initiated, consisting of:

- Responsible RPM
- Expert or representatives of expert groups as required (and depending on the project status)

The SC may assume the following roles and responsibilities:

- Participation and approval of project goals, definition of scope/not-in-scope of the project
- Approval of the PDP
- Approval of resources/ budget
- Approval of toll-gates (sign-off)
- Decision on and approval of major changes in the project (i.e., significant budget exceedance, change in project goal, etc.)

## 4. Conducting a Research Management Project

In general, research projects can be organized into five main phases: i) the project preparatory phase, ii) the project initiation/planning phase, iii) the project implementation phase, iv) the project conduct phase, and v) project closure (see Figure 1).

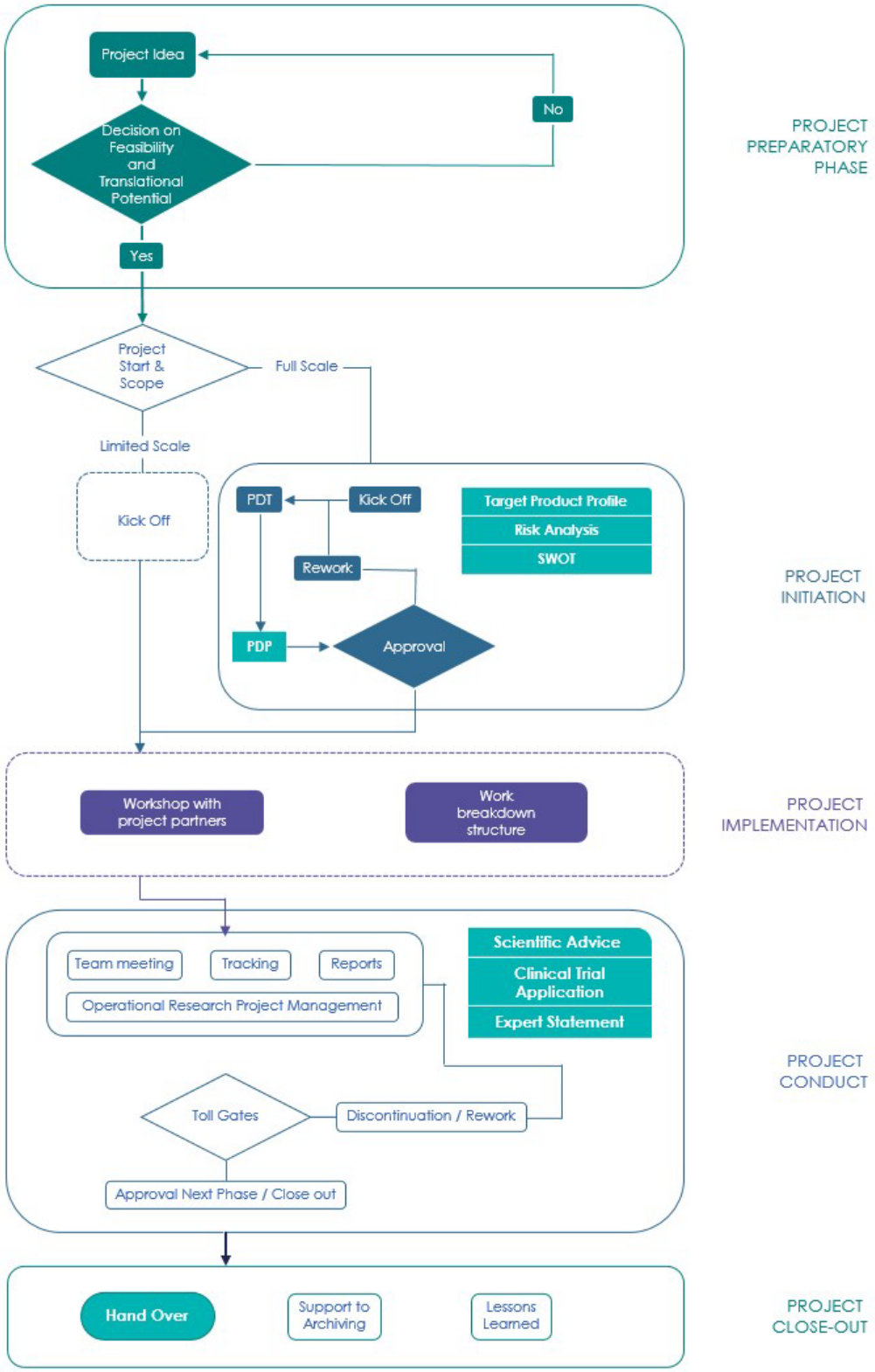


**Figure 1: General Outline of a Research Management Project**

PDT: project development team, PDP: project development plan

Items highlighted in teal are key documents in the process of R&D

Depending on the nature and development status of the product candidate, the project conduct phase can be further distinguished into several development steps and required safety studies. Figure 2 shows examples of those steps for the development of a new chemical entity development (Fig. 2a) and for the development of vaccines (Fig. 2b). In the following, the general rules, and principles for initiating, conducting, maintaining, and completing the project in the respective phases are outlined.

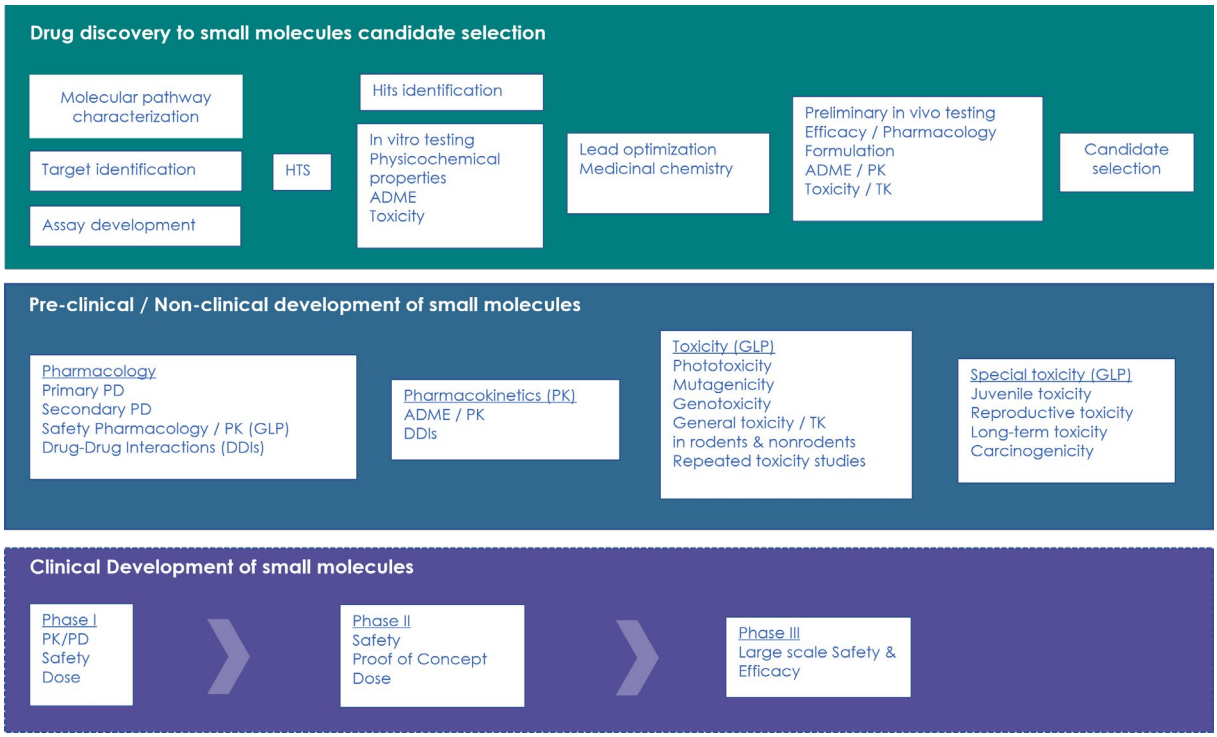


**Figure 2a: New chemical entity development – typical working packages**

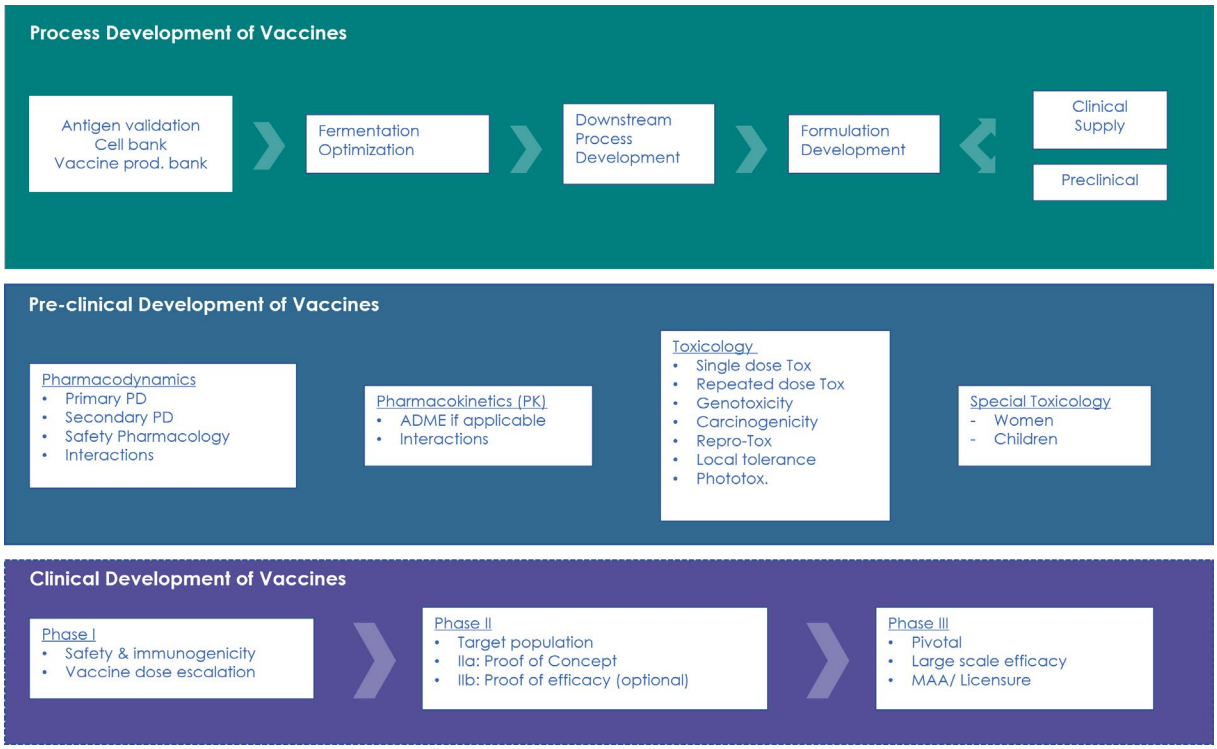


**Figure 3b: Vaccine Development – typical working packages**

## 4.1. Project preparatory Phase

Before starting a project:
1) Ensure that the project is matched to top quality infrastructures with precisely the expertise and facilities required to undertake the proposed activities. This includes non-academic expertise, such as regulatory affairs, product development and business development.

2) Ensure that the project displays high translational potential with a significant expected impact on patient health.

**Translational and patient benefit potential** can be reviewed using four criteria:

- Clear unmet medical need and potential impact on public health (cost-) effectiveness
- Innovative character (no 'me-too' products)
- Clear end-product in mind
- Clear intellectual property position (preferably but not necessarily based on patents) - if rare/neglected disease then prospects for alternative development financing must be in view.

Review of the translational potential and patient benefit of a project can be conducted by external reviewers in conjunction with the Sponsor and related TTO. This is to prevent any potential conflicts of interest.

**Researchers** are encouraged to start thinking more about the process-orientation and goal-directed actions needed to successfully translate their research into development products.

**Define activities:** Once a proposal has the potential to be translational and to benefit the patient, the steps required to reach the intended level of development need to be defined. For each step, specify activities and expertise that are required.

**Perform gap analysis/assemble the team:** Create a list of experts capable of undertaking each activity and ascertain their interest and commitment to the project. Check the feasibility and availability of both the expert and the facility. Assemble the group and engage in detailed discussions on content (after signing of a multi-way Confidential Disclosure Agreement), budgets, timelines and deliverables begin.

**Exploratory phase:** During this phase a project plan is drafted. The duration of this phase will be variable and is dependent on the complexity of the project.
This phase will result in the signing of a Project Agreement, detailing the research activities, duties and obligations of each participant, and the financial arrangements, including nature of the treatment of intellectual property.

**NOTE:** For those projects of sufficient complexity and duration to warrant dedicated project management capacity, the project manager could be sourced from an external organization, such that there is a reduced incentive to prolong projects that fail to meet scientific and operational criteria to warrant continuation.

## 4.2. Project Initiation/Planning Phase

When the project has been prepared, the inauguration of the responsible research project manager (RPM), and project development team (PDT) and the following activities are recommended:

- filing a full target product profile (TPP),
- filing a full project development plan (PDP).

To pursue with a detailed project planning additional information may be gathered by involving external consultants and scientific experts in order to gain an optimal insight to the proposed endeavour.

### 4.2.1. Target Definition or Target Product Profile – TPP

When planning a full development program, a thorough analysis of the final goal is crucial to all subsequent planning steps. Therefore, the future properties of the final product may be evaluated when initiating the project. The properties are summarized in the so-called target product Profile (TPP). The TPP summarises the drug development program in terms of the future product label. It is prepared by the RPM together with the PDT. The TPP is also a living document evolving and maturing with increasing knowledge and experience.
An example for a TPP is given in Appendix 1. Herein, the TPP explores three scenarios, i.e., Target-, Minimal- , Optimal scenario and estimate (for each indication/scenario).

The TPP may be initiated by the user if desired and the establishing/compilation process shall be led by the RPM together with the PDT. It is recommended (but not required) to generate a TPP for complex development programmes.

### 4.2.2. Reverse Planning Process

A "reverse-planning process" is conducted to obtain an in-depth overview on the required steps of a given development project.
Herein, the PDT utilizes the TPP and then plans "backward" the primary clinical outcomes of the pivotal trials, the "label content" to plan clinical phase II, phase I, and nonclinical study requirements and critical success factors for each phase (see Figure 3). With this information in hand the requirements for manufacturing and quality can be deduced (e.g., the amount of clinical trial material needed for the respective development phases).
A template for the reverse planning process is given in Appendix 2.

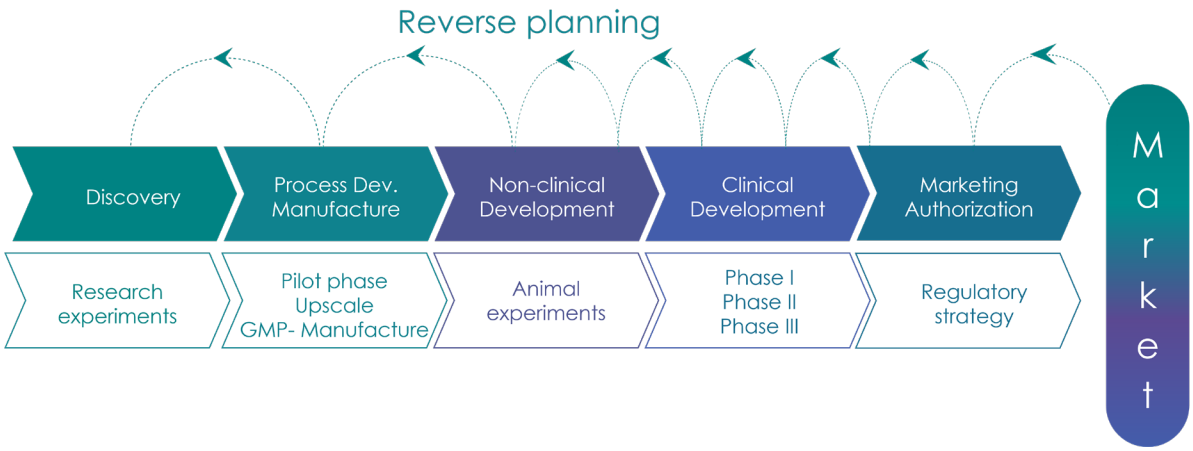


**Figure 4: Backward Planning Scheme**

### 4.2.3. Project Kick-Off

After acceptance/release of the PDP and installation of the RPM, the project is still in an infant planning stage. It is therefore recommended to conduct a project kick-off meeting inviting *all* relevant contributors that are participating on the project. A project kick-off meeting aims at:

- Presentation of the project organisation
- Presentation of the project infrastructure
- Definition of specific rules ("Dos and Don'ts") for the project conduct and working together
- Detailed planning of the working packages and tasks for the individual team members

### 4.2.4. The Project Development Plan (PDP)

The PDP is the major description and planning document for complex projects and the basis for all further planning and implementation steps. Also, the PDP is an essential part of the individual project agreement and therefore has legal implications between the project partners.

A template for a PDP can be found here. In the following, the relevant sections are described, and reference is made to additional tools and templates, key sections of a PDP are highlighted below:

| The Project Development Plan – Relevant sections |
|---|
| Executive Summary<br>The Executive Summary highlights the key issues of the project. |
| Definition of Scope / Not-in-Scope<br>A brief description of what is *not in the scope* of the project should be included here to keep focus during the project execution phase. |
| Scientific Background and Competitors<br>this section, the scientific background and its applicability for bringing a new target/antigen/molecule into the clinics is described in detail.<br>Relevant existing products on the market as well as competing technologies and products under development is described (a summary using a tabular format is helpful). The anticipated advantages of the new approach against competitors will be highlighted. |
| *Intellectual Property Situation* |

Existing intellectual property (IP) in the form of patent, patent applications, copyrighted material, brand names/trademarks assigned, etc., is briefly described together with outcome of an initial freedom-to-operate (FTO) analysis to assess possible competing/hindering IP. A full FTO analysis by an expert (patent lawyer) is not required at this stage but should be conducted latest prior to entering the clinical phase.

*Stakeholder Analysis*

A stakeholder analysis helps identify and classify the stakeholders involved in the project, thus enabling the RPM and the team to optimally address individual expectations and needs. The following steps are suggested to successfully conduct a stakeholder analysis. Make use of the stakeholder analysis template in Appendix 3:

1. Identify the stakeholders of the Project. Identify all persons/organizations that take part or have influence on the project.
2. Determine the stakeholder's type of involvement. Individual stakeholders may have different (and even conflicting) roles in a project. Assign roles (e.g., project manager, team member, SC member, consultant, interested party, etc.) and responsibilities (e.g., planning, decision-making, execution, information-only) for each stakeholder.
3. Estimate the stakeholder's impact for the project. Determine the individual impact of each stakeholder; a "High-medium-low" classification is suitable here.
4. Determine the individual interest to the project. Different stakeholder will have diverting interests in their work and in the project in particular.
5. Determine the individual needs and requirements of each stakeholder. The different stakeholder will have different needs, requirements and expectations in the project (e.g., a user's representative may have a fast access to market in mind, whereas a team member may be interested in scientific publications).
6. Address the individual needs and formulate possible actions for addressing them.

*Strength/Weaknesses/Opportunities/Threats (SWOT) and Risk Analysis*

A so-called "SWOT analysis" shall be conducted to characterize the project and to identify possible weaknesses at the beginning.

In the SWOT analysis matrix displayed in Figure 4, the project-intrinsic characteristics ("Strengths and Weaknesses") and extrinsic properties ("Opportunities and Threats") are tabulated.
A risk assessment procedure shall be included when planning the development project to identify, prioritize, and plan mitigating actions against risks. A simple and straightforward tool for assessing project development risk is the failure mode and effect analysis (FMEA) applying three successive steps:

1. Identify and list project risks. The project team identifies project risks (for example utilizing a brainstorm technique).
2. Evaluate Risks. The identified risks are evaluated concerning severity, occurrence, and detectability. These parameters may be prioritized using a number system (1 – 3,

1 – 5, or 1 – 10). The product of the three parameters gives an overall "risk prioritization number" allowing for an overall prioritization of the risks.

3. Plan mitigating actions. For all risks with a certain priority (as assessed during the evaluation process) mitigating actions and counter measures shall be assigned.

The results of an FMEA may be summarized in an appropriate template as outlined in Appendix 4.

| | *Helpful* *for achieving the objective* | *Harmful* *for achieving the objective* |
|---|---|---|
| ***Internal Origin*** *(organisational)* | ***Strengths*** | ***Weaknesses*** |
| ***External Origin*** *(environmental)* | ***Opportunities*** | ***Threats*** |

**Figure 4: A SWOT analysis matrix**

*Working Package Definition*

Based on the overall objectives and the medical indication that is described in the scientific section the necessary steps are planned in detail. As outlined in Figure 2 certain working packages and non- clinical studies are mandatory to apply for a clinical study and should be considered when planning the overall program.
Examples for working packages are shown below and these must be adapted according to the specific development requirements for each product type (small molecules, ATMPs and biologics, vaccines, imaging tracers, biomarkers) to ensure regulatory compliance:

1. Research & Process Development

    1.1. Proof-of-Principle studies (incl. MoA, exposure-response relationship)
    1.2. Technical feasibility studies (incl. reproducibility)
    1.3. Pilot scale manufacturing

2. Quality & Manufacturing

2.1. GMP Manufacturing development process
  2.1.1. Definition of critical manufacturing steps
  2.1.2. Definition of critical intermediates
  2.1.3. Virus safety studies (if applicable)
2.2. Release assay development
2.3. (preliminary) Definition of release criteria (and specifications)
2.4. GMP Batch manufacturing
  2.4.1. Bulk Production
  2.4.2. Filling, labelling, packaging
  2.4.3. QC Testing and Release as clinical trial material
  2.4.4. GMP Batch record review

3. Nonclinical Development

3.1. Pharmacodynamics studies
3.2. Pharmacokinetics studies
3.3. Safety pharmacology studies
3.4. Toxicology studies
3.5. Special Toxicology studies

4. Clinical Development

4.1. Clinical phase I studies in healthy volunteers
  4.1.1. Legal sponsor definition
  4.1.2. Study synopsis, protocol
  4.1.3. ICF
  4.1.4. Monitoring
  4.1.5. TMF Handling
4.2. Clinical phase II in patients showing efficacy
  4.2.1. Management of multi-site studies
  4.2.2. Pharmacovigilance
4.3. (Pivotal) clinical phase III in patients showing safety & efficacy
  4.3.1. Management of multi-site /multi-national studies

5. Regulatory Affairs

5.1. Scientific Advice/ Protocol assistance (if applicable) or other regulatory interactions such as ATMP classification, Qualification of novel methodologies for medicine development, Health Technology assessment or other regulatory support tools available at EMA
5.2. Clinical trial Application (CTA) and essential documents for the conduct of a clinical trial such as IMPD (see Appendix 5), IB (Appendix 6), study protocol, ICF, and the IMP release certificate.
5.3. Marketing Authorisation Application dossier / electronic Common Technical Document (eCTD)

The EMA's glossary of regulatory terms gives definitions for the main regulatory terms used on this website and in EMA documents.

*Definition of Milestones / Timelines*

Based on the working packages that have been identified and planned in the previous section appropriate milestones and timelines for accomplishing the milestones needs to be established.
In order to facilitate the timeline planning for complex projects the use of computer software is advised (e.g. Microsoft Project®). These software programs also allow for easy and quick visualization of milestones/timelines and their interdependencies ("Gantt-chart").

*Resource Planning*

Based on the above-described working packages, milestones, timelines, the financial planning is feasible. Appendix 7 gives an example for a simple budget planning Microsoft Excel sheet.

## 4.3. Project Implementation

The project implementation mainly includes specific workshops at participating labs/facilities and signature of *project-specific contracts*.

### 4.3.1. Work breakdown structure (WBS)

In order to define the individual work packages for the participating labs and facilities the use of a *work breakdown structure (WBS)* is highly recommended. The WBS can be prepared using the overall working packages as defined in section 3.2.4.7.
A general outline for a WBS is given in Figure 4 below. Importantly, a WBS is an accumulation of work packages, successively defining it into smaller units. A WBS specifies what will be done, not how or when. It is therefore not a project plan or a schedule. A WBS per se is not an organizational hierarchy, although it may be used when assigning responsibilities.
When preparing the WBS, the RPM will, together with the project team:

- Break down the working packages into smaller work units to the level of single deliverables
- Include *all* work packages/activities that might come up in the project (100% rule)
- Assign a work package to only one responsible person. In case more than one person appears responsible, break-down the work package further (mutually exclusive elements)
- Plan for results, not activities (for example, the deliverable of a nonclinical study is a signed study report, not the study conduct itself)

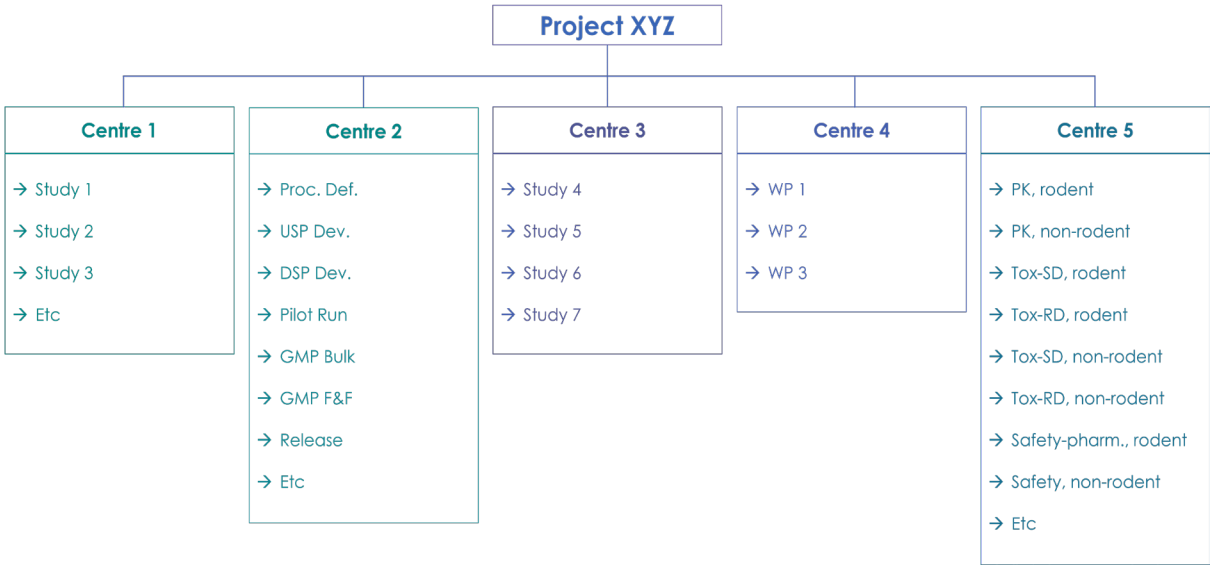


**Figure 5: Work Breakdown Structure – WBS**
An example for an organisational WBS, based on division by centres is given.

A WBS can be prepared using project management tools
6

## 4.4. Project Conduct

In the project realization or project conduct phase, the agreed working packages are executed by assigned study sites. To effectively control and manage the project progress, the (R)PM makes use of a number of project management tools. These tools are described in detail in the following sections.

### 4.4.1. Team Meetings

Team meetings are the essential tool for the (R)PM to steer the project and to manage timelines and cost. Team meetings allow dedicated information exchange of the (R)PM with the team members and among the team members. However, meetings should be limited to the minimum and conducted efficiently. Good preparation and adherence to the agenda is key here.
Team meetings are scheduled by the (R)PM, ideally on a fixed schedule (weekly, bi-monthly, etc.) and discussion topics are fixed through an agenda that is distributed upfront. A template for a meeting agenda is given in Appendix 8.
The (R)PM leads the meeting and takes care of minutes (although that may be delegated to team members, also on a rolling basis). Critical issues may be discussed in the beginning and for complex topics a time limit for discussion may be assigned upfront.

For every project meeting:

- Assigned tasks and scheduled timelines will be checked for the actual status. Unresolved tasks will be documented in the meeting minutes (allowing continuous control of assigned tasks)
- The meeting agenda items will be discussed; new tasks will be assigned and documented.

Meeting minutes will be prepared for every meeting according to a template (Appendix 9) and made available to all participants of the meeting. Additional information or documents may be added as appendices.
The guiding principle is: *"No meeting without agenda and minutes"*

### 4.4.2. Project Documentation Checklist

To have an overview and to keep track with the status of the documents, a project documentation list is maintained by the (R)PM. In this list the essential documents with initiation (drafting) date, finalization (sign-off) date, and potential changes are compiled. A template for this checklist is given in Appendix 10.

### 4.4.3. Project Reports

Team Members, steering committee members and other stakeholders are regularly informed by the RPM. The reporting, given at least monthly, is standardized to allow for a quick and efficient update of the parties involved and to provide key information to them.
In Appendix 11, a project reporting template is given. Herein, the main information needed to reflect the conduct of the project is included:

- Overall project status (Traffic lights system; green, amber, red)
- Brief description of the project activities
- Brief description of the planned activities until the next report
- Next milestones and decision points
- Statement on budget spent/planned and resource allocation
- Dated signature by the responsible (R)PM

### 4.4.4. Toll-Gates

During complex development programs a number of critical milestones shall be predefined, termed "Toll-Gates". Toll-gate shall be predefined in the Project Description (PD) or Project Development Plan (PDP), but typical toll-gates in drug development would be:

- Entering formal (GLP) nonclinical studies
- Initiating a GMP-compliant production campaign

- Entering clinical phase I (First-in-Man)
- Entering clinical phase II (patients)

Typical toll-gates require the decision upon entering the next phase which involves a significant portion of financial resources and project risks. Therefore, the toll-gate is connected with a formal release procedure by the SC.
The RPM prepares, together with the team, a toll-gate decision document (see Appendix 12 for a template), in which the relevant findings, study results, and experiences of the past development efforts are summarized. Furthermore, the planned activities until the next toll-gate, project risks, and resources are described in detail.
The RPM will present this decision document to the SC and the SC will decide and give written consent to the decision document.
The toll-gate approval process itself is part of the project risk management based on a transparent and well-defined decision-making procedure.

## 4.5. Project Close-out

The project finalization phase involves several close-out activities with the aim to transfer a complete and concise data package to the User/Sponsor. Usually, the project finalization is the most challenging project phase because it faces multiple challenges:

- Team members may already be involved in other projects, so they do not have the required priority to follow-after the project finalization activities
- The circumstances/aims for finalizing and handing-over are not clear, resulting in "never-ending" project activities.
- Projects are somewhat "put to rest" without clear priority
- No budget is allocated for project finalization activities

It is the RPM's tasks to plan and to involve all relevant parties to facilitate a proper project close out.

### 4.5.1. Close-out Meeting

The Project close-out meeting has the same importance as the project kick-off.
Here, all relevant parties meet and initiate the final report, which is prepared by the RPM. During the project close-out the following topics should be discussed:

- Overall impression of the project
- Accomplishments: Working packages, studies, timeline- and budget-adherence
- Discussion of "open issues" and definition of follow-up activities
- Lessons-learned: "What was good? What can be improved in the future? How should it be improved?"

- What results are eligible for further exploitation and sustainability after project close-out, to maximise impact of the overall project.

The topics above will constitute the final report (see Appendix 13).

### 4.5.2. Final Report

The final report will be prepared by the RPM and will be approved by the User. Upon approval, the project is formally closed.

# 5. Key aspects for Translational research projects

## 5.1. Quality Standards of Pharmaceutical Development

In pharmaceutical development, science is officially regulated by law concerning research in the areas of quality (development of manufacturing techniques and actual manufacturing of medicinal products according to Good Manufacturing Practice), safety and efficacy (nonclinical and clinical research according to Good Laboratory Practice and Good Clinical Practice). For basic research, e.g., discovery, pharmacodynamic and pharmacokinetic properties of a compound, no official regulations "by law" are available. However, Funding Agencies, academic facilities (e.g., Universities, Centres, Institutes or Working Groups) and other extramural bodies often have own sets of regulations under the label of Good Scientific Practice (GSP).

Figure 6 lays down the standards applicable for every phase of development.

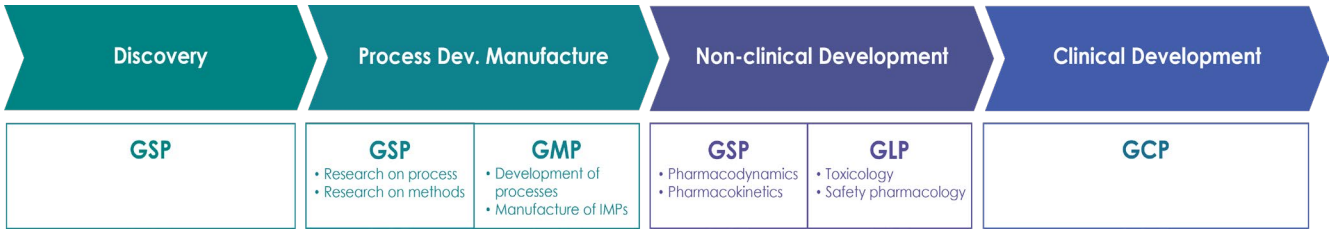


**Figure 7: Development chain and Quality Standards.**
GSP: "Good Scientific Practice"; GMP: Good Manufacturing Practice; GLP: Good Laboratory Practice; GCP: Good Clinical Practice

Appendix 14 focusses on major aspects and the applicability of these standards.

## 5.2. Patient engagement

For translational medicine to succeed, the research and development ecosystem must strive towards more responsible research practices, ensuring the involvement of all relevant stakeholders. Most importantly, this includes the patients who ultimately benefit from research. To reach societal impact, it becomes increasing important to engage with patients in research in a meaningful manner. To encourage fruitful, sustainable and enduring partnerships between scientists and patient organisations, co-leading the way for systematic patient-centered research, a short guide on patient partnerships in rare disease research projects has been developed by the European Joint Programme for Rare diseases. The guide describes the role and added value of patient partnerships in research proposals and aims to foster a partnership culture and contribute to an improved understanding of the added value of patient engagement and involvement in basic, pre-clinical, translational and social research for the Rare Disease Community in Europe and beyond

## 5.3. Data management

There is growing interest in the degree to which digital resources adhere to the goals of FAIR – that is, to be Findable, Accessible, Interoperable, and Retrievable by both humans and, more importantly, by machines acting on behalf of their human operator. In consortia that aim to generate or collect data, or that require resources to be Findable, Accessible, Interoperable, Reusable for humans and machines (FAIR), it is recommended to implement FAIR principles in research projects as well as involve FAIR expertise as early as possible. It is recommended to generate a Data management plan (DMP) as an early project deliverable, describing your plans at a high level, including data fairification and data sharing during and after the project. The recently published EJPRD Deliverable 12.2. describes a suite of tools, resources, and standards that align with the FAIR principles. It is recommended to utilise some of these resources in the project, to help FAIRify your data.

## 5.4. Sustainability

For projects developing services, tools, training or infrastructure for the research community, it is important to consider early in the project how these outputs can be sustained after the project's lifetime. It is recommended to describe a sustainability plan for the project outputs and sustaining data from the project long term, e.g. any plans related to commercialisation, early Health technology assessment, regulatory assessment, CE Marking. A Business Model Canvas is a useful tool to collected data on the key resources, activities and partners, the stakeholders' segment and relationships, channels, value proposition, costs and revenues needed to maintain the outputs.

# 6. Appendixes

## Appendix 1: Target Product Profile (TPP) – Example for a new Pharma Product *

**A target product profile (TPP) outlines the desired characteristics of a new drug or other medical intervention (e.g diagnostic tool). TPPs describe intended use, target populations and other desired attributes of products, including safety and efficacy-related characteristics. TPP can guide product research and development (R&D):**

- **In industry, in-house target product profiles (TPPs) are used as planning tools that guide development towards desired characteristics.**
- **In the regulatory context, TPPs are considered as tools to frame development in relation to submission of product dossiers**

**Below you can find a set of questions that will guide you when creating a TPP. An example TPP can be found here.** The WHO also provides a list of TPPs by disease area and can be found here.

I. Summary-Overview

| PROJECT NAME | | (NAME) |
|---|---|---|
| 1. | *Project Description* | *Summary description of the product* |
| 2. | *Project Category* | *Is the project an additional indication for an existing drug or a new project?* |
| 3. | *Strategic Fit and Value* | *How well does this drug/biologic fit with the core expertise and capabilities of the User/client?* |
| 4. | *Value to Patients* | *What is the specific value of this drug/biologic to patients? Does it offer therapeutic, safety or ease of use advantages over existing or upcoming drugs/biologics* |
| 5. | *User/Client's competitive position* | *Does the User/Client have a competitive advantage?* |
| 6. | *Company's IP position* | *Brief summary of the IP position regarding this drug* |
| 7. | *Rationale for success* | *Brief summary as to why the developing team believes that this product would be successful* |
| 8. | *Factors for success* | *Brief statement as to the User/Client's core competencies and market conditions that would drive a successful outcome* |
| 9. | *Key risk factors* | *Brief statement identifying possible risks* |
| 10. | *Consequences for not pursuing the project* | *What would happen if this project is not pursued?* |
| 11. | *Possible alternatives to this project* | *Are there any alternatives to this project?* |

Note: The Parameters for evaluation may be changed or extended, depending on the nature of the project/product regarding e.g.:

- Product design and formulation
- Purity
- Contaminants
- Storage Conditions
- Shelf Life

- Any delivery system associated with the drug
- Projected dates of submissions, regulatory approval and launch
- Cost of goods, pricing, market size
- Target, optimistic, and minimal conditions may be set for these elements as well

## II. Additional information

| PROJECT NAME | (NAME) |
|---|---|
| 1. *Non-clinical Properties* | *Define properties of the drug in non-clinical development, e.g.*<br>• *Pharmacokinetics*<br>• *Toxicology*<br>*Efficacy in animal models* |
| 2. *Target Indication(s)* | *Define target indication(s). Evaluate each indication separately (TPPs)* |
| 3. *Competitive Experience*<br>*Other molecules on the marked against the same disease* | *Examine approved claims of competitors (efficacy and safety)* |
| 4. *Competitive Environment*<br>*Awareness of competition that may influence patenting of your drugs* | *Examine the competitive environment for compounds currently in development and likely to be approved in the near future* |
| 5. *Scenarios* | *Elaborate on minimal and optimal profiles* |

## III. Efficacy Evaluation for the Primary Indication

| | Minimum Scenario | Target Scenario | Optimistic Scenario |
|---|---|---|---|
| *Primary Clinical Outcome 1* | *Equal to Target* | *The primary endpoint of the pivotal study or studies* | *It is possible that secondary endpoints may result in additional claims* |
| *Primary Clinical Outcome 2* | *Equal to Target*<br>*(If essential for regulatory success)* | *Provide entries if more than one primary endpoint* | *Better than or equal to Target* |
| *Target Patient Population* | *Equal to or smaller than Target*<br>*(If successful in a more limited population)* | *Target*<br>*(Describe target population)* | *Larger than or equal to Target* |
| *Route of Administration* | *Equal to or worse than Target*<br>*(If the least desirable tested route is successful)* | *Target*<br>*(Describe target route of administration)* | *Better than or equal to Target*<br>*(if more than one route is tested)* |
| *Target Regimen* | *> Higher dosing and more frequent administration than target may still be acceptable* | *Target*<br>*(Describe target regimen)* | *> Lower doses and/or less frequent administration may provide advantages* |

## IV. Safety Evaluation for the Primary Indication

| | Minimum Scenario | Target Scenario | Optimistic Scenario |
|---|---|---|---|
| *Non-clinical Safety* | *Equal to Target (Less than Target would be acceptable if risk/benefit ratio is favourable)* | *Laboratory or other findings similar to those observed for the same class or similar classes of compounds that have been approved* | |
| *Clinical Safety* | *Equal to Target (Less than Target would be acceptable if risk/benefit ratio is favourable)* | *Target safety is usually equivalent to the known safety of the same class or similar classes of compounds that have been approved* | *Better than Target if fewer and less severe AE profile Or else: Equal to Target* |
| *Drug Interactions* | *Equal to Target (Less than Target acceptability criteria should be explained)* | *Interactions similar to those observed for the same class or similar classes of compounds that have been approved* | *Better than Target if fewer and less severe interactions Or else Equal to Target* |
| *Precautions* | *Equal to Target (Less than Target acceptability criteria should be explained)* | *Precautions similar to those observed for the same class or similar classes of compounds that have been approved* | *Better than Target if no or fewer precautions Or else: Equal to Target* |
| *Contraindications* | *Equal to Target (Less than Target acceptability criteria should be explained)* | *Contraindications similar to those observed for the same class or similar classes of compounds that have been approved* | *Better than Target if no or fewer contraindications Or else Equal to Target* |

## Appendix 2: Reverse Planning Template

**When you plan in reverse, you start with your end goal and then work your way backwards from there to develop a plan of action. Working backwards in this way can give you a much clearer picture of what and how much must be accomplished during each phase of a project. It can also help you identify and avoid unnecessary activities.**

| Phase | What to do | What you should know for rare diseases |
|---|---|---|
| TPP<br>A target product profile (TPP) is a document that outlines the desired 'profile' or characteristics of all relevant information needed in validating product development | Envision and briefly describe the target scenario of the primary indication of the TPP/marketed product | |
| Clinical Phase III<br><br>The aim is to determine a drugs therapeutic efficacy (25-30% pass this phase). Typically, 300-3000 people with specific disease are included in this trial.<br><br>Outcome: Determine a drugs therapeutic efficacy (25-30% of drugs pass this phase) | Envision and briefly describe the pivotal clinical phase III trials need to apply for a marketing authorisation the primary indication of the marketed product.<br>Ask yourself:<br>“What is the ideal patient population for phase III?”<br>“Can we test against placebo or comparator products?”<br>“How many patients will be needed to show efficacy and safety (and also to identify rare side effects, if applicable)?”<br>Based on incidence and prevalence in the indication of interest, how long will a phase III trial last and how many sites need to be enrolled?”<br>“How much study material will we need or testing?” | Often enrol small samples, and often with high inter-individual variability in clinical course, and patients often are spread out all over the world. FDA proposes a trial regimen with a safety cohort operating at the same time as the efficiency trial. Natural history and patient registries can be used to identify key milestones in diseases progression, determine clinical meaningful difference, develop inclusion/exclusion criteria. |

| Phase | What to do | What you should know for rare diseases |
|---|---|---|
| Clinical Phase II<br>100-300 participants with specific disease (therapeutic dose)<br><br>Outcome: Estimate efficacy and side-effects (Success rate ~ 33%) | Envision and briefly describe the cornerstones of the phase II clinical programme when considering TPP and phase III in order to show efficacy in a dedicated patient cohort.<br>Ask yourself:<br>"What is the ideal patient population for phase II?"<br>"Can we test against placebo or comparator products?"<br>"How many patients will be needed to show efficacy?"<br>"Suitable secondary endpoints and exploratory parameters?"<br>"How much study material will we need or testing?" | In rare diseases, many of which cause a shortened lifespan, there are ethical concerns about placebo-controlled trials, parents may be reluctant to enroll their child in a trial where he or she may receive a placebo rather than the intervention under study.<br><br>Patients are more willing to participate if they have an open-label or crossover design option, rather than a randomized, placebo-controlled trial. |
| Clinical Phase I<br><br>10 to 100 healthy volunteers (sub-therapeutic with ascending doses)<br><br>Outcome: Dose-ranging to determine if it is safe to test for efficacy (Success rate ~70%) | Envision and briefly describe the cornerstones of the (First-in-Man, FiM) phase I clinical programme when considering the previous planning phases in order to show safety in healthy volunteers.<br>Ask yourself:<br>"Healthy volunteers or patients required?"<br>"Open-label? Controlled?"<br>"What is the optimal dose, what is the dose range?"<br>"What is the route of administration?"<br>"Suitable secondary endpoints and exploratory parameters?"<br>"How much study material will we need or testing?"<br>"Is the study material for clinical phase I comparable to the non-clinical?" | Alternative trial design:<br>Statistical techniques that maximize data from a small and heterogeneous group of subjects are needed.<br>Precedent for approval of drugs with an orphan designation based on pivotal studies that are not randomized, placebo-controlled, or double-blind, with smaller trial sizes compared to studies of drugs without such a designation |

| Phase | What to do | What you should know for rare diseases |
|---|---|---|
| Non-clinical Programme (preclinical development)<br>Preclinical studies objective is to provide detailed information about safety and efficacy of a drug and requires appropriate animal models that mimic human disease | Envision and briefly describe the cornerstones of the non-clinical programme when considering the previous planning phases in order to show safety in suitable animal models.<br>Ask yourself:<br>“What is the suitable animal model to show safety/efficacy?”<br>“What are the analytical methods for characterizing pharmacokinetics and metabolic of the test substance?” | Most rare diseases are juvenile:<br>Use juvenile animal models in reasonable cohort sizes in case of paediatric rare diseases<br>Evaluation of the drug dosing and response considering the differences in the anatomy and physiology between adults and children.<br>Adult disease:<br>Using forward and reverse genetic manipulation in mice and occasionally with other animals. This approach although is expensive and time-consuming is now a fundamental experimental strategy.<br>Cultured cells from mouse models of rare disease.<br>Mice with humanized livers can be a boon in the case of drug toxicity testing<br>No mice model: consider using zebrafish, or use of human cells, both normal and those derived from patients with genetic defects. |

## Appendix 3: Stakeholder Analysis Template

**Stakeholder analysis is a process of systematically gathering and analysing qualitative information to determine whose interests should be taken into account when developing and/or implementing a drug development program. The stakeholder analysis identifies these people before the project begins; grouping them according to their levels of participation, interest, and influence in the project; and determining how best to involve and communicate each of these stakeholder groups throughout.**

| NAME (Organisation) | Project role | Involvement in project | Impact to the project | Individual needs | Ways to address needs |
|---|---|---|---|---|---|
| | | *- Initiation*<br>*- Planning*<br>*- Execution*<br>*- Control/Decision making*<br>*- Information only* | *- High*<br>*- Medium*<br>*- Low* | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

## Appendix 4: Risk Assessment: Failure Mode and Effects Analysis

| | | | | |
|---|---|---|---|---|
| **Project / Process:** | | | **Risk Assessment-Version** | |
| | | | **Date of Risk Assessment** | |
| **Risk Assessment Team (Name, Signature)** | | | | |
| | | | | |

| No. | Function element / work step | Failure description (type & cause) | Failure implications | Occurrence O | Severity S | Detection D | Risk priority number | Prevention / Measure |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |

FMEA (see IEC 60812) provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce or control the potential failures. FMEA relies on product and process understanding. FMEA methodically breaks down the analysis of complex processes into manageable steps. It is a powerful tool for summarizing the important modes of failure, factors causing these failures and the likely effects of these failures.

**Potential Areas of Use(s)**

FMEA can be used to prioritize risks and monitor the effectiveness of risk control activities. FMEA can be applied to equipment and facilities and might be used to analyze a manufacturing operation and its effect on product or process. It identifies elements/operations within the system that render it vulnerable. The output/ results of FMEA can be used as a basis for design or further analysis or to guide resource deployment.

Appendix 5: Investigational Medicinal Product Dossier (IMPD) Template

TABLE OF CONTENTS

*Explanatory text: The table of contents for the pharmaceutical part follows the headings as given by the guidelines. The table of contents for the pre-clinical medical parts is based on the assumption that the detailed information will be provided by the Investigational Brochure. Please note that only relevant information will have to be provided and several headings can in general remain empty.*

2.1.S.4 **Control of Drug Substance:**
2.1.S.4.1 Specification
2.1.S.4.2 Analytical Procedures
2.1.S.4.3 Validation of Analytical Procedures
2.1.S.4.4 Batch Analyses
2.1.S.4.5 Justification of specification

2.1.S.5 **Reference Standards or Materials**

2.1.S.6 **Container Closure System**

2.1.S.7 **Stability**

2.1.P MEDICINAL PRODUCT

2.1.P.1 Description and Composition of the Medicinal Product

2.1.P.2 **Pharmaceutical Development:**
2.1.P.2.1 Components of the Medicinal Product
2.1.P.2.2 Medicinal Product
2.1.P.2.3 Manufacturing Process Development
2.1.P.2.4 Container Closure System
2.1.P.2.5 Microbiological Attributes
2.1.P.2.6 Compatibility

2.1.P.3 **Manufacture:**
2.1.P.3.1 Manufacturer(s)
2.1.P.3.2 Batch Formula
2.1.P.3.3 Description of Manufacturing Process and Process Controls
2.1.P.3.4 Controls of Critical Steps and Intermediates
2.1.P.3.5 Process Validation and/or Evaluation

2.1.P.4 **Control of Excipients:**
2.1.P.4.1 Specifications
2.1.P.4.2 Analytical Procedures
2.1.P.4.3 Validation of Analytical Procedures

2.1.P.4.4 Justification of Specifications
2.1.P.4.5 Excipients of Human or Animal Origin
2.1.P.4.6 Novel Excipients

2.1.P.5 **Control of Medicinal Product:**
2.1.P.5.1 Specification(s)
2.1.P.5.2 Analytical Procedures
2.1.P.5.3 Validation of Analytical Procedures
2.1.P.5.4 Batch Analyses
2.1.P.5.5 Characterization on impurities
2.1.P.5.6 Justification of Specification(s)

2.1.P.6 **Reference Standards or Materials:**

2.1.P.7 **Container Closure System:**

2.1.P.8 **Stability:**

2.1.A APPENDICES
2.1.A.1 Facilities and Equipment
2.1.A.2 Adventitious Agents Safety Evaluation:
2.1.A.3 Novel Excipients:
2.1.A.4 Solvents for Reconstitution and Diluents:

2.2 NON-CLINICAL PHARMACOLOGY, PHARMACOKINETICS AND TOXICOLOGY

2.2.1 Test Materials used in Toxicity Studies

2.2.2 Integrated Assessment of the data package

2.2.3 List of studies Conducted & References

2.2.4 GLP statement and Bioanalytical Methods

References

## 2.3 CLINICAL DATA

### 2.3.1 Clinical Pharmacology

### 2.3.2 Clinical Pharmacokinetics

### 2.3.3 Human Exposure

## 2.4 BENEFITS AND RISKS ASSESSMENT

LIST OF FIGURES

It is recommended to provide a list of figures with their titles and page numbers.

LIST OF TABLES

It is recommended to provide a list of table with their titles and page numbers.

## Appendix 6: Table of Contents of Investigator's Brochure

- Title Page
- Confidentiality Statement (optional)
- Signature Page (optional)

1. Table of Contents
2. Summary
3. Introduction
4. Physical, Chemical, and Pharmaceutical Properties and Formulation
5. Nonclinical Studies
    - 5.1 Nonclinical Pharmacology
    - 5.2Pharmacokinetics and Product Metabolism in Animals
    - 5.3Toxicology
6. Effects in Humans
    - 6.1 Pharmacokinetics and Product Metabolism in Humans
    - 6.2 Safety and Efficacy
    - 6.3 Marketing Experience
7. Summary of Data and Guidance for the Investigator

NB: References on 1. Publications
2. Reports
These references should be found at the end of each chapter
Appendices (if any):

- Single dose
- Repeated dose
- Carcinogenicity
- Special studies (e.g. irritancy and sensitisation)
- Reproductive toxicity
- Genotoxicity (mutagenicity)
    - A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:
    - Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).
    - Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.
    - Population subgroups (e.g., gender, age, and impaired organ function).
    - Interactions (e.g., product-product interactions and effects of food).
    - Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).

Author: European Medicines Agency, Source link

## Appendix 7: Budget Planning Template

budget%20planning.xls

Appendix 8: Meeting Agenda Template

# Agenda for <PROJECT No & TITLE>
# <DATE AND TIME>

Location <Where>
Invited participants: <Names or Initials>

| Time | | Chairs |
|---|---|---|
| **10h30** | Topic 1 | <Name> |
| **10h50** | Topic 2 | <Name> |
| **11h30** | Topic 3 | <Name> |
| **12h15** | Topic 4 | <Name> |
| **12h45** | Topic 5 | <Name> |
| **13h30** | etc. | |

Appendix 9: Meeting Minutes Template

# Meeting minutes

| | | | |
|---|---|---|---|
| Project number | | | |
| Project Title | | | |
| Sub project: | | | |
| Date: | | Time: | |
| Location: | | Room | |
| Address: | | | |
| Participants | | | |
| Distribution | | | |

| Open Action Items from Previous Team Meetings | | | | |
|---|---|---|---|---|
| No. | Topic/Action Item | ST | Resource | Date Due |
| | A = Action D = Decision I = Information R = Recommendation S=Statement | | | |
| 01. | | | | |
| 02. | | | | |
| 03. | | | | |
| 04. | | | | |
| 05 | | | | |

| New Action Items from this Meeting | | | | |
|---|---|---|---|---|
| No. | Topic/Action Item | ST | Resource | Date Due |
| | A = Action D = Decision I = Information R = Recommendation S=Statement | | | |
| 01. | | | | |
| 02. | | | | |
| 03. | | | | |
| 04. | | | | |
| 05. | | | | |
| 06. | | | | |
| 07. | | | | |
| 08. | | | | |

| | | |
|---|---|---|
| Prepared by (Init.) / Date: | Review by (P)RM manager / Date: | Distributed / Date: |

Appendix 10: Project Documentation List

# Meeting minutes

| | | | |
|---|---|---|---|
| Project number | | | |
| Project Title | | | |
| Sub project: | | | |
| Date: | | Time: | |
| Location: | | Room | |
| Address: | | | |
| Participants | | | |
| Distribution | | | |

| Open Action Items from Previous Team Meetings | | | | |
|---|---|---|---|---|
| No. | Topic/Action Item | ST | Resource | Date Due |
| | A = Action D = Decision I = Information R = Recommendation S=Statement | | | |
| 01. | | | | |
| 02. | | | | |
| 03. | | | | |
| 04. | | | | |
| 05 | | | | |

| New Action Items from this Meeting | | | | |
|---|---|---|---|---|
| No. | Topic/Action Item | ST | Resource | Date Due |
| | A = Action D = Decision I = Information R = Recommendation S=Statement | | | |
| 01. | | | | |
| 02. | | | | |
| 03. | | | | |
| 04. | | | | |
| 05. | | | | |
| 06. | | | | |
| 07. | | | | |
| 08. | | | | |

| | | |
|---|---|---|
| Prepared by (Init.) / Date: | Review by (P)RM manager / Date: | Distributed / Date: |

Appendix 11: Project Report Template

# Project report

| | |
|---|---|
| **Project Code:** | |
| **Project Title:** | |
| **User:** | |
| **RM Manager:** | |

Overall Project Status:

| | | |
|---|---|---|
| Good; everything on track | Currently good; but issues may arise | Delays and/or resource conflict need resolution |

| | |
|---|---|
| **Recent project activities:** | <Describe the project-related activities from the last report> |
| **Next/Planned project activities:** | <Describe the project-related activities planned until the next report> |
| **Next Milestones** | Milestone: Date Anticipated: |
| **Next Decisions** | Decision on: Date Anticipated: |
| **Financial Statement:** | <Describe the project-related budget and expenditure> |
| **Other Information:** | |

| | | |
|---|---|---|
| Date prepared: | RPM signature: | Presented to Steering Committee? Date |

Appendix 12: Toll-Gate Decision Document

# Toll-Gate Decision Document
# <Project Title>
# <Project Number>

## Decision for

## <Description of Decision>

| | |
|---|---|
| Version | 01 |
| Released by | xax |
| Date of release | xax |

1. Table of Content

2. Executive Summary
    2.1. Introduction and Scientific Background
    2.2. Toll-Gate and Aim of the Decision
    2.3. Previous Works
    2.4. Planned Works, Finance, and Risk

3.Introduction and Scientific Background

4. Toll-Gate and Aim of the Decision

5. Summary Description of the Previous Work

*<Highlight and summarise the experiments and studies conducted so far. Draw conclusions for the toll-gate>*

    5.1. Research Experience
        5.1.1.Conclusions
    5.2.Process Development and Manufacturing Experience
        5.2.1.Conclusions
    5.3.Non-Clinical Experience
        5.3.1.Conclusions
    5.4.Clinical Experience
        5.4.1.Conclusions

6. Detailed Description of the Planned Work
*<Describe in detail the planned activities, working packages or studies. Also provide information on timelines, milestones, deliverables, and risks>*

7. Financial Planning
    7.1Budget Spent
    7.2.Budget Planned

8. Risk Assessment

## 9.Signature Page

The signees hereby approve the decision as described in section 3.

**<Steering Committee Member 1, USER>**
Name:
Position:
Place and date:
Signature:

**<Steering Committee Member 2, EATRIS C&S>**
Name:
Position:
Place and date:
Signature:

**<Steering Committee Member 3, other>**
Name:
Position:
Place and date:
Signature:

**Research Project Manager**
Name:
Position:
Place and date:
Signature:

Appendix 1: Project Final Report Template

# Final report

| | |
|---|---|
| **Project Code:** | |
| **Project Title:** | |
| **User:** | |
| **RM Manager:** | |

| | |
|---|---|
| **Overall Assessment:** | <Give a general statement of the project performance> |
| **Performance: Working Packages, Timelines** | <Assess the adherence to timelines and completion of agreed milestones, working packages, etc.> |
| **Performance: Budget and Resource planning** | <Assess the adherence to the planned budget and resources> |
| **Open Issues and additional actions** | <Describe activities that have not been completed. Assess and propose potential next action items> |
| **Lessons-Learned:** | |

| RPM Signature, Date: | Approval User, Date: | Approval EATRIS C&S, Date |
|---|---|---|
| | | |

Appendix 14: Quality Standards of Pharmaceutical Development

This section has been written under the current regulatory landscape (2022). However, regulations are subject to changes, so we advise you to check the status of the regulations as the links will not be updated going forward, but the general guidance provided below are still applicable.

## 1. Product Areas

### 1.1.Medicinal Products

In pharmaceutical development, science is officially regulated by law concerning research in the areas of quality (development of manufacturing techniques and actual manufacturing of medicinal products according to Good Manufacturing Practice), safety and efficacy (nonclinical and clinical research according to Good Laboratory Practice and Good Clinical Practice). For basic research, e.g., discovery, pharmacodynamic and pharmacokinetic properties of a compound, no official regulations "by law" are available. However, Funding Agencies, academic facilities (e.g., Universities, Centres, Institutes or Working Groups) and other extramural bodies often have own sets of regulations under the label of Good Scientific Practice (GSP).

### 1.2.Medical Devices and In vitro diagnostics

The basic scientific requirements for the development of Medical Devices, and Medicinal Products are generally comparable and totalled under GSP. As well, clinical trials always follow the requirements of GCP. However, manufacture and nonclinical safety testing of Medical Devices follows a different set of regulations based on their intended use:

In vitro diagnostics are regulated in Regulation (EU) 2017/7461, which applies since 26 May 2022, while Medical Devices fall under Regulation (EU) 2017/74522. Requirements for quality systems for the design and manufacture of medical devices is given in ISO 13485.

[1] Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

[2] Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

## 2. Quality standards for Basic Research

As mentioned above, academic research is not equipped with legal or statutory quality standards. However, it is stipulated that scientists follow the principles of scientific integrity as e.g., laid down by the European Science Foundation3:

Highest professional and ethical standards in designing and conducting investigations.
A critical, open-minded approach in conducting research and scholarship and in analysing data.
Frankness and fairness regarding the contributions of partners, competitors, and predecessors.
Absolute honesty at all stages in scientific enquiry avoiding:
any form of fraud, such as fabricating or falsifying data or records.
piracy or plagiarism.
sabotaging the work, records or protocols of other scientists.
breach of confidence as a reviewer or supervisor, and
complicity in such actions by fellow scientists.

Quality Standards by contract
On a project specific basis, specific standards, or aspects to be followed or implemented can be laid down in detail in a contract between the User and the provider.

### 2.1.Areas of applicability

In general, these quality standards are applicable for any operation for which quality standards are not defined by regulation, directive, or law. These operations include, as given above, basic research and discovery, research on manufacturing process and methods and nonclinical pharmacodynamics and –kinetics.

## 3.Quality standards for Manufacture of Medicinal Products

Manufacture is defined according to the EU Guidelines to Good Manufacturing Practice (EU GMP guide)4 as “All operations of purchase of materials and

[3] European Science Foundation Policy Briefing; Good scientific practice in research and scholarship; December 2000; http://archives.esf.org/fileadmin/Public_documents/Publications/ESPB10.pdf
4 EU Guidelines to Good Manufacturing Practice. https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en

products, Production, Quality Control, release [to the market or for the use in clinical trials], storage, distribution of medicinal products and the related controls."

Pharmaceuticals products are defined by their quality, safety and efficacy. In this regard, manufacture relates to the term "quality".
The applicable quality standard is termed "Good Manufacturing Practice (GMP)" in Directive 2003/94/EC5 and describes the minimum standard that a medicines manufacturer must meet in their production processes. GMP is harmonized in different levels. Globally, valuable guidance can be found at the International Conference on Harmonization (ICH). ICH brings together regulatory authorities and pharmaceutical industry of Europe, Japan, and the US, and they discuss scientific and technical aspects of drug registration. They issue harmonized guidelines concerning different aspects of pharmaceutical development including the quality-part6. On a European level, which is the most relevant level for European users, the legal basis for quality standards of manufacture is laid down in Directive 2001/83/EC OF THE EUROPEAN PARLIAMENT, Article 46 "„The holder of a manufacturing authorization shall at least be obliged…to comply with the principles and guidelines of GMP"7. These principles of GMP are laid down in DIRECTIVE 2003/94/EC as mentioned above. Both directives also link to the EU GMP guide.
To be of legal authority for each Institute or centre involved in the mentioned tasks, the European directives are transposed into national laws of the European member states which will not be detailed here. In general, and if conflicting, provision by European or national law are superior to provisions mentioned here.

### 3.1.Areas of applicability

Principles of GMP apply to the actual development of a manufacturing process (e.g. for the IMP Dossier to be submitted to the regulatory authority in the course

5 Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32003L0094
6 http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html
7 DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001, http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_cons2009/2001_83_cons2009_en.pdf

of a clinical trial application as defined in ICH Q88 and Q119) and subsequently the manufacture of the IMP to be used in a clinical trial itself. All aspects of research on process development need to be documented and available. However, formal GMP standards are not used. A manufacturing license for a process development is not needed (or available), but data generated during the process will be the basis for assessment of a manufacturing authorization application by an authority.

It has to be stated that products used for GLP-safety studies (see 4.4) need to be comparable to the actual GMP-material used in the clinics. In this regard, "comparable is defined by ICH Q5E10 as

> "a conclusion that products have highly similar quality attributes before and after manufacturing process changes and that no adverse impact on the safety or efficacy, including immunogenicity, of the drug product occurred. This conclusion can be based on an analysis of product quality attributes. In some cases, nonclinical or clinical data might contribute to the conclusion".

## 4.Quality standards for non-clinical laboratory studies

Up to the 1970s, the FDA assumed that nonclinical studies performed to assume marketing authorization of chemicals and pharmaceuticals were performed according to the state of the art, and reported in a scientifically valid manner. However, suspicion was raised that this was not always the case during review of safety studies submitted by pharmaceutical and chemical companies. During "for cause" inspections following this suspense, a significant degree of misconduct concerning the performance of such studies as well as fraud was detected. Therefore, the first set of principles of "Good Laboratory Practice" (GLP) for the conduct of laboratory safety studies was published by the FDA in 1976. To

[8] ICH Q8 (R2) Pharmaceutical Development, https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-19.pdf

[9] ICH Q11 on development and manufacture of drug substances, https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-q11-development-manufacture-drug-substances-chemical-entities-biotechnological/biological-entities_en.pdf

[10] ICH Q5E, COMPARABILITY OF BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS, http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf

generate an international standard that allows free trade of such products, a GLP-Expert Group was established in 1979 under the roof of the Organization for Economic Cooperation and Development (OECD). This group developed the OECD-principles of GLP which were adopted in 1981 and continually revised11. The purpose of these principles of GLP is to promote the development of quality test data. Comparable quality of test data forms the basis for the mutual acceptance of data among countries. If individual countries can confidently rely on test data developed in other countries, duplicative testing can be avoided, thereby saving time and resources. The application of these principles should help to avoid the creation of technical barriers to trade, and further improve the protection of human health and the environment.

On a European level, DIRECTIVE 2004/10/EC, Art.3 (1) installs the OECD-principles of GLP for the testing of chemical substances12:

> Member States shall adopt the measures necessary for verification of compliance with the principles of GLP. These measures shall include inspections and study checks in accordance with the recommendations of the OECD in this area.

The link to pharmaceuticals is given by DIRECTIVE 2001/83/EC, Annex I (9)13:

> Nonclinical safety-pharmacology and toxicology studies shall be carried out in conformity with the provisions related to Good Laboratory Practice laid down in Council Directives 87/18/EEC [revised by DIRECTIVE 2004/10/EC] on the harmonization of regulations and administrative provisions relating to the application of the principles of good laboratory practice […].

To be of legal authority for each Institute or centre involved in the mentioned tasks, the European directives are transposed into national laws of the European member states which will not be detailed here. In general, and if conflicting,

[11] OECD Principles on Good Laboratory Practice, http://www.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/mc/chem%2898%2917&doclanguage=en

[12] DIRECTIVE 2004/10/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 11 February 2004, http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:050:0044:0044:EN:PDF

[13] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:311:0067:0128:en:PDF

provision by European or national law are superior to provisions mentioned here.

## 4.1Areas of applicability

DIRECTIVE 2004/10/EC, Section 1(1)14 defines the area of application of GLP:

> These principles of good laboratory practice should be applied to the nonclinical safety testing of test items contained in pharmaceutical products, [...]. These test items are frequently synthetic chemicals, but may be of natural or biological origin and, in some circumstances, may be living organisms. The purpose of testing these test items is to obtain data on their properties and/or their safety with respect to human health and/or the environment.
>
> Nonclinical health and environmental safety studies covered by the principles of good laboratory practice include work conducted in the laboratory, in greenhouses, and in the field.
>
> Unless specifically exempted by national legislation, these principles of good laboratory practice apply to all nonclinical health and environmental safety studies required by regulation for the purpose of registering or licensing pharmaceuticals [...].

Thus, GLP-obligatory testing refers to

- Safety pharmacology: pharmacodynamic effects of the test substance on vital functions and the CNS, Cardiovascular and Respiratory System
- Toxicology: adverse effects of products on health and environmental safety, e.g. characterized by single & repeated dose toxicology, gene toxicology, carcinogenicity, reproduction toxicology, local tolerance, photosafety, immuntoxicology and others.

ICH also issues guidance on safety-related studies (ICH S15). As they do not implement quality standards in their first sense, they are not discussed here.

[14] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:050:0044:0059:EN:PDF

[15] ICH Safety guidelines, http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html

Principles of GLP do not necessarily apply to other nonclinical testing on

- Pharmacodynamics: e.g. primary & secondary pharmacodynamics, mode of action
- Pharmacokinetics: e.g. studies on absorption, distribution, metabolism and excretion of products
- For those tests and studies, standards as mentioned in section 4.2 apply.

## 5.Quality standards for Clinical Research

REGULATION (EU) No 536/201416 defines a clinical trial as

> "a clinical study which fulfils any of the following conditions: (a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned; (b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or (c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects"

Whereas a clinical study is defined as

> "an investigation in relation to humans intended: "(a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products; (b) to identify any adverse reactions to one or more medicinal products; or (c) to study the absorption, distribution, metabolism, and excretion of one or more medicinal products; to ascertain the safety and/or efficacy of those medicinal products."

Clinical trials are complex and usually lasting one or more years. They may involve numerous participants and, as multi-national multi-centre trials, one trial might be performed in different countries. The practices on applying for and performing clinical trials and the quality standards varied between the EU member states, delaying and complicating their performance. Therefore, a

[16] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC; https://eur-lex.europa.eu/eli/reg/2014/536/oj

harmonized approach was introduced in 2001 with above mentioned DIRECTIVE 2001/20/EC "on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use". A new Regulation (EU) No 536/201417 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC entered in application on 31 January 2022 .The main aim of this Regulation is acceleration and streamlining of the assessment process, reduction of the administrative burden for the sponsor and facilitation of the cross-border cooperation.

The basis for Regulation (EU) No 536/2014 is the protection of human rights and the dignity of the human being regarding the application of biology and medicine, as for instance reflected in the 1996 version of the Helsinki Declaration18. The regulation defines "Good Clinical Practice" (GCP)

> means a set of detailed ethical and scientific quality requirements for designing, conducting, performing, monitoring, auditing, recording, analysing and reporting clinical trials ensuring that the rights, safety and well-being of subjects are protected, and that the data generated in the clinical trial are reliable and robust.

While Reg. (EU) 536/2014 sets the European frame of GCP and focuses on major aspects, detailed guidance are established by the ICH. ICH was introduced above as organization that brings together regulatory authorities and pharmaceutical industry of Europe, Japan and the US, and they discuss scientific and technical aspects of drug registration. Concerning clinical research, the harmonization of technical requirements for the development of medicinal products is also pursued through the ICH in Section "Efficacy (E)"19:

> The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety, and reporting of clinical trials. It also covers

[17] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC; https://eur-lex.europa.eu/eli/reg/2014/536/oj

[18] WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

[19] ICH Efficacy guidelines, http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/ pharmacogenomics techniques to produce better targeted medicines.

ICH E6 on GCP[20] was implemented in Europe as NOTE FOR GUIDANCE ON GOOD CLINICAL PRACTICE (CPMP/ICH/135/95)[21] and Guideline for good clinical practice E6(R2) (EMA/CHMP/ICH/135/1995)[22].

To be of legal authority for each institute or centre involved in the mentioned tasks, the European directives are transposed into national laws of the European member states which will not be detailed here. In general, and if conflicting, provision by European or national law are superior to provisions mentioned here.

### 5.1.Areas of applicability

The GCP standards are followed for every clinical trial performed with

- a novel IMP for which no marketing authorization has been granted.
- already marketed products but used or assembled (formulated or packaged) in a way different from the authorised form, including already marketed products in a different indication or for a different population.
  When trials are conducted with authorised medicinal products and on patients with the same characteristics as those covered by the authorised indication, requirements already fulfilled by these authorised medicinal products, as far as manufacturing or importation are concerned, are taken into consideration.

Thus, they are not applicable to non-interventional trials. Those are trials where the medicinal products are prescribed in the usual manner in accordance with the terms of the marketing authorization. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional

[20] ICH HARMONISED TRIPARTITE GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R1), https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf; https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Addendum_Step2.pdf

[21] CPMP/ICH/135/95; https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e6-r1-guideline-good-clinical-practice_en.pdf

[22] EMA/CHMP/ICH/135/1995; Guideline for good clinical practice E6(R2)

diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data.