Guidebook

# ATMP guidebook for innovators in the Netherlands

FAST

November 2024

## Colophon

FAST (Centre for Future Affordable & Sustainable Therapy Development) is an independent national centre of expertise and collaboration, devoted to driving innovation in therapy development. Serving as a dynamic network infrastructure, FAST consolidates knowledge, fosters dialogues, and engages an extensive range of experts. The centre identifies key opportunities and challenges, addressing them through comprehensive approaches such as use-cases and pilot studies. FAST's primary focus lies in accelerating, strengthening, and innovating the entire therapy development chain, spanning from initial laboratory research to widespread patient access. The centre strategically connects stakeholders actively engaged in innovative therapy development, fostering collaboration among researchers, patients, entrepreneurs, and regulatory bodies to drive innovation.

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2024 version - FAST (Centre for Future Affordable Sustainable Therapy Development)

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# List of abbreviations

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| **ACP** | Advies Commissie Pakket |
| **ADR** | Adverse Drug Reaction |
| **AIP** | Active Pharmaceutical Ingredient |
| **ASMF** | Active Substance Master File |
| **ATMP** | Advanced therapy medicinal product |
| **ATMP Engage PPI** | The Advanced Therapy Medicinal Products Patient and Public Involvement Working Group |
| **BCB** | Besluit centrale beoordeling medisch-wetenschappelijk onderzoek met mensen |
| **BSE** | Bovine Spongiform Encephalopathy |
| **BZV** | Besluit Zorgverzekering |
| **CAT** | Committee for Advanced Therapies |
| **cATMP** | Combined Advanced Therapy Medicinal Product |
| **CBG** | College ter Beoordeling van Geneesmiddelen |
| **CCMO** | Centrale Commissie Mensgebonden Onderzoek (Central Committee on Research involving Human Subjects) |
| **CEP** | Certificate of suitability |
| **CHMP** | Committee for Medicinal Products for Human Use |
| **CieBAG** | Commissie Beoordeling Add-on Geneesmiddelen |
| **CIOMS** | Council of International Organisations of Medical Sciences |
| **CMDh** | Coordination Group for Mutual Recognition and Decentralised Procedures – Human |
| **COGEM** | Commission on Genetic Modification |
| **CTD** | Common Technical Document |
| **CTIS** | Clinical Trials Information System |
| **CTR** | Clinical Trial Regulation |
| **DARE-NL** | Dutch infrastructure for cancer-specific ATMP Research |
| **DBC** | Diagnose-Behandel Combinaties (Diagnosis Related Group) |
| **DCEP** | Certification of Substances Division |
| **DCRF** | Dutch Clinical Research Foundation |
| **DOT** | DBC Op weg naar Transparantie |
| **DRG** | Diagnosis Related Group |
| **DT4PCR** | Design Thinking for Patients in Cancer Research |
| **eAF** | Electronic Application Form |
| **EATG** | European Aids Treatment Group |
| **EATRIS** | European Research Infrastructure for Translational Medicine |
| **EBMT** | European Group for Blood and Marrow Transplantation |
| **EC** | European Commission |
| **ECDC** | European Centre for Disease Prevention and Control |
| **EDQM** | European Directorate for Quality of Medicines |

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|---|---|
| **ECTR** | European Clinical Trial Regulation |
| **EMA** | European Medicines Agency (Europees Geneesmiddelenbureau) |
| **Enpr-EMA** | European network of pediatric Research - EMA |
| **EPF** | European Patients' Forum |
| **ESO** | Environmental Safety Officer |
| **EU** | European Union |
| **EUPATI** | European Patients' Academy on Therapeutic Innovation |
| **EVCODE** | EudraVigilance code |
| **FACT** | Foundation for the Accreditation of Cellular Therapy (US) |
| **FAST** | Centre for Future Affordable Sustainable Therapy |
| **FBA** | Financial Based Agreement |
| **FDA** | Food and Drug Administration |
| **GCP** | Good Clinical Practice |
| **GDP** | Good Distribution Practice |
| **GGO** | Genetisch Gemodificeerd Organisme |
| **GMO** | Genetically Modified Organism |
| **GMP** | Good Manufacturing Practices |
| **GTMP** | Gene Therapy Medicinal Product |
| **GVS** | Geneesmiddelenvergoedingssysteem |
| **GVP** | Good PharmacoVigilance Practice |
| **HCI** | Health Care Insurer |
| **HE** | Hospital Exemption |
| **has** | Health Sciences Authority |
| **HTA** | Health Technology Assessment |
| **HTACG** | Member State Coordination Group on HTA |
| **ICH** | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| **IenW** | Ministerie van Infrastructuur en Waterstaat |
| **IGJ** | Inspectie Gezondheidszorg en Jeugd (Dutch Health and Youth Care Inspectorate) |
| **ISCT** | International Society for Cellular Therapy (Europe) |
| **ITF** | Innovation Task Force |
| **IMPD** | Investigational Medicinal Product Dossier |
| **IP** | Intellectual Property |
| **JACIE** | Joint Accreditation Committee EBMT and ISCT |
| **JCA** | Joint Clinical Assessment |
| **JSC** | Joint Scientific Consultation |
| **LoQ** | List of Questions |
| **MA** | Marketing Authorisation |
| **MAA** | Marketing Authorisation Application |
| **MAH** | Marketing Authorisation Holder |
| **MDR/IVDR** | Medical Devices Regulation (MDR) / In Vitro Diagnostics (IVDR). |
| **MEA** | Managed Entry Agreement |

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|---|---|
| **MEB** | Medicines Evaluation Board |
| **MIA** | Manufacturing and Importation Authorisation |
| **MPNE** | Melanoma Patient Network Europe |
| **MoH** | Ministry of Health |
| **MRA** | Mutual Recognition Agreement |
| **MREC (METC)** | Medical Research Ethics Committee (Medisch Ethische Toetsingscommissie) |
| **MSC** | Member States Concerned |
| **NFU** | Nederlandse Federatie van Universitair Medische Centra (Dutch Association of University Medical centers) |
| **NOAEL** | No Adverse Effect Level |
| **NTA** | Notice To Applicants |
| **NVZ** | Nederlandse Vereniging Ziekenhuizen – Dutch Association of Hospitals |
| **NZa** | Nederlandse Zorgautoriteit |
| **OBA** | Outcome Based Agreement |
| **PASS** | Post Authorisation Safety Study |
| **PAES** | Post Authorisation Efficacy Study |
| **PD** | PharmacoDynamics |
| **PERC** | Patient Engagement Resource Centre |
| **PRIME** | PRiority MEdicines |
| **PRAC** | Pharmacovigilance Risk Assessment Committee |
| **PSMF** | Pharmacovigilance System Master File |
| **QPPV** | Qualified Person Responsible for Pharmacovigilance |
| **QIG** | Quality Innovation Group |
| **QP** | Qualified Person |
| **RCT** | Randomised Controlled Trial |
| **RIVM** | Rijksinstituut voor Volksgezondheid en Milieu |
| **RMP** | Risk Management Program |
| **RMS** | Reporting Member State |
| **RPI** | Research Product Identifier |
| **RSNN** | Regulatory Science Netwerk Nederland |
| **RZV** | Regeling Zorgverzekering |
| **SAE** | Serious Adverse Event |
| **sCTMP** | Somatic Cell Therapy Medicinal Product |
| **SME** | Small Medium-Sized Enterprise |
| **SoHO** | Substance of Human Origin |
| **SCB** | SoHO Coordination Board |
| **SPC** | Summary of Product Characteristics |
| **SUSAR** | Suspected Unexpected Serious Adverse Reaction |
| **SWAP** | Stichting Werkgroep Antibiotica Beleid |
| **SW&P** | Stand van Wetenschap en Praktijk (Established medical science and medical practice) |
| **TEP** | Tissue Engineered Product |
| **TRIP** | Transfusion and Transplantation Reactions in Patients' |

| | |
|---|---|
| **TSE** | Transmissible Spongiform Encephalopathy |
| **TTO** | Technology Transfer Centre |
| **UPI** | Unique Product Identifier |
| **VGO** | Verklaring Geschiktheid Onderzoeksinstelling |
| **VIG** | Vereniging Innovatieve Geneesmiddelen (Association Innovative Medicines) |
| **VT** | Voorwaardelijke Toelating (conditional reimbursement) |
| **VWS** | Ministerie van Volksgezondheid, Welzijn en Sport (Ministry of Health, welfare and Sport) |
| **WAR** | Wetenschappelijke Advies Raad (Scientific Board) |
| **WGBO** | Wet geneeskundige behandel overeenkomst (Medical Treatment Contracts Act) |
| **WHO** | World Health Organisation |
| **WMO** | Act on Medical Research Involving Human Subjects |
| **WvkL** | Wet veiligheid en kwaliteit lichaamsmateriaal |
| **XEVMPD** | eXtended EudraVigilance Medicinal Product Dictionary |
| **XEVPRM** | eXtended EudraVigilance Product Report Message |
| **ZIN** | Zorginstituut Nederland |
| **ZN** | Zorgverzekeraars Nederland |
| **ZonMw** | ZorgOnderzoek Nederland Medische Wetenschappen |
| **Zvw** | Zorgverzekeringswet |

# Introduction

## About ATMPs

Advanced therapy medicinal products (ATMPs) represent a cutting-edge class of medicines tailored for human use, leveraging genes, tissues, and cells to restore, correct or modify their inherent biological function. The field of ATMPs is advancing rapidly, with a significant increase in the number of ATMPs expected in the coming years. Many ATMPs are administered only once or twice, aiming for a curative or long-lasting therapeutic effect. ATMPs can be classified into four types:

- gene therapy medicinal products (GTMP)
- somatic cell therapy medicinal product (sCTMP)
- tissue engineered product (TEP) and
- combined ATMPs.

ATMPs represent a category of innovative therapies that sometimes share similar characteristics with treatments such as blood transfusions, skin transplants and organ- or bone marrow transplantation. The European Medicines Agency (EMA) classify ATMPs as medicinal products and assesses ATMPs within that regulatory framework. Due to the specific characteristics of ATMPs, additional ATMP-specific requirements are warranted. These requirements concern training, quality standards, permits and accreditation for production (including starting materials), transportation, storage, administration and supportive care.* They are applicable in the phase of pre-clinical development, in the clinical trials and in clinical practice.

The specific characteristics of ATMPs, coupled with the different sets of laws, regulations and requirements create specific and often substantial challenges in the design, implementation and funding of preclinical and clinical research. These challenges also extend to production and the process of obtaining marketing authorization (MA), national reimbursement and effective integration in healthcare practice. Recently Gort et all (2023)[1] concluded that among developers there's a lack of clarity on the regulatory pathways and involved (governmental) bodies. This might frustrate fast and sustainable ATMP access for patients. An up-to-date overview of all bottlenecks, potential solutions and initiatives across the Dutch ATMP field is described in Gort et al. *"Geneesmiddelen voor Geavanceerde Therapie (ATMP's) in Nederland: Veldverkenning, Knelpuntanalyse en Activiteitenkaart"*(Dec. 2023).[1]

## Purpose of this Guidebook next to all other initiatives

This Guidebook serves as a fundamental resource for all developers, whether academic or commercial, who are involved in conducting ATMP clinical trials or aim to introduce ATMPs to the Dutch market. This Guidebook is primarily designed to help you navigate the European and Dutch ATMP landscape, offering a deeper understanding of the required and optional steps and activities at each stage of the ATMP pathway. It also serves as a collaborative tool, helping you engage with external experts across various specialized topics critical to successful ATMP development. While this Guidebook offers a comprehensive overview, seeking expert guidance is highly recommended. Be aware that rules, regulations and procedures included in this Guidebook are subject to change in the future.

* Note: surroundings, legislation and procedures are subject to change and the applicable procedures differentiate per ATMP.

## The development of this Guidebook

This updated Guidebook builds on the previous version of "Advanced Therapy Medicinal Products: A Guidebook for Companies in the Netherlands, Covering Clinical Trials to Market Access," originally developed by the Association of Innovative Medicines (Vereniging Innovatieve Geneesmiddelen, 'VIG').[2] FAST has taken on the task of revising and expanding the Guidebook to improve understanding of current ATMP procedures for both academic and commercial developers. To address gaps and specific needs identified in the earlier edition, experts were consulted on key topics such as patient involvement, EMA processes, hospital exemptions (HE), and clinical research. A broader expert consultation followed in the summer of 2024 to ensure comprehensive coverage.

## How to use this Guidebook

Contributing to consistency we used formal definitions of ATMPs (EC Nr. 1394/2007 and guideline 2001/83/EG) and incorporated classifications, graphs and recommendations of recent publications/investigations on mapping and analyzing the ATMP field wherever possible.[3][4][5][6][7] This Guidebook is divided in three parts.

### Part 1 (chapter 1-2) - Key take aways and patient involvement

While the importance of patient involvement is widely recognized, effectively integrating it throughout the various phases of an ATMP's lifecycle remains a complex challenge. Here were provide an overview of our key take aways and offer considerations and tools for ATMP developers regarding patient involvement.

### Part 2 (chapter 3-4) – Key Background and Resources for ATMP Developers:

This section provides developers with essential background information regarding context, basic legal guidelines, and an overview of the various steps and procedures at both national and international levels. The information shared here, along with recent lessons learned from other developers, will assist (those new to the field) in navigating the legislation, proactively addressing requirements, and identifying gaps in data and expertise. This knowledge will also help developers anticipate needs and engage with experts early in the ATMP development process. Given the complexity and evolving nature of procedures and requirements, it is highly recommended to consult experts from the very beginning.

### Part 3 (chapter 5-10) – Navigating the ATMP Lifecycle

This section outlines the legislation and procedures regarding the ATMP lifecycle, covering every critical phase from preclinical development to integration into clinical practice. By providing a detailed overview of the regulatory requirements and processes at each stage, this part serves as a comprehensive guide for developers. Understanding these steps is crucial for ensuring compliance, securing marketing authorization, navigating reimbursement, and successfully incorporating ATMPs into clinical practice.

### Overview of Support (chapter 11) and Annexes

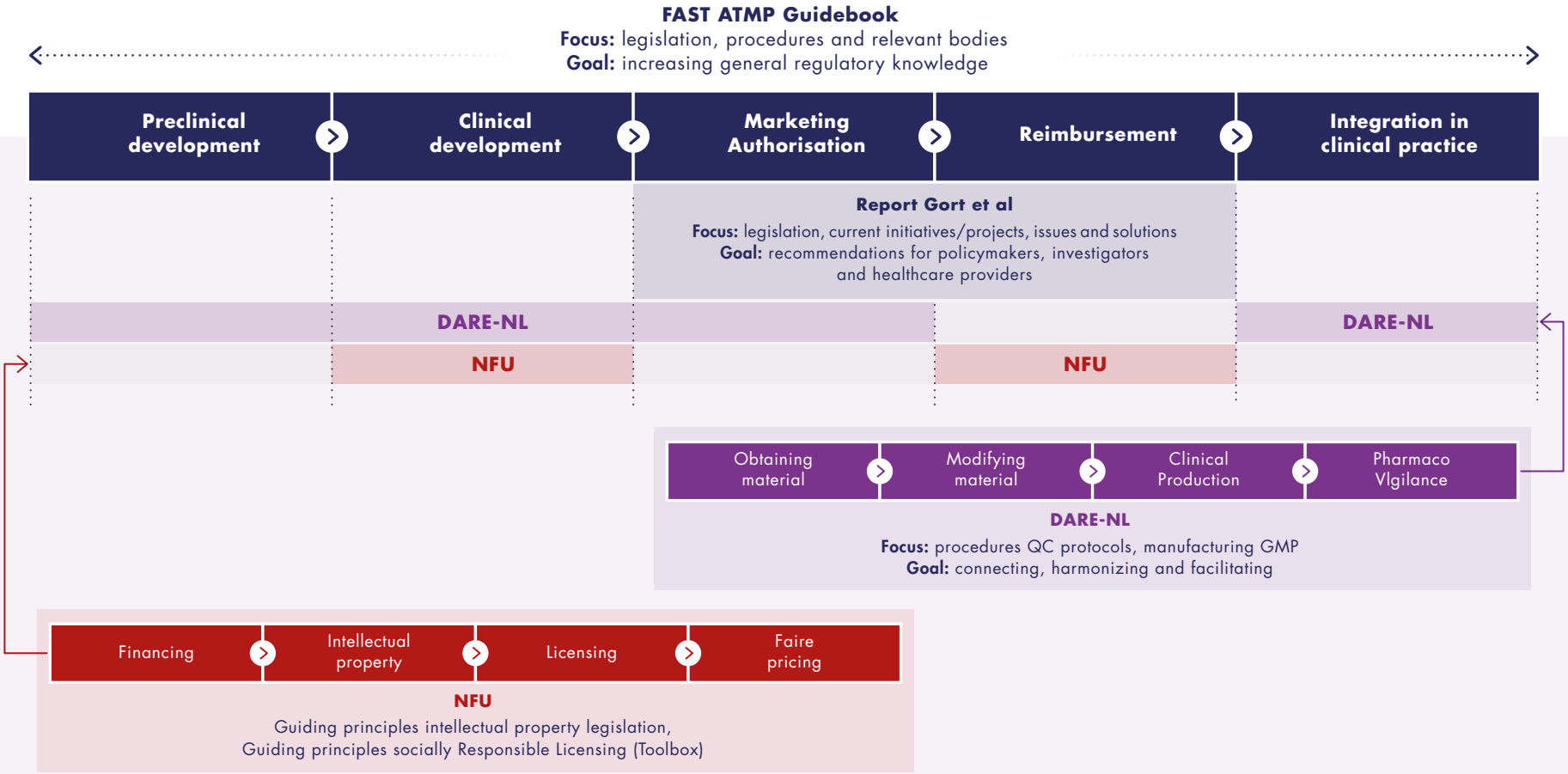
Chapter 11 provides developers with an overview of the various types of support and tools available at both national and international levels. The annexes offer a comprehensive overview of all relevant legislation and regulations, detailed descriptions of key application and registration processes, and a curated list of experts. These annexes serve as a practical reference for developers, providing essential information and guidance to navigate the complex regulatory landscape of ATMPs.

The Guidebook serves as a fundamental source for all developers who conduct ATMP clinical trials or aim to bring ATMPs on the Dutch market (as shown in figure 1). It complements and is supportive to other initiatives like i.e. the Dutch infrastructure for cancer-specific ATMP Research (DARE-NL),* the IP toolbox of the Nederlandse Federatie van Universitair Medische Centra (NFU - Dutch Association of University Medical centers) and different tools from The Advanced Therapy Medicinal Products Patient and Public Involvement and Engagement Working Group (ATMP Engage).**

* DARE-NL is a partnership between all academic developers of ATMPs in the Netherlands. The overarching goal of DARE-NL is to accelerate clinical testing of novel ATMPs for cancer patients. Specifically, DARE-NL centralizes knowledge, harmonizes protocols, develops raw materials, biologics, assays and technologies, and facilitates implementation and patient outreach. To reach this goal DARE-NL is open to collaborate with (non academic) small and medium enterprises.

** ATMP Engage brings together UK-based stakeholders with an interest in ATMPs to discuss and collaborate on PPIE activity. ATMP Engage | EuroGCT

*Figure 1: FAST and other initiatives*



# 1. Most important take aways

### Patient centricity

- Keep the patient in mind throughout the end to end pathway and engage with patient groups, ensuring consideration of the diversity of patient populations.
- Consider the required type of patient expertise, involvement and resource in the different phases throughout the lifecycle. Since availability and resources might be limited, consider involvement of at least two or more patients in every phase.

### Start with the end in mind

- Be aware of the requirements for product development, (non) clinical trials (chapter 5-7) and Marketing Authorisation (chapter 8) already in the beginning of development.
- Use the EMA dossier validation checklist and the different EMA checklists for ATMPs (ATMP Overview guidance) on the EMA website and the Dutch Hospital Exemption application form (Aanvraagformulier hospital exemption ATMP) as the first checklist to make sure all requirements are addressed.
- Assess your data package versus the requirements and discuss early in process (before the data package is ready) during a scientific advice with EMA and/or College Beoordeling Geneesmiddelen (CBG) and CCMO possible solutions like Orphan designation, Priority Medicines (PRIME), Accelerated, Conditional Approval and Hospital Exemption.

### Engage early

- Engage with stakeholders like EMA, CBG and CCMO already in the beginning of development to increase knowledge and get access to the support available. Preliminary / pre submission meetings increase the success rate of applications. Small and Medium size enterprises (SME) and Academia specific: invest in a briefing meeting (EMA) early in the development process.
- Reach out to Reimbursement Authorities like Health Care Institute (ZIN), Health Care Insurers (HCIs) and Ministry of Health (MoH) already in the development phase and start discussion on patient access and funding. Explore possibilities for sustainable funding (together with the Technology Transfer Offices (TTO) of your center).
- In case of Hospital Exemption, reach out early to Inspectie Gezondheids-zorg en Jeugd (IGJ; translated: Dutch Health and Youth Care Inspectorate) and Zorginstituut Nederland (ZIN) to discuss the requirements, the process and reimbursement challenges and possibilities.
- Engage and seek collaboration among ATMP developers and supportive centers of expertise like DARE-NL and FAST, using the expertise and lessons learned of colleagues.

## Seek advice and support of experts

- Every phase requires specific expertise. Check the different phases of the product lifecycle upfront and discuss the available expertise in a multidisciplinary team and acknowledge lacking expertise within the team. Reach out to centres of expertise to address your needs and where to find the lacking expertise.
- Academic developers are encouraged to involve their local TTO to discuss Intellectual Property (IP) and sustainable funding and consult the IP management committee of DARE-NL (collaboration with Oncode Institute) for support in these discussions.
- Make sure that there is sufficient budget available for specific support (ie legal, IP, clinical design, training and manufacturing, marketing authorisation and reimbursement).
- Discuss funding challenges (during development, but also after marketing authorisation) with MoH and ZIN and HCIs.
- Take advantage of the wide range of available guidance and support offered by EMA, CCMO and CBG.

## Minimise complexity

- ATMPs are very complex by nature, in order to speed up time to market and patient access seek to minimise additional complexity where possible and look for possibilities to standardise across ATMPs.

# 2. Patient involvement

## 2.1 Patient involvement throughout the lifecycle

The importance and merits of patient involvement in research and development are commonly acknowledged and offer benefits for all parties involved. The discovery, development, and evaluation of new treatments is improved if patients provide input throughout the design, conduct, and evaluation of studies and projects. These improvements are based on the collaborative identification and understanding of patients' unmet needs, their research priorities, patient-centric clinical study design, meaningful outcome measures and study endpoints. Therefore engagement with patients, caregivers, patient advocates, patient experts, patient organizations and systematically involving patients throughout the lifecycle (as shown in figure 2) of a medicinal product– from its early development through the regulatory process, to ongoing monitoring and safe use in clinical practice - is strongly advised.[8][9] Patients should be engaged in a timely manner in every part of the process, ensuring they are not an afterthought, but active participants from the beginning.

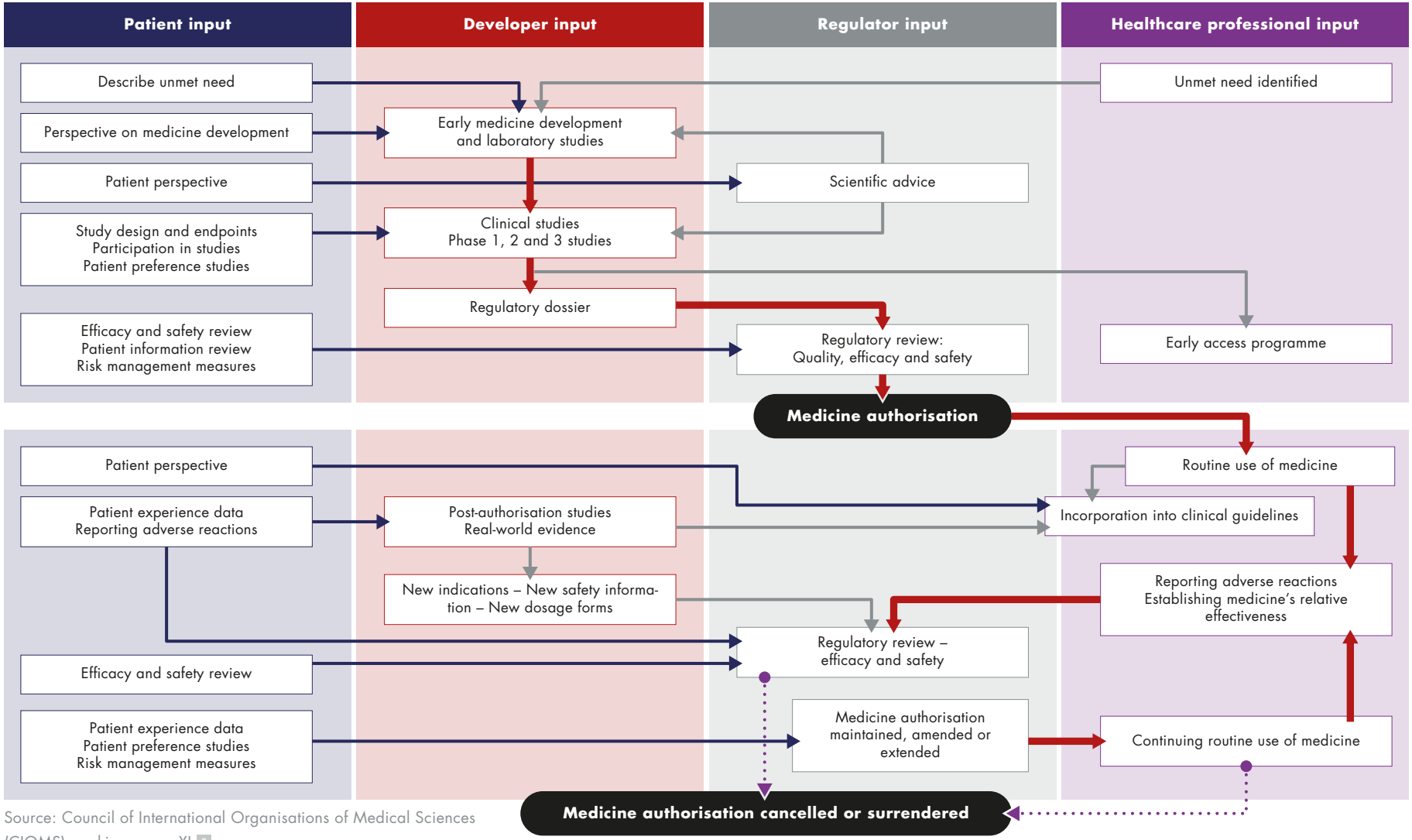
## 2.2 Involvement of the right patients in the right way

The value of patient involvement in medicines research and development is increasingly recognised by all stakeholders. Unfortunately, limited formal documentation of patient involvement activities hampers the sharing of experience and insights, preventing timely and systematic implementation. Patient involvement often lacks structure and consistency in approach and happens too late. An end to end, practical guideline is required. The European Patients' Academy on Therapeutic Innovation (EUPATI) developed the Patient Engagement Roadmap & Toolbox, a process model for patient involvement in medicines Research and Development. The patient involvement roadmap is illustrated in figure 3.

The roadmap as shown in figure 3 highlights key opportunities for patient involvement across the four key stages of the medicines research and development lifecycle and is illustrated with concrete examples. The aim is to provide developers a tool to facilitate and encourage patient involvement during this lifecycle. The roadmap intends to stimulate further discussion among stakeholders.
For maximum benefit, it will require the active participation of academia and the commercial developers (pharmaceutical industry), patient organisations and patients, clinicians and researchers in identifying strategic points for patient involvement and ensuring their effective implementation.

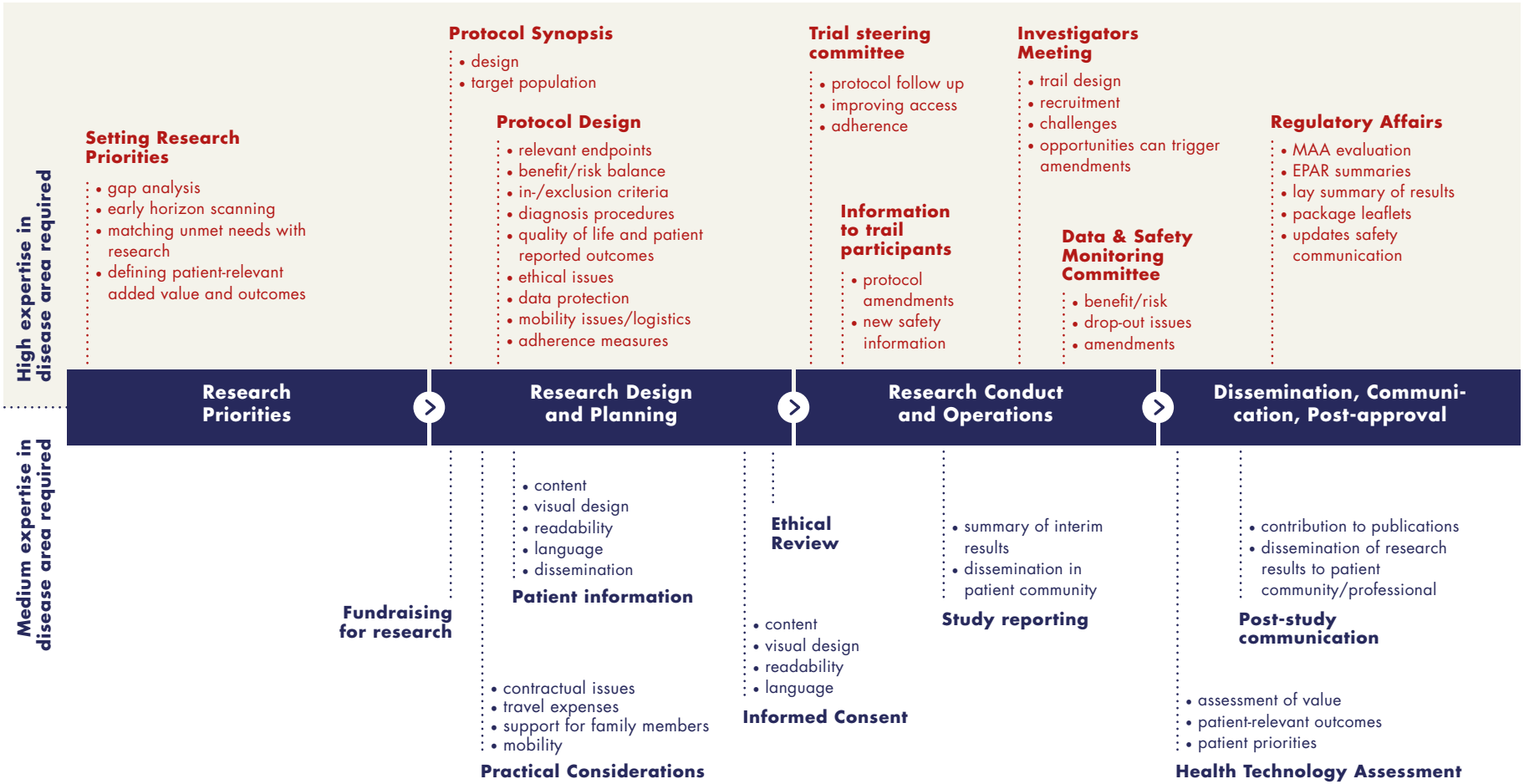
Another initiative aimed at enhancing patient engagement is the Patient Engagement Resource Centre (PERC). This joint initiative from the European Research Infrastructure for Translational Medicine (EATRIS), the European Patients' Forum (EPF) and the European Aids Treatment Group (EATG), is funded by the Horizon 2020 funded project EATRIS-Plus. The PERC was developed to help academic researchers get started with meaningfully engage patients in their research. **The PERC is a repository of publicly available guidance, training and practical tools that support researchers with every stage of their patient engagement activity: planning, conducting and evaluating**. See Patient Engagement Resource Centre for training materials, guidance and formats.

*Figure 2: Types of input throughout the lifecycle*




Source: Council of International Organisations of Medical Sciences (CIOMS) working group XI [9]

*Figure 3: Patient involvement in medicines R&D: a practical roadmap*

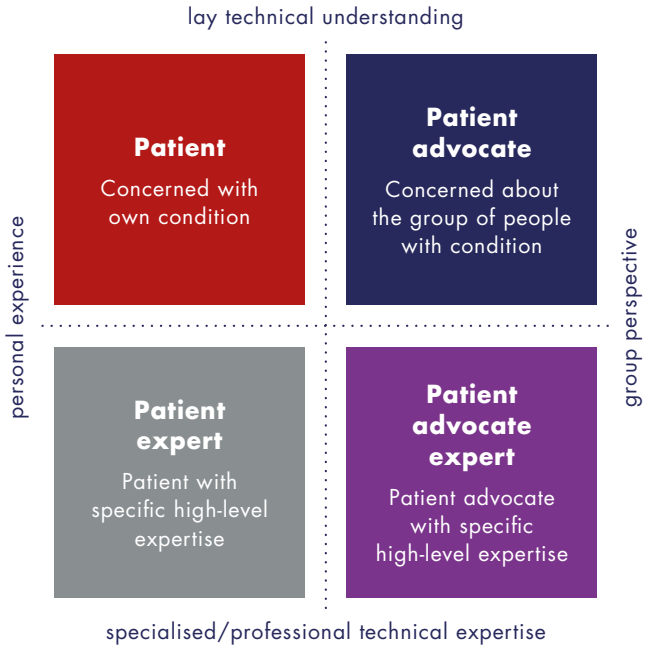



Source: Geissler, J. et al. 2017 [10]

### 2.2.1 Patient selection

In this patient engagement process special attention should be given to the selection of the patients in the different phases, fitting their available time, risk of absence due to disease progression, expertise, needs and the required input. The scheme in figure 4 is developed by the Melanoma Patient Network Europe (MPNE) and could serve as orientation when considering patient engagement/ involvement.

***Figure 4:*** *Patients, patients advocates and levels of expertise (MPNE, 2022).*




Source: MPNE, 2022 [11]

Patients and their families can contribute to a project by sharing their personal experiences with the disease and its care, while a patient expert can also assist with technical topics such as clinical trial design or biobanks. In contrast, the community perspective can be fulfilled by patient advocates: people with personal experience who are concerned about a group with a particular condition and have access to large networks of patients. Patient advocates experts not only bring community insights but also specific technical expertise, and are more likely to access large networks as well as negotiate interfaces with other experts.

### 2.2.2 Type of involvement

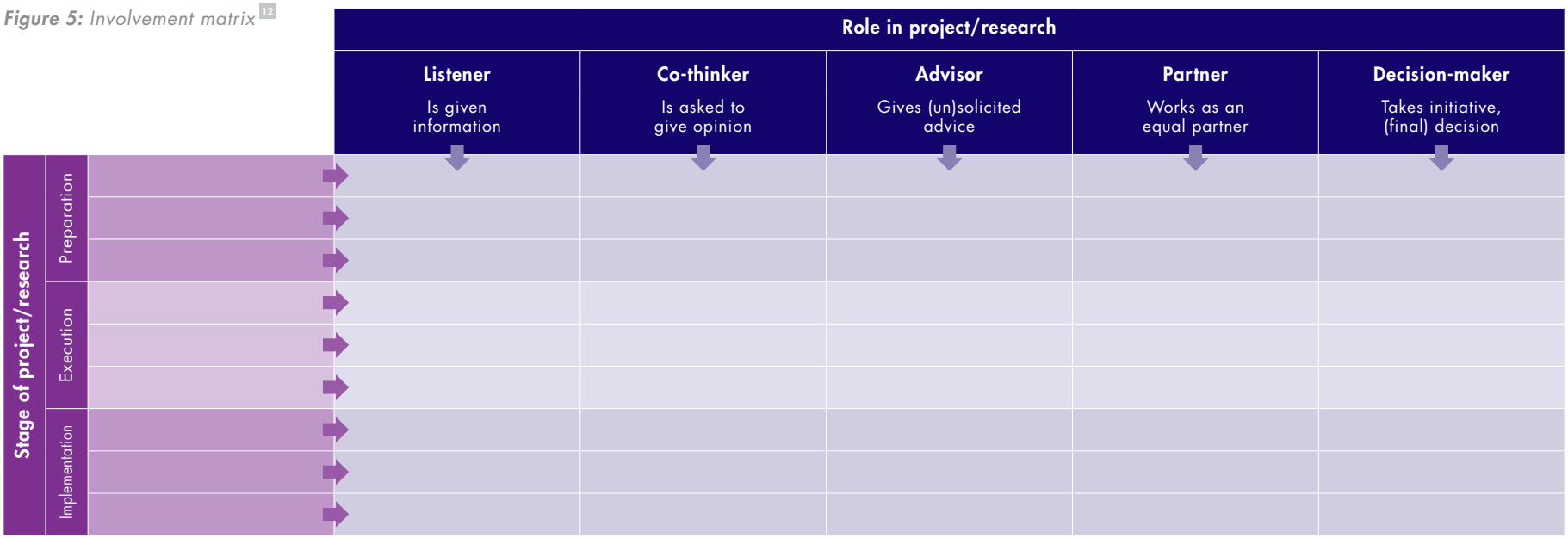
It's important to consider the type of involvement in the different phases of the product lifecycle. Passive Involvement versus Consequential (Active) involvement. Consultation, information, user testing, providing information, advice and data is considered as passive involvement. "Consequential" involvement is when involvement contributes to the research process, as distinct from involvement which is ignored or not incorporated (Jack Nunn et, al, 2019).[12] In the development of ATMPs this could be of interest and requires direct partnership in specific projects e.g. change in regulations or similar with the legal agreements in national and international consortium.

### 2.2.3 Way of involvement

Too often, patients are seen as 'study objects' rather than 'experts by experience' and research projects are about them instead of involving them. It is essential to work together with individuals who have firsthand experience in the area being studied. The Involvement Matrix as presented in figure 5, developed by Smits et al.[13] can help with involving these 'experts by experience' in research projects. This is a tool for project leaders and

patients to engage in regular dialogue about their ideas, needs, roles and expectations. It also helps to establish clear agreements about the nature of involvement in a project. The Involvement Matrix includes five roles for involvement (Listener, Co-thinker, Advisor, Partner, and Decision-maker) over three main phases of research projects (Preparation, Execution, and Implementation). Although patient and public involvement in research is expected, implementing it into practice can often prove challenging for all parties. Applying the Involvement Matrix before and during different phases of a project, has the potential to help researchers and patients to make clear agreements about research involvement and engagement of patients. The tool can be used prospectively, to discuss about possible roles of patients in different phases of projects, and retrospectively to discuss whether roles were carried out satisfactorily.

***Figure 5:*** *Involvement matrix* [12]




Source: Involvement Matrix (kcrutrecht.nl) [12]

### 2.2.4 Mutual Benefits and Return of Engagement (ROE)

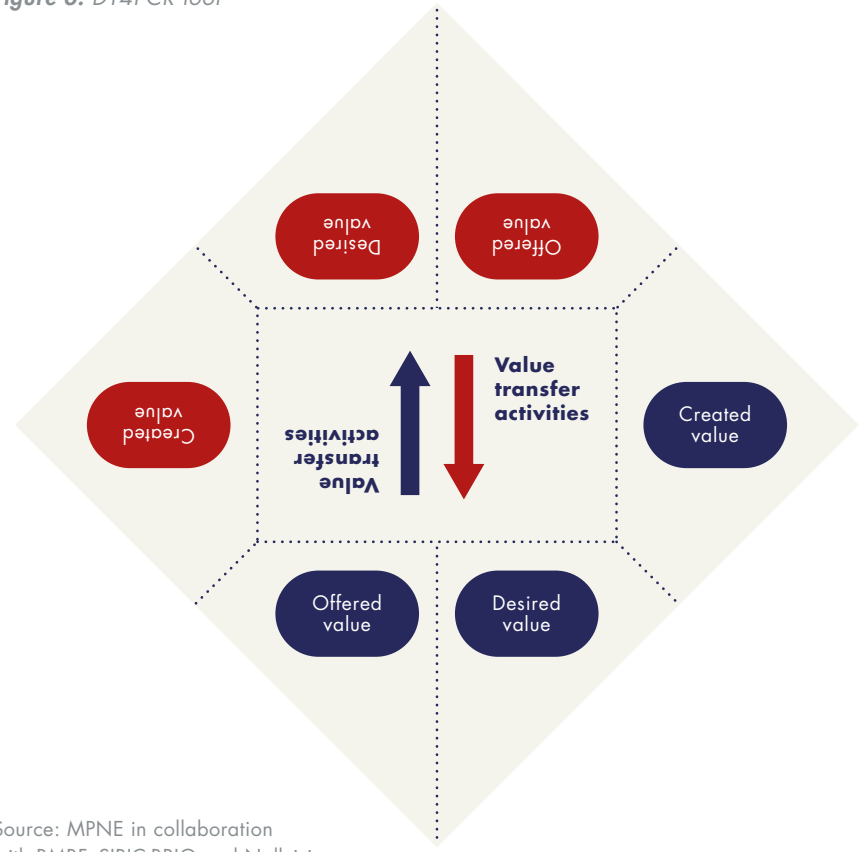
Relationships between patient organizations and partners (developers, regulators, companies, etc.) need to be mutually beneficial, with all parties contributing to and gaining from the interaction. This requires a level of negotiation similar to what we see in real partnerships. Figure 6 presents the Advocacy Partnership Canvas: Design Thinking for Patients in Cancer Research- (DT4PCR) developed by the MPNE. This DT4PCR canvas is a adjusted version of the Business Partnership Canvas. Running the DT4PCR at the start and the end of an activity, phase or project could help to document patients (or every stakeholder) expectations in comparison with the outcomes. DT4PCR tool could be used when considering patient involvement during the lifecycle of an ATMPs (to create clarity on the desired value and in identify new values in collaboration).

It's important to consider the limited resources of patients and patients advocacy groups. MPNE created a simple framework to assess the Return on Engagement for patients, patient advocacy groups and community. For patients and patient advocacy groups four domains of interest are identified:

- making a difference to patients and having impact on the disease;
- learning and acquiring skills that could be used in different contexts later;
- establishing a reputation as trusted party in the ecosystem and;
- funding.

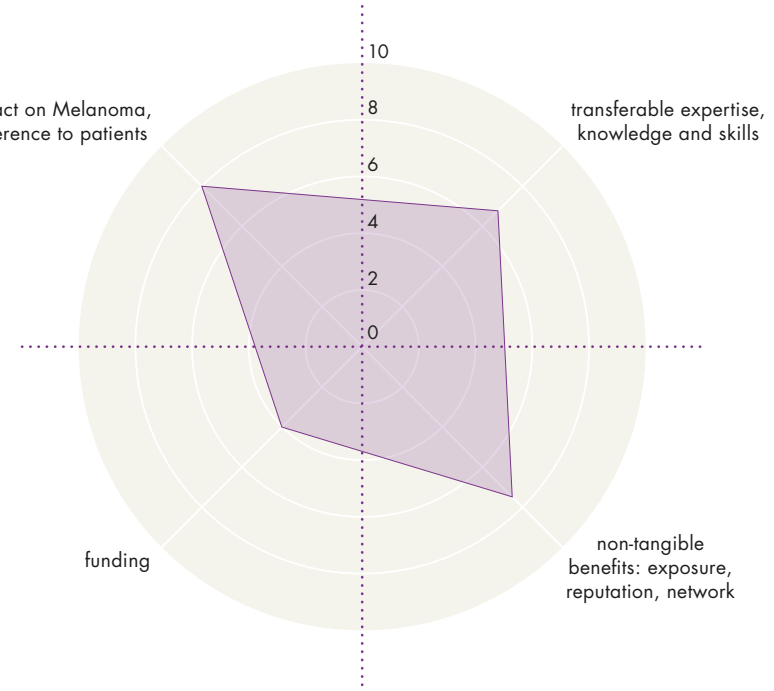
Lack in any of the above domains will lead to disinterest of patients and patient advocates to be involved.

*Figure 6: DT4PCR tool*




Source: MPNE in collaboration with BMBF, SIRIC-BRIO and Nollvision

*Figure 7: Return of Engagement for Patient Organisation (MPNE)*




Source: MPNE [14]

To ensure active involvement in ATMPs development, patient organizations need to see results of their influence and correct recognition of their contribution in the co-creation activities. For that reason measuring the consequences of such involvement could be done by accurate documentation of patient involvement (the involvement matrix could support this). Finally, it's important that their expertise, views and methods are also captured and published in peer reviewed articles.

## 2.3 Patient involvement by EMA-National Authorities

In the Marketing Authorisation (MA) procedure from 2025 onwards, a Joint Clinical Assessment (JCA) will be performed for all participating countries (see chapter 8.3.3 and 8.3.4). Within this JCA, patients, clinical experts, and other relevant experts get the opportunity to provide input on the draft reports prepared by the assessor and the co-assessor. Patients specifically have the opportunity to:

- provide input during the preparation of the draft document;
- participate in a face-to-face or virtual meeting with the developer. In this meeting patients can exchange views with the developer, clinical experts, and other relevant experts;
- review the draft reports and ensure the input they provided previously in the scoping process have been addressed adequately;
- address gaps and uncertainties, if they find the presented results insufficient or believe the research objectives/ interpretations are unclear or fail to reflect information important to patients.

# 3. Classification of ATMPs

## 3.1 Introduction

Regulation (EC) 1394/2007 provides the overall framework for ATMPs.[15] However, the regulatory requirements differ per type of ATMP (gene therapy medicinal product (GTMP), somatic cell therapy medicinal product (sCTMP), tissue engineered product (TEP) or combined ATMP). For that reason a correct classification is critical and, in case of doubt, it is recommended to determine the right classification at an early stage in the development. As of June 2009, the Committee for Advanced Therapies (CAT) provide recommendations on ATMPs classification. The CAT is a multidisciplinary committee, whose primary responsibility is to assess the quality, safety and efficacy of ATMPs and to follow scientific developments in the field.

A classification will depend on whether a product is being 'presented as having properties for treating or preventing disease' (i.e. the claims that are made for the product (Article 1 of Directive 2001/83/EC, definition of a 'medicinal product') and whether the product is intended to be administered to achieve a medicinal purpose. Borderline cases could appear where the classifications of drugs, ATMPs and medical devices overlap and a clear delineation between product types is not immediately obvious.

It is also important to determine whether your product is classified as an ATMP or not, as this defines whether the **Medicines Act** or the **SOHO (Substances of Human Origin)** regulation applies. Additionally, regulatory pathways differ significantly depending on whether you are developing a cell-based product or a gene therapy, which further emphasizes the need for accurate classification at the early stages of product development. See the relevant regulatory differences depending on the classification of your product.

## 3.2 Description of the four types of ATMP[16]

### 3.2.1 A gene therapy medicinal product (GTMP)

GTMP, as defined in Part IV of Annex I to Directive 2001/83/EC, means a biological medicinal product which has both of the following characteristics:

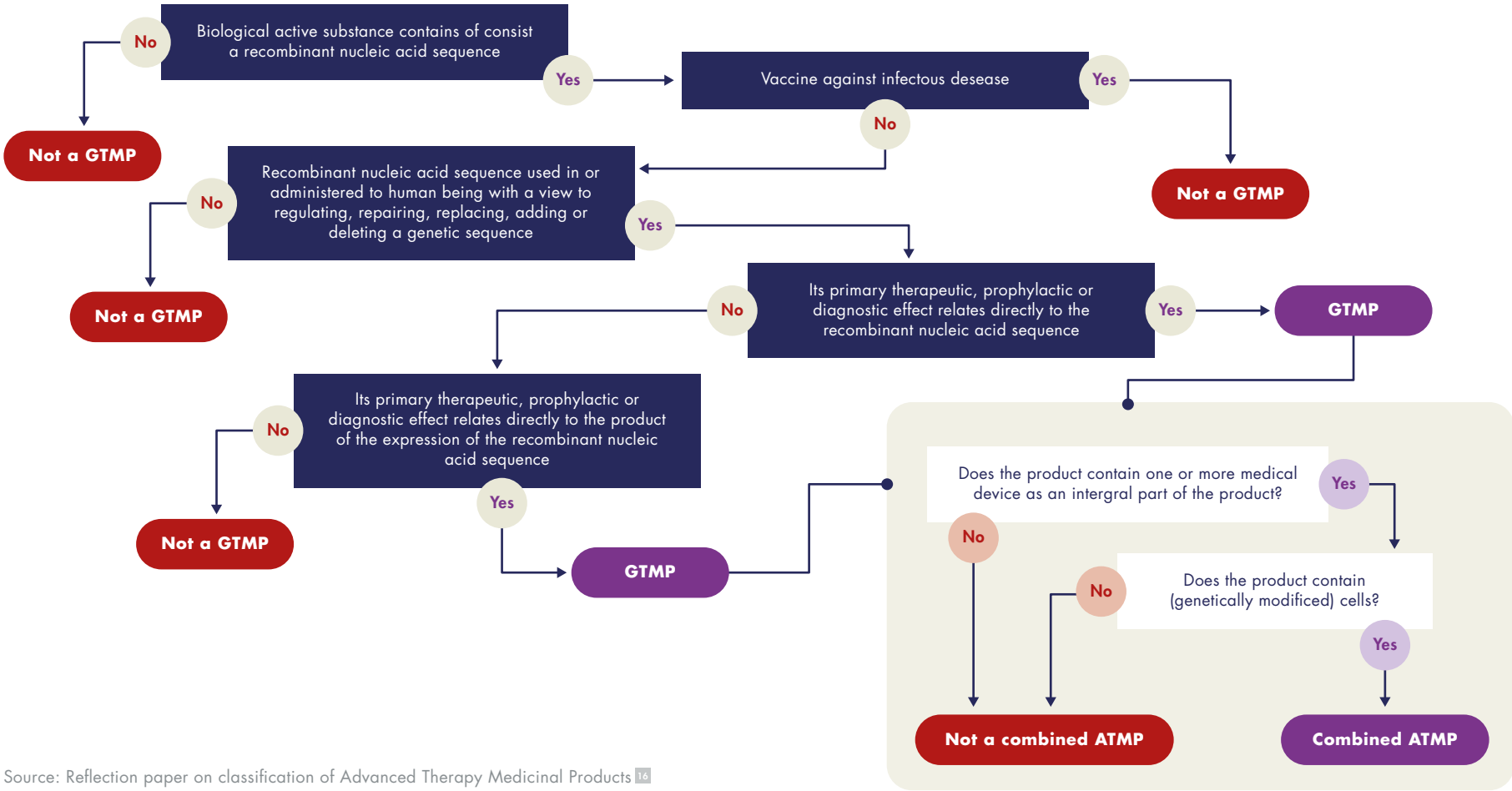
- it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;
- its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence. Gene therapy medicinal products shall not include vaccines against infectious diseases.

The following general inclusion and exclusion criteria apply:

- Products containing or consisting of animal cells or tissues to be administered to humans will always be considered as ATMPs.
- Products containing or consisting exclusively of non-viable cells or tissues and which do no act principally by pharmacological, immunological or metabolic action, will not be considered ATMPs.

The questions presented in the decision tree in figure 8 and 9 can help developers to classify their product.

*Figure 8: Decision tree for GTMP*




Source: Reflection paper on classification of Advanced Therapy Medicinal Products [16]

***Note:*** Oligo, siRNA and also genome editing like CRISPR-Cas9 do not fall within the current definition of GTMP: Indent (a) of the definition of Gene therapy medicinal product: the recombinant nucleic acids should be of biological origin independently from the origin of the vector system used (e.g. viral/bacterial vectors or micellar and liposomal formulations, etc.). Synthetic oligos and siRNA are currently not classified as ATMPs but as small molecules. Note that the European definition is different from the FDA definition.
***Note:*** Genetic manipulation does not necessarily have to take place in the human body, since for example products consisting of genetically modified cells generated ex vivo have also been classified as a gene therapy medicinal product Part IV of Annex I to Directive 2001/83/EC.
***Note:*** That in case a product fulfil the criteria of an sCTMP and GTMP (i.e. CAR-T cel therapy), the GTMP regulations apply since these are the most stringent.

### 3.2.2 A somatic cell therapy medicinal product (sCTMP)

Somatic cell therapy medicinal product, as defined in Part IV of Annex I to Directive 2001/83/EC, means a biological medicinal product which has both of the following characteristics:

- contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;
- is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

For the purposes of the manipulations listed in Annex I to Regulation (EC) No 1394/2007, in particular, shall not be considered as substantial manipulations: cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation, and vitrification. It should be pointed out that this list of non-substantial manipulations is non-exhaustive.

The questions presented in the decision tree in figure 8 and 9 can help developers to classify their product.

### 3.2.3 A tissue engineered product (TEP)

Tissue engineered products, as defined in Article 2(1)(b) of Regulation (EC) No. 1394/2007, means a product that:

- contains or consists of engineered cells or tissues, and;
- is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue.

A tissue engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices.

Products containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, are excluded from this definition.

Article 2(1)(c) of Regulation (EC) No.1394/2007 also states that cells or tissues shall be considered 'engineered', when they fulfil at least one of the following criteria:

- substantial manipulation: the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. The manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations;
- different essential function (non-homologous use): the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.

For more information see Article 2(1)(c) of Regulation (EC) No. 1394/2007) pag. 5 en 6- Reflection paper on classification of advanced therapy medicinal products. The questions presented in the decision tree in figure 8 and 9 can help developers to classify their product.

### 3.2.4 A combined ATMP

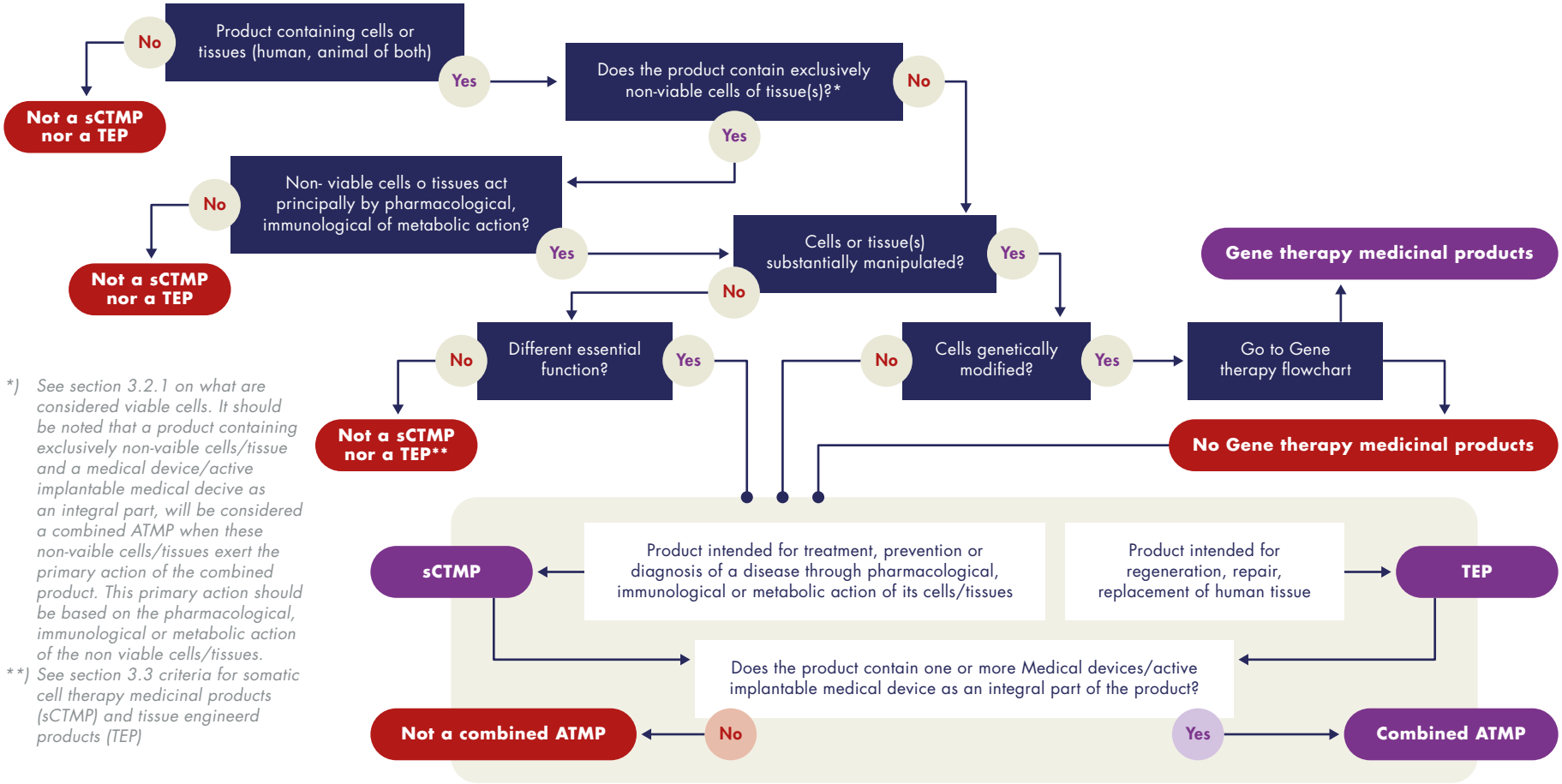
A 'Combined advanced therapy medicinal product' as defined Article (2)(1)(d) of the ATMP Regulation means an ATMP that fulfils the following conditions:

- it must incorporate, as an integral part of the product, one or more medical devices within the meaning of Article 1(2)(a) of Directive 93/42/EEC or one or more active implantable medical devices within the meaning of Article 1(2)(c) of Directive 90/385/EEC, and;
- its cellular or tissue part must contain viable cells or tissues, or;
- its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to.

For requirements for medical devices and implantable medical devices please consult the relevant European Commission guidelines and Medical Device Legislation, as appropriate.

Combined ATMPs incorporate an active substance, i.e. a cellular or tissue part consisting of viable or non-viable cells or tissues and of one or more medical devices or one or more active implantable medical devices as an integral part of the product. The medical device or active implantable medical device(s) should be used in the combination in the same way as its intended use without additional components. If cells or tissues are not viable these must exert the primary action of the combined product. (Article 2(1)(d) of Regulation (EC) No 1394/2007)

***Figure 9:*** *Decision tree for sCTMP and TEP*




**) See section 3.2.1 on what are considered viable cells. It should be noted that a product containing exclusively non-vaible cells/tissue and a medical device/active implantable medical decive as an integral part, will be considered a combined ATMP when these non-vaible cells/tissues exert the primary action of the combined product. This primary action should be based on the pharmacological, immunological or metabolic action of the non viable cells/tissues.*

***) See section 3.3 criteria for somatic cell therapy medicinal products (sCTMP) and tissue engineerd products (TEP)*

Source: Reflection paper on classification of Advanced Therapy Medicinal Products [16]

### 3.2.5 Additional clarification

With regards to products containing cells or tissues, Article 2(2) states that:

- "Where a product contains viable cells or tissues, the pharmacological, immunological or metabolic action of those cells or tissues shall be considered as the principal mode of action of the product."

For Tissue Engineered products their Mode of Action is linked to regeneration, repair or replacement a human tissue, as described in Article 2(1)(b).

- In accordance with Article 2(3), an ATMP containing both autologous and allogeneic cells or tissues shall be considered to be for allogeneic use.

Demarcation rule between ATMPs. Article 2(4) and 2(5) states that:

- "A product which may fall within the definition of a tissue engineered product and within the definition of a somatic cell therapy medicinal product shall be considered as a tissue engineered product. A product which may fall within the definition of a somatic cell therapy medicinal product or a tissue engineered product, and a gene therapy medicinal product, shall be considered as a gene therapy medicinal product."

## 3.3 Classification and differentiation Criteria for sCTMPs and TEPs

### 3.3.1 Criteria for somatic cell therapy medicinal products (sCTMP) and tissue engineered products (TEP)

sCTMP and TEP both contain or consist of engineered cells or tissues. To be considered 'engineered', cells or tissue(s) should fulfil at least one of the following criteria:

**Substantial manipulation:** The cells or tissue(s) have been manipulated during the manufacturing process so that their biological characteristics, physiological functions or structural properties have been modified to be relevant for their intended function. Examples of substantial manipulations include:

- cell expansion (culture), Cell culturing leading to expansion is considered substantial manipulation. Induction of proliferation of cells during cell culture has to be regarded as changes of their biological characteristics and structural properties, either because of an immediate change in cell functionality or cell phenotype, or by increasing cell numbers to augment the desired function of the cells;
- genetic modification of cells;
- differentiation/activation with growth factors.

**Different essential function (non-homologous use)**: In case no substantial manipulation of the cells/tissues takes place, the classification is based on the essential function of the cells/tissues. Such non-substantially manipulated cells or tissues used for the same essential function are not considered ATMPs. The same essential function for a cell population means that the cells when removed from their original environment in the human body are used to maintain the original function(s) in the same anatomical or histological environment.

### 3.3.2 Differentiation between sCTMP and TEP

The main difference between sCTMP and TEP is determined on the basis of the claimed mode of action in association with its associated claimed intended function.

- **sCTMPs**: These are intended for the prevention, diagnosis and/or treatment of diseases via pharmacological, metabolic actions.
- **TEPs**: These are used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue. The CAT considers that a product consisting of engineered cells that induces regeneration, repair or replacement in the native tissue e.g. via secretion of paracrine factors (by the engineered cells/tissue), also fulfils the definition of a TEP.

In many cases, such products would also fulfil the definition of a sCTMP, and therefore the classification as TEP is based on the demarcation rule in art. 2(4) of the ATMP Regulation (the replacement of urethral sphincter muscle cells, or to repair respective injured tissue). It should be noted that the effect of a tissue engineered product can be transient, e.g. autologous human keratinocytes intended for the treatment of acute burns may only transiently repair the underlying structure and later be replaced.

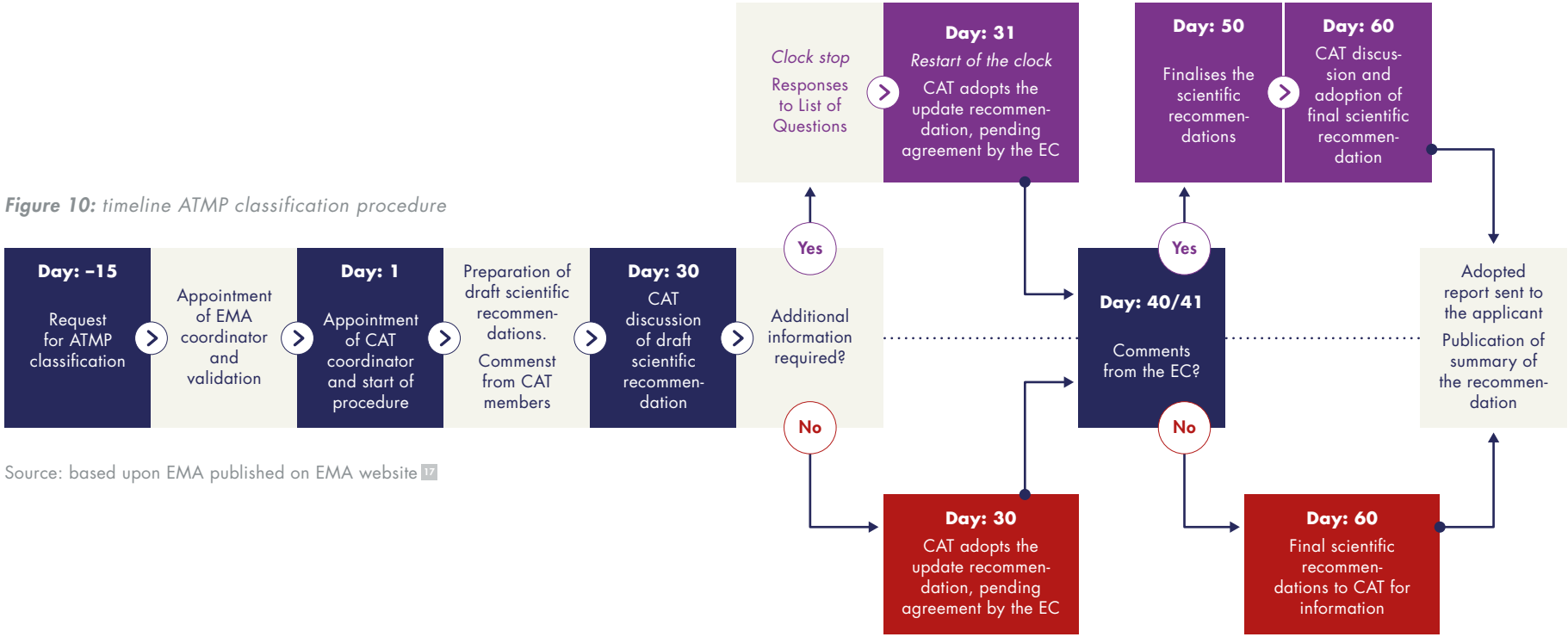
## 3.4 Optional Classification Procedure

The criteria for ATMPs are set out in Article 17 of Regulation (EC) No 1394/2007. In case of questions or borderline cases, applicants have access to an optional procedure which is the EMA's CAT scientific recommendation for the classification of ATMPs. This procedure will determine whether or not the referred product falls within the scope of the definition of ATMPs in the European Union (EU) and will address questions of borderline cases as early as possible. It provides clarity on the development path and scientific-regulatory guidance. The CAT delivers scientific recommendation within 60 days after receipt of the request. EMA publishes the outcome of the classification assessments of ATMPs as summary reports.

### 3.4.1 Guidelines, timelines and publication of the classifications

- The procedure is described in the regulatory procedural guideline (1934/2007).
- For submission the Request form Template is used.
- Dates for submission are mentioned on the EMA advanced therapies website.
- Procedure takes 60 days. At day 30, a clock stop of 1 month is possible when additional information is requested as presented in figure 10.
- EMA publish summaries of the recommendations. In the report a section initially proposed by the applicant and revised by the EMA Coordinator includes information on: product description, therapeutic area, outcome of the scientific recommendation, date.
- Within 7 calendar days, the applicant can comment on this section of the report taking into account the principles of confidential information, as described in the relevant EMA policies.

*Figure 10: timeline ATMP classification procedure*




Source: based upon EMA published on EMA website [17]

### Key take-aways

The correct classification is critical and determines specific requirements from non-clinical research up until reimbursement and use in clinical practice. It is recommended to consult the EMA and determine the right classification at an early stage in the development.

***Support:*** Applicants have access to an optional (not obliged) free of charge procedure, the CAT scientific recommendation for the classification of ATMPs. The procedure will determine whether or not the referred product falls within the scope of the definition of ATMP in the EU and will address as early as possible questions of borderline cases. It provides clarity on the development path and scientific-regulatory guidance. The CAT delivers scientific recommendation within 60 days after receipt of the request. EMA publishes summary reports of the classification assessments of the assessment of the classification of ATMPs as summary reports.

# 4. Regulation and Legislation

## 4.1 Introduction

The EMA classifies ATMPs as medicinal products, making them subject to the European legislation and regulations on medicinal products. Due to the unique and complex nature of ATMPs, additional legislation is required to address the various types specifically. Just as all other modern biotechnology medicinal products, ATMPs are subject to a centralised European marketing authorisation (MA) procedure, involving a single scientific evaluation of the quality, safety and efficacy of the product, carried out by the EMA, resulting in a single MA. The centralised MA is valid in all EU Member States, as well as in the European Economic Area (EEA) countries Iceland, Norway and Liechtenstein.

This chapter provides a general overview of the legislation governing medicinal products, including the newly anticipated General Pharmaceutical Legislation (GPL) for human medicines. It also covers the complementary legislation and regulations that apply to different types of ATMPs. Additionally, the chapter delves into various Good Practice Guidelines and Regulations: Good Laboratory Practice (GLP), Good Clinical Practice (GCP), Good Manufacturing Practice (GMP), and Good Distribution Practice (GDP) and Good Pharmacovigilance Practice (GPV), which are essential for ensuring the quality and safety of ATMPs. The goal is to equip developers with a comprehensive understanding of the legislative landscape and the key requirements concerning ATMPs. This knowledge will support developers in their discussions with legal experts and consultants during the study design phase and the EMA application process.

***Note:*** Given that the legislation is complex and different sets of regulations are applicable, it's strongly advised to seek expert guidance and make use of scientific advice offered by the EMA and the Centrale Commissie Mensgebonden Onderzoek (Central Committee on Research involving Human Subjects - CCMO).

## 4.2 General Pharmaceutical Legislation

### 4.2.1 Current EU pharmaceutical legislation

The current EU pharmaceutical legislation concerning the production, distribution and use of medicinal products includes both general and specific legislation. The following general pharmaceutical legislation (GPL) lays down provisions related to definitions, its scope, the granting of an MA, the different MA procedures, and post-authorisation requirements, pre-authorisation support schemes, regulatory incentives in terms of data and market protection, manufacturing, distribution, pharmacovigilance, advertising and supervision:

- Directive 2001/83/EC (consolidated version 16/11/2012) of November 2001 on the Community code relating to medicinal products for human use.
- Regulation (EC) No 726/2004 (consolidated version 5/6/2013) of March 2004 on the Union procedures for the authorisation and supervision of medicines for human and veterinary use and establishing the EMA.

Directive 2001/83/EC and Regulation (EC) No 74/2006 are complemented by specific legislation on ATMPs (Regulation (EC) No 1394/2007, the 'ATMP Regulation'), orphan medicinal products (Regulation (EC) No 141/2000, the 'Orphan Regulation'), and medicinal products for children (Regulation (EC) No 1901/2006, the 'Paediatric Regulation').

The body of European Union legislation related to medicinal products for human use is compiled in Volume 1 of the publication "The rules governing medicinal products in the European Union". The basic legislation is supported by a series of guidelines that are also published in "The rules governing medicinal products in the European Union":

- The Notice to Applicants
- Scientific Guidelines and Regulatory and procedural guidance documents for MA applications with EMA

They are not legally binding and, in case of doubt, reference should be made to the appropriate Union Directives and Regulations. The Notice to Applicants represents the harmonised view of the Member States, EMA and the European Commission on how the legal requirements of the GPL may be met.

*Complete harmonisation*

Directive 2001/83/EC, Regulation (EC) No 726/2004 and the specific EU legislation bring about complete harmonisation of the system of authorisation procedures for medicinal products, and also complete harmonisation in other fields. The Directive and the Regulations list expressly the cases in which Member States are authorised to adopt provisions departing from the rules laid down by that Directive or Regulation.

*General rules; authorisation principle*

As a main rule, no medicinal product may be placed on the EU market without an MA (Art. 6 Directive 2001/83/EC; Art. 3(1) Regulation (EC) No. 726/2004; Art. 40(1)(2) Gnw). The manufacture of medicinal products and the importation of medicinal products coming from third countries (i.e., from outside the EU/EEA) into a member state is also subject to an Manufacturing and Importation Authorization (MIA) (Art. 40 Directive 2001/83/EC; Art. 18(1) Gnw.). The wholesale distribution is subject to the possession of a Wholesale Distributor Authorisation (WDA) (Art. 76 and 77.1 Directive 2001/83/EC; Art. 18(1) Gnw.). These authorisations entail a prior assessment of medicinal products on the basis of criteria of quality, safety and efficacy (for MA) and a prequalification of those who make/distribute such products (for MIA, WDA).

The manufacturing and import of investigational medicinal products in the Union is also subject to the holding of an authorisation (Art. 61 Regulation (EU) No 536/2014; Art. 18(1) Gnw.). The authorisation requirements are intended to fulfil the objectives of Directive 2001/83/EC: to safeguard public health and elimination of hindrances to trade in medicinal products between Member States.

There are only some exemptions to these main principles. One of these exemptions that is specifically related to ATMPs, is the ATMP hospital exemption. The manufacturing, distribution and supply of ATMPs under the hospital exemption must be approved by the competent authority of the member state concerned (Art. 3(7) Directive 2001/83/EC; Art. 18(1) and Art. 40(3)(d) and Art. 40(8) Gnw.).

*National implementing legislation*

Regulations are legal acts that apply automatically and uniformly to all EU countries as soon as they enter into force, without needing to be transposed into national law. They are binding in their entirety on all EU countries. However, they may require changes in national legislation, and may require implementation by national agencies or regulators.

Directives on the other hand, must be incorporated by EU countries into their national legislation. In the Netherlands, Directive 2001/83/EC and some specific provisions related to the Regulations were implemented in the Dutch Medicines Act (Gnw) and the Medicines Act Regulations (RGnw).

*Competent authorities*

The MA for an ATMP will be granted by the European Commission, after an evaluation by EMA. The Dutch Minister of Health (MoH) is tasked with the granting of an MIA for the manufacture of medicinal products – including ATMPs – within the Netherlands. The MoH is also the competent authority for the granting of a WDA for wholesale distribution activities from premises located in the Netherlands. The Health and Youth Inspectorate (IGJ) is tasked with the granting of an approval for the supply and use of ATMPs under the hospital exemption in the Netherlands. It is important to note that such an approval cannot be equated to an MA.

### 4.2.2 Proposed reform of General Pharmaceutical Legislation (GPL)

In April 2023, the European Commission adopted proposals for a reform of the general pharmaceutical which will consist of two legislative proposals:

- a Commission proposal for a new directive, repealing and replacing Directive 2001/83/EC and Directive 2009/35/EC and incorporating relevant parts of the Paediatric Regulation (Regulation (EC) No 1901/2006) (COM/2023/192 final);
- a Commission proposal for a new regulation, repealing and replacing Regulation (EC) No 726/2004, repealing and replacing the Orphan Regulation (Regulation (EC) No 141/2000) and repealing and incorporating relevant parts of the Paediatric Regulation (Regulation (EC) No 1901/2006)(COM/2023/192 final).

This proposed reform is comprehensive, targeted and focuses on provisions relevant to achieving its specific objectives. It covers all provisions apart from those concerning advertising, falsified medicinal products, and homeopathic and traditional herbal medicinal products. Medicinal products for rare diseases and for children will continue to fall under the same provisions as any other medicinal product concerning their quality, safety and efficacy, for example concerning the MA procedures, pharmacovigilance and quality requirements. However, specific requirements will continue to apply to these types of medicinal products in order to support their development. These requirements, which are currently laid down in separate legislative acts, should be integrated into this regulation and the directive in order to ensure clarity and coherence of all the measures applicable to these products.

Points specifically related to ATMPs that are being discussed are (inter alia) exemptions for orphan medicinal products and ATMP developers related to regulatory data protection and the obligation to file for pricing and reimbursement upon request by Member States within 12 months, the clarification of the scope of the ATMP hospital exemption (HE products),

cross-border exchange of HE products and provisions on more transparency and reporting in connection with HE products.

In April 2024, the European Parliament adopted its position on the reform of the core EU pharmaceutical legislation. Discussions on the Commission proposals are ongoing in the Council. Once the Council has adopted its position, trialogue negotiations between the Commission, Parliament and Council can start. It is not expected that the legislation will be adopted before 2026. Also, transitional and implementation periods are likely to be lengthy (18 months or more).

## 4.3 Complementary specific legislation

### 4.3.1 Regulatory Framework for Advanced Therapy Medicinal Products

The regulatory framework for ATMPs is designed to ensure the free movement of these medicines within the EU, EEA and the effective operation of the internal market in the biotechnology sector, to facilitate their access to the EU market, and to foster the competitiveness of European pharmaceutical companies in the field, while guaranteeing the highest level of health protection for patients. Regulation (EC) No 1394/2007 of the European Parliament and of the Council on ATMPs (consolidated version) (ATMP Regulation) introduces additional provisions and Directive 2001/83/EC and Regulation (EC) 726/2004. It lays down specific rules concerning the marketing authorisation, supervision and pharmacovigilance of ATMPs. Commission Directive 2009/120/EC (amending Directive 2001/83/EC) updated the definitions and detailed scientific and technical requirements for gene-therapy medicinal products and somatic cell-therapy medicinal products. It also established detailed scientific and technical requirements for tissue-engineered products, as well as for ATMPs containing devices and combined ATMPs. The CAT issues scientific recommendation on ATMPs classification in accordance with Article 17 of the ATMP Regulation. Its recommendations are based on the legal definitions laid down in the ATMP Regulation (See also chapter 3).[15]

### 4.3.2 Regulatory framework for ATMPs Containing Genetically Modified Organisms (GMOs)

If an ATMP contains genetically modified organisms (GMOs), developers must follow relevant legislation on the deliberate release of genetically modified organisms into the environment. In the Netherlands medicinal products containing GMOs are regulated under Directive 2001/18/EC, which provides a step-by-step process to assess possible environmental and health risks and is implemented under the terms of the Environmental Management Act. However, in some countries GMOs are regulated under national provisions implementing Directive 2009/41/EC ("Contained Use"). National regulatory requirements (EU countries and Norway) for medicinal products containing GMOs can be found here: GMO aspects for investigational medicinal products.

### 4.3.3 European Pharmacopoeia

The European Pharmacopoeia (Ph. Eur.) is a compendium of texts on the qualitative and quantitative composition of medicines, and on the tests to be carried out on. As laid down in the Council of Europe Convention on the Elaboration of a European Pharmacopoeia and in EU and national pharmaceutical legislation, these standards are legally binding.

With gene therapy advancing, the European Pharmacopoeia Commission (EPC) recognized the need for a standardized way of controlling GTMPs.

In March 2020, the EPC outlined a new approach to GTMPs for human use, prioritizing this area for 2023-2025.

In 2024, the EPC adopted the general monograph *Gene therapy medicinal products for human use (3186)* and the accompanying general chapter *Additional information on gene therapy medicinal products for human use (5.34)*, which will replace general chapter *5.14. Gene transfer medicinal products for human use*.

In addition to a general requirements section containing provisions on the production of all GTMPs and specific requirements for recombinant vectors and genetically modified cells for human use, general monograph 3186 contains three individual sections describing additional requirements for the classes of GTMPs currently approved in Europe:

- Genetically modified human autologous cells modified by integrating retroviral or lentiviral vectors;
- Adeno-associated virus vectors for human use;
- Oncolytic herpes simplex virus for human use.

The accompanying general chapter 5.34 includes recommendations on product classes that are not yet on the European market to assist users and contains:

- The revised remaining sections of chapter 5.14, covering:
  - Plasmid vectors for human use;
  - Adenovirus vectors for human use;
  - Poxvirus vectors for human use;
  - Retroviridae-derived vectors for human use.
- A newly drafted section on genetically modified bacterial cells for human use.

In addition, general chapter *5.2.12. Raw material of biological origin for the production of cell-based and gene therapy medicinal products* has also been revised to align it with this new approach.

### 4.3.4 Regulatory Framework for ATMP Starting Materials: Human Tissues, Cells, and Blood Components

When starting materials of ATMPs exist of cells or tissue, Directive 2002/98/EC of January 2003 (amending Directive 2001/83/EC) is relevant. It covers standards for donation, procurement and testing, processing, preservation, storage and distribution of human tissues and cells, as well as its technical implementing directives:

- Directive 2006/17/EC, the First Technical Directive, covering certain technical requirements for the donation, procurement and testing of human tissues and cells.
- Directive 2006/86/EC, the Second Technical Directive, covering standards for traceability, notification of serious adverse reactions and events (SAE), and requirements for coding processing, preservation, storage and distribution of human tissues and cells.
- Directive 2015/565, amending Directive 2006/86/EC, as regards certain technical requirements for the coding of human tissues and cells.
- Directive 2015/566, as regards the procedures for verifying the equivalent standards of quality and safety of imported tissues and cells.

When starting materials of ATMPs exist of Human blood and blood components, Directive 2002/98/EC (amending Directive 2001/83/EC) of January 2003 sets standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components.

Although these directives have, to a certain degree, harmonized the national rules in the area of safety and quality of blood, tissues and cells, they allow a significant number of options for Member States in terms of how they implement the rules. Divergences between national rules can create obstacles to cross-border sharing of these substances. The two directives are interconnected and contain very similar provisions. As underlined by the Commission in its proposal, it would make sense to merge the revised provisions into one directly applicable legal act (a regulation).[18]

### 4.3.5 Substance of Human Origin

On 17 July 2024, the new Regulation (EU) 2024/1938 on standards of quality and safety for substances of human origin intended for human application (SoHO Regulation) was published in the Official Journal of the EU. The new SoHO Regulation is aimed at improving the safety and quality of blood, tissues and cells used in healthcare and facilitating cross-border circulation of these substances in the EU. The SoHO Regulation will ensure better protection for donors and recipients, as well as for children born following medically assisted reproduction. The new rules aim to strengthen the existing legal framework while also increasing flexibility in order to keep up with scientific and technical developments. It also aims to future-proof the EU's legislation by covering other SoHO that may be applied to humans in the future and by allowing more flexible future updates. The regulation covers a wide range of activities from registration and testing of donors, collection and processing to human application, clinical outcome monitoring of substances of human origin and vigilance.

The SoHO Regulation should apply to blood and blood components, as well as to tissues and cells, including haematopoietic peripheral blood, umbilical-cord blood and bone-marrow stem cells, reproductive cells, tissues and embryos, foetal tissues and cells and adult and embryonic stem cells, are used as starting materials for ATMPs. The provisions of this Regulation will also apply to the storage, import and export of SoHO until their distribution to a manufacturer regulated by other Union legislation. This means that close interaction between this regulatory framework and other related frameworks (i.e.) Directive 2001/83/EC and Regulations (EC) No 1394/2007 is essential to ensure coherence between relevant legal frameworks, without gaps or overlaps.

The proposal will introduce the following new rules:

- All substances of human origin would be covered (examples of new substances added include human breast milk and intestinal microbiota), with the exception of solid organs for transplantation, which are governed by Directive 2010/53/EU; other substances of human origin that may, in the future, be applied to patients would automatically fall within the scope of this legislation.
- Protection would be improved for recipients of SoHO therapies, as well as for donors of SoHO and offspring from medically assisted reproduction.
- The expertise of existing technical bodies in Europe (notably the European Centre for Disease Prevention and Control and the European Directorate for the Quality of Medicines & HealthCare (Council of Europe)) would be used to keep technical guidelines up to date.
- Entities working with SoHOs would be required to report their annual activity data. This would allow Member States to implement measures to improve donation collection rates when needed. Entities working with

critical SoHOs would need to alert their authority in the event of a sudden fall in supply and would be required to have emergency plans in place.
- Provision is made for stronger support for innovation, with a common procedure to assess and authorise SoHO preparations, proportionate to the risks these bring; all entities carrying out activities affecting the safety and quality of SoHO would be required to register.
- A SoHO Coordination Board (SCB) would work with and for the Member States to support implementation of the new regulation, to support companies to decide on a particular substance, to connect different legal frameworks and document best practices.
- An EU SoHO Platform should contribute to improve transparency of reporting and SoHO supervisory activities and to the exchange of information between relevant parties, including decisions on the regulatory status of substances, products or activities. The EU SoHO Platform should also serve as a reliable source of information for the general public regarding the work of the SCB, SoHO National Authorities, expert bodies, including the European Directorate for Quality of Medicines (EDQM) and the European Centre for Disease Prevention and Control (ECDC), and SoHO entities. The online platform should be further used for the sharing of best practices agreed and documented by the SCB on SoHO supervisory activities.

With regard to SoHO preparations that pose a risk other than negligible, the developer/applicant should propose a plan for clinical outcome monitoring that should fulfil different requirements appropriate to the risk indicated. The most up-to-date guidance of the EDQM should be considered relevant in the design of clinical follow-up plans proportionate in extent and complexity to the identified level of risk of the SoHO preparation. In the case of low risk and a positive benefit-risk assessment, in addition to the mandatory continuous vigilance reporting, the applicant should organize proactive clinical follow-up for a defined number of SoHO recipients.

The new Regulation will apply as from 7 August 2027, 3 years after its publication and entry into force, with an extra year for certain provisions. It is important to note that certain topics have not been harmonized at an EU level, meaning that there is some room for national provisions.

### 4.3.6 Rare diseases/Orphan designation for ATMPs

If an ATMP is also an orphan medicine, the following framework for orphan medicines can also apply, in addition to the ATMP Regulation, Regulation (EC) No 726/2004 and Directive 2001/83/EC:

- Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.
- Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts ‘similar medicinal product’ and ‘clinical superiority.
- Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products (C/2016/7253).

For more legal background to the procedure for orphan designation in the European Union visit: Legal background: orphan designation.

### 4.3.7 Pediatric Regulation and ATMPs

Provisions of the Paediatric Regulation are applicable for ATMPs including the obligation to include the results of studies as described in an agreed

paediatric investigation plan, unless the medicine is exempt because of a deferral or waiver. The Paediatric Regulation is comprised of:

- Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004.
- Regulation (EC) No 1902/2006, an amending regulation in which changes to the original text were introduced relating to decision procedures for the European Commission.

For more background information visit: Paediatric Regulation.

## 4.4 Good Practice Legislations

### 4.4.1 Good Laboratory Practice (GLP)

Good laboratory practice (GLP) defines a set of rules and criteria for a quality system concerned with the organisational process and the conditions under which **non-clinical studies** are planned, performed, monitored, recorded, reported and archived.

Detailed information about GLP can be found on:

- website of the Organisation for Economic Co-operation and Development (OECD).
- Directive 2004/9/EC.
- Directive 2004/10/EC.
- Annex I to Directive 2001/83/EC (consolidated version) indicates that safety tests reported in Marketing Authorisation Application (MAA) should be performed in compliance with the principles of GLP.

IGJ is tasked with the supervision of test facilities within the Dutch territory to verify that safety studies are being conducted in accordance with the GLP requirements.

### 4.4.2 Good Clinical Practice (GCP)

GCP is an international ethical and scientific quality standard for designing, recording and reporting trials that involve the participation of human subjects. All **Clinical trials** conducted within the European Union must comply with the requirements of the EU rules concerning clinical trials. The sponsor of a clinical trial and the investigator shall ensure that the clinical trial is conducted in accordance with the protocol and with the principles of Good clinical practice (GCP). Compliance with GCP provides public assurance that the rights, safety and wellbeing of trial subjects are protected; consistent with the principles that have their origin in the declaration of Helsinki, and that the clinical trial data are credible.

If clinical trials are conducted outside the EU but submitted for marketing authorisation in the EU, they have to follow similar principles to the provisions of the Regulation as regards the rights and safety of the subject and the reliability and robustness of the data generated in the clinical trial.

The legal requirements to conduct clinical trials within the European Union, including GCP, GMP and inspections, are set out in the:

- Clinical Trials Regulation 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.
- Commission Implementing Regulation 2017/556 and Commission Delegated Regulation (EU) 2017/1569.

- Guidelines on clinical trials are available under 'EudraLex – Volume 10' of "The rules governing medicinal products in the European Union"; these include guidelines specific to ATMPs:
  - Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials - Scientific guideline, guidance on the structure and data requirements for a clinical trial application for exploratory and confirmatory trials with ATMPs.
  - Guideline on quality preclinical-clinical aspects gene therapy.

From 31 January 2025 onwards only the Clinical Trials Regulation (EU) 536/2014 (CTR) and its Delegated Acts will apply. Ongoing clinical trials currently governed by the Clinical Trial Directive 2001/20/EC (CTD) and expected to continue after 30 January 2025 will need to transition to the CTR regulatory framework. If such clinical trials have not transitioned to the CTR by that date, they will be considered non-compliant and in breach of the CTR.

The provisions of the Clinical Trials Regulation are implemented in the Netherlands through the Medical Research (Human Subjects) Act (WMO) and the Gnw.

### 4.4.3 Good Manufacturing Practice (GMP)

Good manufacturing practice (GMP) is defined as that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use. Compliance with these principles and guidelines is mandatory.

Manufacturers are required to comply with GMP (Art. 46 Directive 2001/83/EC; Art. 27(1) Gnw and Art. 2.1 RGnw). Compliance with GMP is also required for the manufacturing of investigational medicinal products (Art. 63 Regulation (EU) No 536/2014). It is assumed that GMP also applies to the manufacturing of ATMPs under the hospital exemption. Directive 2001/83/EC also includes certain provisions relating to GMP and the manufacture, import and distribution of active substances.

Principles and guidelines for GMP laid down in:

- For investigational medicinal products: Commission Delegated Regulation (EU) 2017/1569.
- For medicinal products for human use Commission Directives (EU) 2017/1572.

EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines contains guidance for the interpretation of the principles and guidelines of GMP. There are specific Guidelines on Good Manufacturing Practice for Advanced Therapy Medicinal Products. EMA has published "Questions and answers on the use of out-of-specification batches of authorised cell/tissue-based advanced therapy medicinal products."

More information is provided:

- On the EMA website.
- On the website EudraGMDP (manufacturing/importation authorisations and GMP certificates).

The national competent authorities of the member state are responsible for:

- The granting of a manufacturing authorisation for the manufacture of medicinal products within their territory and for imports coming from third countries (i.e. from outside the EU/EEA) into a member state (in the Netherlands: the MoH);
- Performing site inspections (in the Netherlands: IGJ);
- Where applicable, issuing a GMP certificate after an inspection and registering these certificates into the EudraGMDP database (in the Netherlands: IGJ);
- Where applicable, issuing a statement of non-compliance / non-compliance report and registering such statements into the EudraGMDP database (in the Netherlands: IGJ);
- Imposing penalties for infringement of the provisions related to manufacturing.

A Marketing Authorisation Holder (MAH) is obliged to comply with GMP requirements and to use as starting materials only active substances manufactured in accordance with the guidelines on GMP for starting materials. The active pharmaceutical ingredient (API) registration certificates are publicly accessible through the EudraGMDP database. Finished product manufacturers are required to verify that the active substances used in their products are manufactured according to GMP through audits of the manufacturer.

The falsified medicines Directive 2011/62/EU introduced, for human medicines, strengthened provisions for the supervision of active substance manufacture, which includes an obligation for national competent authorities to register active substance manufacturers, importers and distributors established on their territories. Information on the legal framework on the falsified medicines directive can be found on the European Commission website.

### 4.4.4 Good Distribution Practice (GDP)

The distribution of medicinal products is an important activity in the integrated supply chain management. Good distribution practice (GDP) should be implemented through a quality system. The aim of GDP is to ensure that the level of quality of authorised medicines, determined by GMP, is maintained throughout the distribution network up until to the patient. The quality system should also ensure the right products are delivered to the right addressee within a satisfactory time period. A tracing system should enable any faulty products to be found and there should be an effective recall procedure.

The wholesale distribution of medicinal products is subject to the possession of an authorisation to engage in activity as a wholesaler in medicinal products, stating the premises for which the authorisation is valid (Art. 77(1) Directive 2001/83/EC; Art. 18(1) Gnw). Wholesalers must fulfil certain minimum requirements, including compliance with GDP (Art. 80(g) Directive 2001/83/EC; Art. 36(1) Gnw and Art. 2.1(2) RGnw). The GDP Guidelines are published by the European Commission (Art. 84 Directive 2001/83/EC; Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use, 2013/C 343/01).

- Directive 2001/83/ EC, principles of GDP.
- Commission Guideline 2015/C 95/01, guidance on good distribution practice.
- Directive 2011/62/EU, obligations for wholesale distributors and brokers.
- on the website EudraGMDP (manufacturing authorisations and GDMP certificates).

### 4.4.5 Good Pharmacovigilance Practice (GPV)

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. Good pharmacovigilance practices (GVP) are a set of measures drawn up to facilitate the performance of pharmacovigilance in EU. GVP apply to marketing-authorisation holders, EMA and medicines regulatory authorities in EU Member States. They cover medicinal products authorised centrally via the Agency as well as medicinal products authorised at national level. Many of the challenges in safety monitoring of medicines stem from the limited amount of information available from clinical trials at the time of authorisation. Patients in clinical trials are selected carefully and followed up very closely under controlled conditions. After authorisation, however, patients using a medicine may have other diseases and may be taking other medicines. It will also be used in a larger number of patients, raising the possibility that rare side effects could start to be seen only once the medicine is being used in practice. Some side effects may only start to emerge once a medicine has been used for a long time. By continuing to collect information once a medicine is available and taking action in response, regulators can continue to protect the public from emerging safety issues throughout a medicine's lifecycle.

Most relevant legislation is:

- Directive 2001/83/EC (consolidated version).
- Regulation (EC) No. 726/2004 (consolidated version).
- Commission Implementing Regulation No 520/2012, concerns operational aspects of implementing the new legislation.

Guidelines:

- Good pharmacovigilance practices (GVP) modules, Practical measures to facilitate the performance of pharmacovigilance are available in the guideline on good pharmacovigilance practices (GVP).
- EMEA/149995/2008, ATMP-specific guidelines.
- Guideline on safety and efficacy follow-up - risk management of ATMPs, The EU Risk Management Plan (EU-RMP) and the Detailed Description of the Pharmacovigilance System (DDPS) have additional requirements for ATMPs.

For more information, see:

- Pharmacovigilance legislation.
- Pharmacovigilance for ATMPs.

### 4.4.6 Pharmacovigilance system master file

MAHs are required to maintain a Pharmacovigilance System Master File (PSMF) which includes an overview of the MAH's current pharmacovigilance system related to one or more products. The PSMF should be permanently available for submission or inspection by the national competent authority within seven days of request. It should be located either at the site in the EU where the main pharmacovigilance activities of the MAH are performed or at the site in the EU where the qualified person responsible for pharmacovigilance (QPPV) operates. This file may be also stored in electronic form. At time of MAA, the applicant should submit electronically in the extended EudraVigilance medicinal product dictionary (XEVMPD) information on the PSMF location using the agreed format for an extended EudraVigilance product report message (XEVPRM). The XEVMPD will then assign a unique code (EVCODE) to the master file location, which can be noted in the application. After the granting of the MA, any change to the PSMF should

be communicated to the authorities through the Article 57 database only, without the need to submit a variation.
The PSMF is not part of the MA dossier and is maintained independently from the MA. The MAA contains only a reference to the location and a summary of the applicant's pharmacovigilance system. A list of locations where PSMFs are kept and contact information for pharmaco vigilance enquiries is published by EMA. GVP module II provides guidance on the requirements for the PSMF, including its maintenance, content and associated submissions to the competent authorities.

### 4.4.7 Additional RMP and PharmacoVigilance reguirements for ATMPs

The EU Risk Management Plan (EU RMP) and the Detailed Description of the Pharmacovigilance System (DDPS) have additional requirements for ATMPs. Because of their novelty, complexity and technical specificity, they may bring along new, unexplored risks to public health and to individual patients (See chapter 4.4.5).
The specific rules described in a specific Guideline on safety and efficacy follow-up - risk management of ATMPs of Regulation (EC) No 1394/2007 and should facilitate early detection of such risks and provide a framework for effective mitigation of their consequences to public health or to individual patients.
The guideline provisions are of "overarching" character, which means that they describe a framework of regulatory requirements applicable to all ATMPs. Specific provisions for gene therapy, cell therapy and tissue engineering products are included in product type specific guidelines.
The guideline encourages developers of ATMPs to plan timely interactions with EMA to discuss:

- early detection of risks during development;
- a framework for the effective mitigation of their consequences for patients;
- the design of appropriate post-authorisation studies to follow up on the safety and efficacy.

*In addition to the requirements for RMP detailed in Volume 9A, the following parts should be included in the RMP of an ATMP:*
*In Part I of the EU-RMP* a new chapter for ATMPs is introduced within the section Additional EU Requirements of the Safety Specifications. Groups of risks that are more targeted to ATMPs should be discussed there in an order that follows the procurement in living donors, the product manufacturing, administration, and follow-up of patients.

- flow-chart of the logistics of the therapy (for instance, harvesting, transport, controls, manipulation, conditioning, administration, clinical follow-up);
- risks to living donors (where applicable);
- risks to patients in relation to quality characteristics, storage and distribution of the product;
- risks to patients related to administration procedures;
- risks related to interaction of the product and the patient;
- risks related to scaffolds, matrices and biomaterials;
- risks related to persistence of the product in the patient;
- risks to healthcare professionals, care givers, offspring and other close contacts with the product or its components, or with patients, presented in a summary fashion and based on the environmental risk assessment.

*Part II of the RMP* shall contain a new discussion on the need of efficacy follow-up. If the need is identified, details of an efficacy follow-up plan should be submitted as Annex 9 of the RMP. The guideline also lists some points to be considered for efficacy post-authorisation studies, in particular sample size, use of data, reporting, choice of endpoints and examples of events of particular interest.

- Any specific aspects of routine pharmacovigilance if applicable, e.g. any adjustment of spontaneous reporting, targeted reports follow-up/ investigation, use of reports from patients/caregivers, specific methodology for signal detection, additional chapters of PSURs etc.
- Active surveillance should often be put in place, particularly when the ATMP is expected to be used in a few "centres of excellence" that could serve as sentinel sites.
- It is expected that for ATMPs, a specific clinical follow-up including laboratory investigations will become a part of normal practice described in the Summary of Product Characteristics (SPC). Non-interventional post-authorisation safety studies should be designed in a way that maximises the use of data from these normal practice laboratory investigations.
- Any ongoing compassionate use and follow-up of patients exposed to the product in clinical trials needs to be described and should serve as a basis for the development of long-term surveillance/post-authorisation safety studies. The length and form of safety follow-up should be set up according to existing guidelines, and on a case by case basis.
- Use of traceability data for surveillance purposes (e.g. an established registry of batches of products distributed to a particular centre and its record linkage to the pharmacovigilance database of reports received from that centre.)
- Measures proposed to ensure essential safety follow-up of patients even if the MAH ceased to exist (e.g., link to risk minimisation patient alert cards informing a treating physician about essentials of clinical follow-up, websites with further information).

## 4.5 Personal Data protection

Regulation (EU) 2016/679 (consolidated version) is the reference text, at European level, on the protection of natural persons with regard to the processing of personal data and on the free movement of such data. It sets up a regulatory framework which seeks to strike a balance between a high level of protection for the privacy of individuals and the free movement of such data within the EU.

# 5. Product Development

## 5.1 Introduction

The pharmaceutical quality of a medicinal product consists of two main pillars: **active substance** and **finished product**. The purpose of pharmaceutical development is to develop a formulation that is fit for its intended use, which involves consistent delivery of the active substance at the site of action at the required dose. Furthermore, the formulation must guarantee that the finished product remains stable throughout its shelf-life, retaining its characteristics during storage and distribution. Developers of ATMPs must ensure that the required data is generated to support (pharmaceutical) product development and to ensure product quality.

*Specific guidelines for ATMPs are:*

- Guidelines relevant for advanced therapy medicinal products.

*Specific rules and regulations for ATMPs to be placed on the market with an MA are:*

- Regulation (EC) No 726/2004 (consolidated version).
- ATMP Regulation (Regulation (EC) No 1394/2007) (consolidated version).
- Directive 2001/83/EC (consolidated version) (as implemented in national law, NL: the Dutch Medicines Act).
- European Pharmacopoeia (Ph. Eur.).
- GLP principles ATMP.
- GMP (with specific GMP guidelines for ATMPs).
- GDP.

*Specific rules and regulations for ATMPs as investigational medicinal products are:*

- Clinical Trials Regulation (EU) No 536/2014.
- NL: the Dutch Medicines Act and the Medicines Act Regulations.
- European Pharmacopoeia (Ph. Eur.).
- GLP principles ATMP.
- GMP (with specific GMP guidelines for ATMPs).

*Specific rules and regulations for ATMPs under the hospital exemption (HE) are:*

- Article 3.7 Directive 2001/83/EC (consolidated version).
- NL: Article 40(3)(d) and Article 40(8) of the Dutch Medicines Act.
- European Pharmacopoeia (Ph. Eur.).
- GLP principles ATMP.
- GMP (with specific GMP guidelines for ATMPs).

*Modifying GTMP:*

- CHMP/BWP/245/03.
- EMA/CAT/80183/2014.
- EMA/CAT/GTWP/671639/2008 Rev 1 corr.
- EMA/CHMP/GTWP/587488/2007 Rev 1.
- EMA/CAT/GTWP/44236/2009.
- CHMP/GTWP/125491/06.
- EMEA/CHMP/ICH/607698/2008.
- CAT/190186/2012.
- CPMP/ICH/295/95.

*Modifying sCTMP, TEP:*

- EMEA/CHMP/410869/2006.
- EMEA/CHMP/CPWP/83508/2009.
- EMEA/CHMP/BWP/706271/2010.
- Ph. Eur.2.7.29.
- CPMP/ICH/139/95.
- CHMP/ICH/294/95.
- CHMP/ICH/365/96.
- CHMP/BWP/157653/07 01/2008:50203.
- EMA/CAT/571134/2009.

The chapters and monographs of the Ph. Eur. are not only relevant for MA applications for ATMPs (see Annex I to Directive 2001/83/EC), but also for the manufacturing of ATMPs used in clinical trials, and ATMPs manufactured and supplied under the hospital exemption. The following general chapters and monographs from the Ph. Eur. should be consulted where applicable:

*General Chapters:*

- Sterility (2.6.1).
- Bacterial endotoxins (2.6.14).
- Microbiological examination of cell-based preparations (2.6.27).
- Monocyte-activation test (2.6.30).
- Test for bacterial endotoxins using recombinant factor C (2.6.32).
- Microbiological examination of human tissues (2.6.39).
- Mycoplasmas (2.6.7).
- Alternative methods for control of microbiological quality (5.1.6).
- Viral safety (5.1.7).
- Raw material of biological origin for the production of cell-based and gene therapy medicinal products (5.2.12).
- Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (5.2.8).
- Cell-based preparations (5.32).
- Additional information on gene therapy medicinal products for human use (5.34).

*Monographs*

- Bovine serum (2262)
- Human haematopoietic stem cells (2323)
- Gene therapy medicinal products for human use (3186)
- Quantification and characterisation of residual host-cell DNA (2.6.35)
- Numeration of CD34/CD45+ cells in haematopoietic products (2.7.23)
- Flow cytometry (2.7.24)
- Colony-forming cell assay for human haematopoietic progenitor cells (2.7.28)
- Nucleated cell count and viability (2.7.29)

***For an overview of all relevant laws & regulations see annex***

## 5.2. Active substance (drug substance)

The EMA user guide for SME provides an overview of product development. An active substance means a substance with physiological or pharmacological activity, which is responsible for the claimed clinical effect of the product, be it therapeutic, prophylactic or diagnostic. Depending on their source, active substances can be classified as inorganic substances, herbal substances and herbal preparations, 'chemical' (synthetic or semi-synthetic,

or isolated and purified from herbal sources or microorganisms) and biological active substances. The amount of information to be generated during development depends on whether the active substance is a new substance, being used for the first time in a medicinal product in the EU, or an existing active substance (either described in a pharmacopoeia, or not). However, in all cases the active substance should be well characterised and manufactured by well described and adequately controlled manufacturing methods.[19]
For new active substances, developers are encouraged to apply for an international non-proprietary name (INN) as early as possible in the clinical development. INNs are assigned by the World Health Organisation (WHO), to whom requests should be submitted. More information on INN and the application process can be found here.

When developing a medicinal product, the following key issues should be addressed with regards to active substances:

*General information*

Structural formula, including relative and absolute stereochemistry, molecular formula, and relative molecular mass. The solid-state properties that might affect the in vivo performance are of particular importance. Additionally for proteinaceous biological active substances the schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and biological activity should be available.[19]

For **ATMPs**, the active substance is often a living entity or a complex biological system, such as genetically modified cells or viral vectors.
In such cases, the structural characterization must go beyond the standard molecular formula. It should include detailed genetic sequence data, the specific modifications made (e.g., gene insertions, deletions, or edits), and information on the vector or delivery system used. For gene therapies, viral vector characterization (e.g., serotype, replication status) and payload integrity are crucial. Cell-based therapies need documentation on the cell type, source (autologous or allogeneic), and the nature of the modification (e.g., gene-editing methods, ex vivo manipulations).

*Manufacture*

The manufacturing process should be well described and understood. All critical process parameters should be identified and appropriately controlled. It should also be demonstrated that the process can reproducibly produce a substance with the desired quality characteristics. In addition, the starting materials, that is all the materials from which the active substance is manufactured, should be evaluated and documented.
Biological active substances are often generated by cell substrates (microbial cells or cell lines derived from human or animal sources that possess the full potential for generation of the active substance). For cell substrates having a cell banking system, all procedures to generate the master cell bank and the working cell bank(s) should be documented. Characterisation and testing of banked cell substrates should be carried out to confirm their identity, purity, stability and suitability for manufacturing use. Particular attention should be given to potential contamination from adventitious agents.
When there is a change in the manufacturing process of a chemical or biological active substance, it should be ensured that it will not affect the product quality, safety and efficacy. For biological active substances in particular, consideration should be given to performing a comparability exercise. If the analytical data are not sufficiently reassuring, additional evidence from bridging non clinical and clinical studies will be required.[19]

For **ATMPs**, the process can involve complex techniques such as viral vector production or gene editing. Cell banking systems for gene-modified or expanded cells must be robust and thoroughly tested for genetic stability and absence of contaminants. The scalability of the manufacturing process, environmental monitoring and control, and validation of aseptic techniques are critical.

*Characterization*

Extensive characterization is performed in the development phase and, where necessary, following significant process changes. Characterization is necessary to allow relevant specifications to be established. The potential for isomerism, identification of stereochemistry, and polymorphism should be evaluated. The purity of a substance is often judged by examining the impurities it contains. Therefore, special emphasis should be given to characterizing the impurities which arise from the method of manufacture and also those produced during storage, caused by degradation. Similarly, how impurities are generated should be described. If the level of impurities exceeds thresholds specified in EMA's scientific guidelines on impurities in drug products and drug substances, European Pharmacopoeia requirements and in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on impurities, their toxicological significance becomes important from a safety point of view. Therefore, these impurities have to be 'qualified' (usually with reference to formal toxicology studies) to demonstrate they are safe.[19]

For **ATMPs**, characterization includes a potency assay related to the mechanism of action (e.g., gene expression or cytokine profiles). The biological activity of an ATMP must be measured using a suitable potency assay. These assays are critical tests used to measure the biological activity of the product and to identify non-potent batches. This helps evaluate the therapeutic effect of ATMPs by assessing their ability to achieve a specified response, which is indicative of their efficacy. The development of robust potency assays is crucial for quality control and regulatory approval of ATMPs, especially given the complexity and variability of these products.

*Control of active substance*

Specifications are critical quality standards that are based on thorough characterisation and on the mechanistic understanding of how formulation and process factors can impact product performance. Specifications should reflect the characteristics an active substance should possess to achieve its intended purpose. Conformity with specifications should provide assurance that product quality is maintained from the time of release to the end of the shelf-life/re-test period. The acceptance criteria should be established and justified based on data obtained during development, including manufacturing consistency studies, stability studies and lot-to-lot comparison used in non-clinical and/or clinical studies. The analytical procedures that will be used to test the critical-to-quality attributes should be adequately validated in accordance with (V)ICH guidelines (ICH Q2).[19]

For **ATMPs**, specifications generally include identity, purity, potency, and stability. Release testing may include functional assays to assess cell viability, gene expression, or biological activity. Given the dynamic nature of living cells or complex biologics, additional quality control measures may be required. ATMPs may exhibit variability, so developers must set robust criteria for impurities, such as residual host DNA or replication-competent viruses.

*Stability*

The developer should study how the quality of the active substance varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. This will allow the definition of practical storage conditions and a 'window of use' called the shelf life/re-test period (during which the substance may be used without further testing).[19]

For **ATMPs**, stability is more complex due to the sensitivity of cells or viral vectors to environmental conditions. Cryopreservation (for cell therapies) or stability of vectors in solution must be evaluated. Handling conditions, such as freeze-thaw cycles, should also be studied.

*Submission of information for active substances*

There are three ways to present the information related to the active substance in a MAA:

- Full data is presented in the dossier.
- Active Substance Master File (ASMF): An ASMF contains all the necessary information on the active substance and is composed of two separate sections. The "applicant's part" contains the majority of the information (non-confidential) and is available to the applicant. However, in the "restricted part" the active substance manufacturer can submit detailed information related to the manufacturing process, controls and validation and this is submitted directly to the competent authorities in order to protect the manufacturer's intellectual property. The concept of the ASMF applies only to "well defined active substances". It therefore cannot be used for e.g. biological active substances, excipients, finished products, container materials.
- Certificate of suitability (CEP): The manufacturer of the active substance may apply to the Certification of Substances Division (DCEP) of the EDQM with documentation requesting evaluation of the suitability of the relevant European Pharmacopoeia (Ph. Eur.) monograph for the control of the chemical purity and microbiological quality of their active substance. If a CEP is available from the active substance manufacturer, reference to this is made in the application and no additional information needs to be submitted for those parts of the dossier covered by the CEP. However, additional information might be necessary depending on how the attributes of the active substance affect the finished product performance, for example, particle size or sterility. Manufacturers or suppliers of excipients, herbal substances and preparations used in the production or preparation of pharmaceutical products or any product with transmissible spongiform encephalopathy (TSE) risk, may also choose to apply for a CEP. An active substance can only have a CEP if there is a substance-specific monograph in the European Pharmacopoeia. Many raw materials used in the preparation of ATMPs do not have a monograph and therefore automatically do not have a CEP.

## 5.3 Finished product

The key issues that developers should address during the development of the finished product are:

*Formulation development*

It is important to identify attributes that are critical to the quality of the finished product, taking into consideration its intended usage, route of administration and the specific needs of the intended patient population (for example, paediatrics or the elderly). The potential effect of the physicochemical

properties of the active substance (for example, water content, solubility, particle size distribution, polymorphic or solid-state form) on the performance of the finished product should be evaluated. Other key issues to be investigated are the compatibility of the active substance with the excipients, containers and closures. The compatibility of the drug product with reconstitution diluent(s) or dosage devices (e.g. precipitation of drug substance in solution, sorption on injection vessels, stability) should also be demonstrated. For combination products, the compatibility of active substances with each other should also be evaluated. It is highly likely that during the products development there will be changes in the formulation and manufacturing process. In all cases the differences between the clinical formulations used and the formulation intended to be marketed should be discussed and their equivalence demonstrated (using either in vitro or comparative in vivo studies, as appropriate).
If the formulation contains a novel excipient, that is, an excipient used for the first time in an EU authorised medicinal product, or by a new route of administration, then full details of its manufacture, characterisation and control, with cross references to supporting safety data (non-clinical/safety and/or clinical) should be provided. As there can be no confidential master file for excipients, applicants should provide all such information in the application for MA.[19]

For **ATMPs**, formulation development poses unique challenges:

- *Cell-based therapies* must ensure cell viability throughout the process and storage, and formulation must account for nutrients and preservatives required for cell survival.
- *Gene therapies* rely on vector stability, and the excipients used must not interfere with gene expression or delivery efficiency.
- For *tissue-engineered products*, scaffold integrity and biocompatibility with both the cells and delivery system are critical to ensure adequate product performance.

### *Microbiological attributes*

All parameters relevant to the microbiological attributes of the dosage form should be evaluated. Examples include the selection and effectiveness of preservative systems in products containing anti-microbial preservatives, and, for sterile products, selection and description of the sterilisation process and the integrity of the container/closure system for prevention of microbial contamination.[19]

For **ATMPs**, microbiological control is particularly important due to the complexity of living cells and gene-based products. Sterility must be maintained throughout the entire manufacturing and storage process until patient administration. For cell-based therapies, ensuring that the entire product remains free from microbial contamination is challenging, especially when cryopreservation or transport is involved. The compatibility of the product with reconstitution diluents or administration devices (e.g., syringes or infusion pumps) must also be demonstrated, with particular focus on cell viability, viral vector activity, or stability of tissue-engineered constructs after reconstitution. Rapid microbiological methods can be employed to ensure the sterility of ATMPs, especially given their short shelf life. These methods enable the quick detection of contaminants, such as bacteria, fungi, and endotoxins, allowing for timely release of the product while maintaining high safety standards.

*Process development*

It is important to consider the critical formulation attributes, together with the manufacturing process options, in order to address the selection of the most suitable manufacturing process and confirm the appropriateness of its components. The manufacturer must have thorough knowledge of the manufacturing process in order to ensure that material and process variability is adequately understood and effectively managed. In general, process development studies should provide the basis for process optimization, process validation and continuous process verification. In some cases, e.g. for complex products, the developer may decide to perform enhanced development studies over a wider range of material attributes, manufacturing process options and process parameters. These studies coupled with the use of statistical experimental design techniques, risk management principles and on-line, in-line or at-line analytical methods may lead to a better understanding of the process and the product. Such studies may be used to support real time release testing and more flexible regulatory approaches in setting the operational limits of the process as well as potential process changes during the lifecycle of the product. For manufacturing process changes for biological/ biotechnological products, the same recommendations as mentioned above (for active substances) apply.[19]

For **ATMPs**, process development involves more complex considerations:

- For *gene therapies*, vector production must be optimized, ensuring consistency in viral vector titers and activity.
- For *cell therapies*, the cell expansion process, possible cryopreservation, and thawing steps must be robustly validated to guarantee cell viability and functionality at the point of administration.
- *Tissue-engineered products* require precise control over scaffold production and cell seeding processes, ensuring that the final product retains its intended properties.

Process validation for ATMPs must account for the inherent variability in biological materials. In some cases, developers may adopt advanced analytical methods to monitor critical steps in real time, ensuring that the final product is consistent in quality and functionality.

*Manufacture, control of excipients and stability of the finished product*

As with active substances, the manufacturing process used for the finished product should be carefully designed so that it consistently yields a product of the intended quality. All critical steps should be identified and controlled with appropriate in process controls. Batch-to-batch consistency must be demonstrated using appropriate process validation studies. The usual process validation approach is to manufacture a number of production scale batches to confirm that the process is under control. For non-standard processes (e.g. manufacture of specialised dosage forms, or use of new/highly specialised technologies, as well as non-standard sterilisation methods), the validation data usually need to be provided with the submission. For all other processes these data may be generated in accordance with approved protocols once production starts. It is also possible to follow other validation approaches, e.g. a continuous process verification scheme, provided that this is appropriately justified and supported by adequate development studies. Additionally, **Compatibility studies** must also confirm that the container or delivery system does not negatively interact with the biological material over time, ensuring the stability and efficacy of the product. Extractables and leachables studies should be performed on the materials used during

manufacturing and packaging. Extractable studies identify potential contaminants that could arise from contact with the container materials under stress conditions, while leachable testing evaluates whether any harmful chemicals migrate into the ATMP product over time during normal storage conditions. The container closure integrity should be demonstrated to ensure that the sterile barrier is maintained and that the living or biological components are protected from contamination.

Appropriate specifications should be set for the excipients and the finished product and validated methods should be used for their testing. The stability of the finished product should be demonstrated throughout its proposed shelf-life under the proposed storage conditions. The stability studies should be performed in accordance with the (V)ICH recommendations (e.g. storage conditions, duration) unless otherwise justified. The in-use stability of the finished product should be demonstrated for both single-dose units (e.g., after thawing, dilution, or preparation in an administration system) and multiple-dose containers.[19]

As mentioned in section 5.2, **ATMP** development involves complex processes like viral vector production, gene editing, and cell banking systems for gene-modified or expanded cells. These systems require thorough testing for genetic stability and contamination.

For **ATMPs**, the key challenges include:

- *Scalability of manufacturing*: Ensuring consistent quality during upscaling of production.
- *Consistent batch-to-batch production*: Inherent variability of the starting materials might pose additional challenges for process validation.
- *Environmental control*: Strict regulation of the production environment and validation of aseptic techniques.
- *Stability*: Due to the sensitivity of cells and viral vectors, stability testing is more complex. Factors such as cryopreservation for cell therapies, vector stability in solution, and freeze-thaw cycles must be carefully evaluated to maintain product integrity throughout its lifecycle.

## 5.4 Other specific issues

*Adventitious agents*

All materials of human or animal origin used in the manufacturing processes of either the active substance or the finished product or coming into contact with the active substance or finished product during the manufacturing process, should be identified. The risk with respect to potential contamination with adventitious agents of human or animal origin should be assessed.[19]

*Transmissible Spongiform Encepha lopathy (TSE) agents*

The latest Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human medicinal products should be applied (EMA/410/01 rev.3). Suppliers of any substances with a TSE risk used in production or preparation of medicinal products can apply to the Ph. Eur. for a TSE certificate. Such certificates can then be used by MA applicants (for more information, see the European Directorate for Quality of Medicines (EDQM) website).

*Viral safety*

The risk of introducing viruses into the product and the capacity of the manufacturing process to remove or inactivate viruses should also be evaluated.

*Other adventitious agents*

Detailed information regarding other adventitious agents, such as bacteria, mycoplasma and fungi should be provided Nitrosamine impurities: Applicants are required to have appropriate control strategies to prevent or limit the presence of nitrosamine impurities and, where necessary, improve their manufacturing processes. For more information, see the EMA website.

*Chain of custody/chain of identity*

Robust chain of custody and chain of identity processes must be implemented for ATMPs. Chain of custody and chain of identity are vital in ensuring the traceability and integrity of ATMPs throughout their lifecycle. Chain of custody refers to the documented trail of handling, from collection through manufacturing to delivery. Chain of identity ensures that the correct product is administered to the intended patient, especially important for autologous therapies, where the patient's own cells are used. These processes safeguard the product's safety, efficacy, and regulatory compliance.

# 6. Non-clinical Development

## 6.1 Introduction

Before initiating any clinical trial, non-clinical study results must demonstrate the medicine's safety for the proposed human testing. The primary concern in first-in-human studies is the safety of participants. While non-clinical testing can identify potential risks associated with investigational medicinal products (IMPs), its ability to predict safety concerns in humans may be limited due to factors such as the human-specific nature of the target. Careful consideration must be given to estimating the initial dose for human use and to the process of dose escalation.

The non-clinical development consists of four main parts:

- Pharmacology
- Pharmacokinetics & Metabolism
- Toxicology & toxicokinetics
- Environmental Risk Assessment.

The purpose of non-clinical development is to evaluate the pharmacodynamic and toxicity profiles by the clinical route of administration prior to initiating clinical studies. This helps to predict potential safety problems at a given exposure and to investigate particular safety aspects.
Non-clinical safety studies should be planned and designed to represent an approach that is scientifically and ethically appropriate. The 3Rs principles – the replacement, refinement and reduction of animal use in research – should be considered in the design of the preclinical program. The non-clinical program required to support clinical trials or MA depends on several factors including the modality of the active substance (e.g. chemical, biological or ATMP), the intended clinical trial population, target indication and the maximum duration of dosing. For guidelines on non-clinical safety studies and CHMP guidance on first-in human clinical trials, see ICH M3. For ATMPs, a risk-based approach should be applied to identify the necessary non-clinical data on a case-by-case basis.

Data requirements for non-clinical development are laid down in EU legislation. The EMA provides a number of guidelines on Non-Clinical and Clinical development. The main guidelines related to **early clinical development** are the following.

*Non-clinical*

- Non-Clinical Safety Studies For The Conduct Of Human Clinical Trials For Pharmaceuticals (ICH M3), CPMP/ICH/286/95.
- Preclinical safety evaluation of biotechnology-derived pharmaceuticals (ICH S6).
- The Non-clinical Evaluation of the Potential for delayed Ventricular Repolarisation (QT Interval Prolongation) by Human Pharmaceuticals (ICH S7B).
- Safety pharmacology studies for human pharmaceuticals.
- Toxicokinetics: the assessment of systemic exposure in toxicity studies (ICH S3A).
- Position Paper on the non-clinical safety studies to support clinical trials with a single microdose (CPMP/SWP/2599/02).

*Specific guidelines for ATMPs are:*

- Guidelines relevant for advanced therapy medicinal products.

*Preclinical development GTMP*

- E MA/CAT/80183/2014
- EMA/CAT/GTWP/671639/2008 Rev 1 corr
- EMEA/273974/2005
- EMEA//CHMP/GTWP/125459/2006
- EMEA/CHMP/GTWP/125459/2006 Rev 1, Corr 1
- EMEA/CHMP/ICH/318372/2021
- EMEA/CHMP/ICH/449035/2009.

*Preclinical development sCTMP, TEP*

- EMEA/CHMP/BWP/271475/2006 Rev 1
- CPMP/BWP/328/99
- CHMP/ICH/731268/1998
- EMEA/CHMP/410869/2006
- EMEA/CHMP/CPWP/83508/2009
- EMEA/CH,P/BWP/706271/2010.

***For an overview of all relevant laws & regulations see annex***

## 6.2 Pharmacology

Pharmacodynamics includes the investigation of "primary" pharmacodynamics, which comprises in vitro, and in vivo effects related to the proposed therapeutic indication. There are many established animal models for various conditions. If there are no models available, sponsors should investigate the added value of developing a relevant model.

Moreover, several novel products react only with human epitopes which may be different in experimental animals. In this case sponsors may consider developing a homologous product which would react with the animal epitope or develop transgene animal models. In addition, investigation of "secondary" pharmacodynamics (effects other than those related to the proposed therapeutic indications) is required. Safety pharmacology addresses undesired pharmacodynamic effects on specific physiological systems. The minimum safety pharmacology requirements are the core battery exploring the vital functions of the central nervous, cardiovascular and respiratory systems in relation to exposure in the therapeutic range and above, generally after a single dose administration. See ICH S7A: Safety pharmacology studies for human pharmaceuticals and ICH S7B: ICH S7B Non clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals for detailed guidance.

## 6.3 Pharmacokinetics & metabolism

Pharmacokinetics & metabolism studies investigate the absorption, excretion, tissue distribution, metabolism and pharmacokinetic drug interactions. The area under the matrix level concentration-time curve (AUC), Cmax at the expected peak concentration and C (time) at certain time points after administration are the most commonly used parameters in assessing exposure in pharmacokinetics studies. Other parameters include urinary and faecal excretion, bioavailability, elimination half-life, fraction of unbound drug, volume of distribution and tissue distribution. Metabolism is important to consider in the evaluation of the relevance of toxicity for humans. Many of these investigations, particularly those on distribution and excretion, are preferably conducted using radiolabeled compound. Where appropriate, placental transfer and transfer into milk can be studied. In vitro models

(e.g. liver microsomes or hepatocytes in culture) comparing the metabolic profile between animal species and humans contribute to the choice of the most relevant animal species to support clinical trials and MA.

## 6.4 Toxicology & toxicokinetics

Toxicology is the study of how substances can have harmful effects on living organisms, focusing on symptoms, mechanisms, detection, and treatment of poisoning. The toxicity of a substance largely depends on the dose, or the amount of exposure.
Toxicokinetics, a branch of pharmacokinetics, examines how the body processes a substance at toxic doses, including its absorption, distribution, metabolism, and excretion. It evaluates factors such as the duration and concentration of the substance in the body, its distribution to specific sites, metabolic efficiency, and how it is excreted. Toxicokinetics differs from pharmacokinetics due to the higher doses used, which can significantly affect how the substance behaves in the body. The following studies should generally be performed during therapy development:

*Single and repeated dose toxicity*

The primary goal is to characterise the toxicological profile of the medicinal product following repeated daily administrations. This includes identification of target organs of toxicity, determination of a No Adverse Effect Level (NOAEL), exposure response relationship and potential reversibility of toxic effects. Unless justified, experiments in two species are required, one of which should be non-rodent, and the duration depends upon the planned human use. Single dose toxicity studies are not required unless this is the intended clinical use. Preliminary dose range finding studies may be necessary to aid in selection of doses in the GLP-compliant pivotal non-clinical studies. The duration of administration required in pivotal toxicology studies will depend on the duration of clinical trials or, for MA, the intended treatment duration. For products for chronic use in humans, repeated dose toxicity studies of at least six months duration are requested (see ICH M3). In addition to investigating toxicity, kinetic parameters, in particular exposure (AUC) should be investigated in the pivotal repeated-dose toxicity studies (toxicokinetics). Toxicokinetics provide means of obtaining multiple dose pharmacokinetic data in the test species in the range of doses used in toxicology; the ratio of AUCs in humans and at the NOAEL in animals allows the calculation of a safety margin (see ICH S3A Toxicokinetics: the assessment of systemic exposure in toxicity studies and ICH S3B Pharmacokinetics: repeated dose tissue distribution studies for further guidance).

*Reproductive toxicity*

The primary goal is to investigate the effects of the medicinal product on the following steps of reproduction: fertility and early embryonic development, embryo foetal development (development of organs during pregnancy) and prenatal and postnatal development. The need for reproductive toxicity studies will depend on the chemical modality (e.g. expanding beyond traditional small molecules), on the clinical trial population and on the anticipated use in the target population.

*Juvenile toxicity*

For medicinal products intended for paediatric use, possible effects of the product on the ongoing developmental processes in the age group(s) to be treated are taken into consideration. In some instances, studies in juvenile

animals are required to allow benefit/risk assessment in these patient populations. The design of non-clinical studies in juvenile animals will vary depending on the findings observed in adult human studies and previous animal studies. The CHMP guideline on non-clinical testing in juvenile animals and the ICH guideline S11 on non-clinical safety testing in support of development of paediatric pharmaceuticals provide recommendations on such studies.

*Genotoxicity*

Genotoxicity tests are *in vitro* and *in vivo* tests designed to detect compounds which induce genetic damage in the DNA directly or indirectly by various mechanisms. The standard battery comprises tests for mutagenicity in bacteria (Ames test), as well as in vitro tests for genotoxicity in mammalian cells and in vivo test for chromosomal damage (micronucleus test usually in the mouse). Compounds which are genotoxic have the potential to induce cancer and/or heritable defects. Genotoxicity tests are required for all products, with the exception of most biological products (see ICH S2(R1) on genotoxicity testing and data interpretation for pharmaceuticals intended for human use).

*Carcinogenicity*

The objectives of carcinogenicity studies are to identify tumorigenic potential in animals and to assess the relevant risk in humans. They are required for pharmaceuticals expected to be administered regularly over a period of at least 6 months and for pharmaceuticals used frequently in an intermittent manner in the treatment of chronic or recurrent conditions. For pharmaceuticals administered infrequently or for a short duration of exposure (e.g. anaesthetics and radiolabelled imaging agents) carcinogenicity studies are not needed unless there is cause for concern. For anticancer medicinal products carcinogenicity studies are normally also not required (see ICH guideline S9 on nonclinical evaluation for anticancer pharmaceuticals). The carcinogenicity battery consists of two long term (2-year) studies in the rat and mouse or one long-term study in the rat and one short-term study (6-months) in a transgenic model (see ICH S1A, S1B and S1C).

*Immunotoxicity*

Immunotoxicity studies unintended immunosuppression or enhancement. All new human pharmaceuticals should be evaluated for the potential to produce immunotoxicity. Methods include evaluating parameters of the immune system in the standard repeated dose toxicity studies mentioned above and additional immunotoxicity studies conducted, as appropriate, if there is cause for concern. In case additional specific immunotoxicity studies are required, a generally accepted study design in rodents is a 28-day study with consecutive daily dosing. Endpoints can include functional tests, such as T-cell dependent antibody response, as well as immunophenotyping of leucocyte populations.

*Local tolerance*

The purpose of these studies is to investigate whether pharmaceuticals are tolerated at sites of the body that may come into contact with the product as a result of its administration in clinical use. Usually, one species is required for each type of test (e.g. ocular tolerance and skin toxicity in the rabbit) and the route of administration is guided by the envisaged clinical use. The local tolerance can be specifically evaluated as part of the repeated dose toxicity study or as a specific study (usually single or repeated administration over a number of days).

*Phototoxicity*

If a significant potential human phototoxicity risk is identified based on all available data, non-clinical (and clinical) experimental evaluation should be undertaken (see ICH M3(R2) and ICH guideline S10 on photosafety evaluation of pharmaceuticals).

## 6.5 Environmental Risk Assessment

The Environmental Risk Assessment (ERA) aims to evaluate the potential environmental risk of the medicinal product following its use in patients. This ERA follows a stepwise approach. The initial phase of the investigation estimates environmental exposure to the active substance and the potential for bioaccumulation and persistence in the environment. If the estimated exposure remains below an action limit, the assessment of environmental risk may conclude at this stage. If exposure exceeds this limit, the active substance's environmental fate and effects are investigated in a second phase of the ERA. Some product classes (e.g. endocrine active agents) require this second part irrespective of predicted environmental exposure. The required tests for this second phase typically include a chronic toxicity study in fish, and tests in daphnia and algae to determine a predicted no-effect concentration. If there are concerns further tests may be required. Guidance on testing requirements is given in the 'Guideline on the environmental risk assessment of medicinal products for human use' and related Q&A document. The ERA is mandatory for all MAA, although in some cases, a justification may be provided for not submitting data.

In the case of medicinal products consisting of, or more likely containing, a GMO, the requirement for conducting an Environmental Risk Assessment (ERA) stems from provisions appearing in both pharmaceutical sector and environmental sector legislation. For GMOs, a specific ERA is required. A specific guideline on environmental risk assessments for medicinal products containing, or consisting of, GMOs summarises the legal situation and explains how the legislative requirements should be implemented by regulators and complied with by developers for such products. (see this Guideline).

Applicants are reminded that the objective of the ERA exercise is stated in Annex IIA of Directive 2001/18/EC, i.e. the objective of an ERA is, on a case by case basis, to identify and evaluate potential adverse effects of the GMO, either direct or indirect, immediate or delayed, on human health and the environment which the placing on the market of the GMO may exert; the ERA should be conducted with a view to evaluating if there is a need for risk management, and if so, the most appropriate methods to be used.

The fundamental dossier requirements for ERAs for GMOs proposed to be placed on the market as or in products are outlined in Directive 2001/18/EC and in Commission Decision 2002/623/EC. It´s important to quantify (and in case this is not possible qualify) the risk that GMOs come in contact with human beings other than the intended patient, or enter the environment. For those GMOs with insufficient data (quantitative and/or qualitative) to estimate the risk to environment, a realistic theoretical worst-case scenario may be invoked.

*Timelines*

In view of the procedural and scientific complexities associated with the ERA evaluation, it is recommended that prospective applicants request pre-submission meetings with the EMEA six months to one year in advance

of submission of the application. Applicants may also find it useful to apply for scientific advice or protocol assistance during the development of their medicinal products. For any scientific advice questions relating to the ERA, necessary consultations will be held with the designated GMO CAs.

The practical implementation of the application/assessment process begins with the presentation of the GMO environmental data in Module 1.6.2 of MA application dossiers submitted in the EU. It should be noted that this module section should be bound separately from the remainder of the dossier, and that there is no formal provision for a summary of Module 1.6.2 to be included in Module 2 of the dossier. The Co-rapporteur of the CHMP MA assessment will collaborate with the GMO CA. (For more information see this Guideline).

# 7. Clinical Development / Phase I-II-III-IV Trials

## 7.1 Introduction

Studies are executed in phases in the development of a medicinal product so that the results of prior studies can influence the plan of later studies. However, the phases do not mean that the order of studies is fixed. Data that come forth during development will often prompt a change of the development strategy. New data may also suggest the need for additional studies that are typically part of an earlier phase. The early clinical development of a medicine involves critical questions that must be answered across different phases of trials:

*Phase I:*

- *Safety and Tolerance:* Is the medicine safe for human use, and at what dosage levels?
- *Pharmacokinetics (PK):* How does the body process the medicine, including absorption, distribution, metabolism, and excretion?
- *Pharmacodynamics (PD):* What effects does the medicine have on the body?
- *Interactions:* What interactions might occur with other medicines, substances, food, or drink?

*Phase II:*

- *Safety in Patients:* Is the medicine safe for use in the target patient population?
- *Pharmacodynamics (PD):* What are the specific effects of the medicine in patients?
- *Efficacy:* Does the medicine appear to be effective in patients, and at what dose?
- *Designing Confirmatory Trials:* How should subsequent confirmatory trials be structured in terms of endpoints, target population, and concomitant medications?

*Phase III:*

- *Confirmation of Efficacy and Safety:* The goal is to confirm the preliminary evidence from earlier phases. These studies are intended to provide an adequate basis for establishing the benefit/risk ratio and marketing approval. Typically, this phase involves enrolling a large number of patients (hundreds to thousands) which are exposed to the investigational medicinal product for a duration which will provide adequate efficacy and safety data for the envisaged clinical use. These trials are usually randomized, double-blind to reduce bias and involve comparisons with a placebo or existing treatments. Generally, phase III studies have more in- and exclusion criteria compared to phase IV studies. Normally, two phase III trials would be required for approval, but under specific circumstances one well conducted large trial may be sufficient. For rare diseases it's important to discuss early in process these requirements.

*Phase IV:*

- *Post-Marketing Studies:* Post-Marketing Studies: These trials investigate the medicine's clinical utility after marketing approval, focusing on its benefits, risks, and optimal use in a broad population. Common studies include drug-drug interaction studies, long-term safety studies, and research to support the approved indication, such as mortality/morbidity studies and epidemiological studies.

The way clinical trials for human medicines are conducted in the European Union (EU) and the European Economic Area (EEA) has undergone a major change with the coming into force of the Clinical Trials Regulation (Regulation (EU) No 536/2014).

## 7.2 European Clinical Trial Regulation

The European legislation that regulates clinical trials in the European Union (EU) – and therefore in the Netherlands, is the European Clinical Trial Regulation (ECTR). The provisions of the ECTR are implemented in the Netherlands via the provisions of the Medical Research (Human Subjects) Act (clinical trials) and the Medicines Act (i.a. re. manufacturing authorisation of IMPs and exemptions). The ECTR lays down the medical ethics review process.

### 7.2.1 Guidelines

- Guidelines relevant for advanced therapy medicinal products
- Quick guide for sponsors - European Clinical Trial Regulation in practice
- Guideline on quality, non-clinical and clinical requirements for investigational ATMPs in clinical trials
- Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products
- General Considerations for Clinical Trials ICH E8
- Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products
- Guideline for GCP
- Guideline on dose response information
- Guideline on studies in support of special populations: geriatrics
- Guideline on evaluation of the pharmacokinetics in patients with impaired hepatic function
- Guideline of evaluation of PK in patients with decreased renal function
- Guideline on evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs
- Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials

### 7.2.2 Guidelines specific for GTMP

- EMA/CAT/80183/2014
- EMA/CAT/GTWP/671639/2008
- EMEA/CHMP/GTWP/ 587488/2007 Rev.1
- EMEA/CHMP/GTWP/ 60436/2007
- EMA/CAT/190186/2012.

### 7.2.3 Guidelines specific for sCTMP or TEP

- EMEA/CHMP/410869/2006
- EMEA/CHMP/CPWP/ 83508/2009
- CPMP/ICH/539/00.

## 7.3 National Clinical Trial Legislation

In the Netherlands following laws and regulations regarding clinical trials are applicable, in addition to the ECTR:

- The Medical Research Involving Human Subjects Act (WMO). All clinical trials with medicinal products falling under the scope of the ECTR also fall under the scope of the WMO. Other clinical studies can also fall under the scope of the WMO when it concerns:
  - scientific research with medicinal products intended to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products, or to identify any adverse reactions to one or more medicinal products, or to study the absorption, distribution, metabolism and excretion of one or more medicinal products with the objective of ascertaining the safety and/or efficacy of those medicinal products;
  - scientific research and participants are subject to procedures/require to follow rules of behavior.

- Medicines Act (Gnw), the Medicines Act Decree (BGnw) and the Medicines Act Regulations (RGnw).
- The Healthcare Quality, Complaints and Disputes Act (Wkkgz).
- The Individual Health Care Professions Act (Wet BIG).
- The Dutch Medical Treatment Contracts Act (WGBO) regulates the relationship between patients and care providers. Among other things the WGBO stipulates that those involved in medical scientific research have to be adequately informed about the research and must give their legally valid permission for their data to be accessed. The WGBO is applicable to medical scientific research that is not covered by the scope of the WMO or the Embryo Act. However, the WGBO may also be applicable to medical scientific research that is covered by the scope of the WMO or the Embryo Act.
- GDPR.

If it concerns a clinical trial with GMP products:

- Environmental Management Act.
- Besluit genetisch gemodificeerde organismen milieubeheer 2013 (Besluit ggo).
- Regeling genetisch gemodificeerde organismen milieubeheer 2013 (Regeling ggo).

## 7.4 Clinical Trial Application and the investigational medicinal product

### 7.4.1 Application evaluation (CCMO)

A clinical trial application consists of administrative information and the scientific data necessary for demonstration of the quality, safety and efficacy of the investigational medicinal product (IMP). With regards to the quality of the IMP, it is anticipated that in the early development stages information on the analytical methods, their validation, the setting of specifications and the stability might be incomplete.

***Note:*** Be aware different requirements are set for IMPs to be used in phase I, II and III trials. Please check this Guideline on the chemical and pharmaceutical quality documentation.

***Note:*** SMEs & Academia should be aware that if the final formulation differs from that of the IMP used in earlier clinical trials, the relevance of the earlier material compared to the product tested in later phases should be described. Special consideration should be given to changes in quality parameters with potential clinical relevance e.g. in vitro dissolution rate.

The way clinical trials for human medicines are conducted in the European Union (EU) and the European Economic Area (EEA) has undergone a major change due to the Clinical Trials Regulation. The ECTR simplified the process:

- The maximum lead times of the review process for clinical trials are equal for all EU countries. As a result, all sites in participating countries can start recruiting subjects at the same time.
- Central submission of study protocols and other study-related documents within Clinical Trials Information System (CTIS), a web portal and a database specifically for this purpose (CTIS training and support).
- Safety reporting:
  - The assessment of safety reports is done per product instead of per study.

  - One EU member state is responsible for the safety reporting for each investigational drug.
  - Sponsors must report Suspected Unexpected Serious Adverse Reactions (SUSARs) directly in the EudraVigilance database.
- The publication of trial data:
  - Trial-specific information will be disclosed via the EU web portal. Decision rules determine when specific information will be disclosed. Disclosure rules document and Appendix on disclosure rules EMA/228383/2015.

### 7.4.2 Application database (CTIS)

From 31 January 2023, all new CTAs must be submitted under the new legislation (CTR) using **Clinical Trials Information System** (CTIS). This system is the single entry point for the submission, authorisation and supervision of clinical trial applications. A detailed CTIS registration and application instruction is presented in annex 3.

Trials that were submitted under the old legislation Common Technical Document (CTD), utilizing EudraCT, prior to 30 January 2023, will be able to continue to run until completion under that Directive until 30 January 2025. As from 31 January 2025, clinical trials authorized under the CTD must either have ended in the EU/EEA or have been transitioned before the transition period 31 January 2025) expires.

***Note:*** In October 2023, EMA revised the CTIS transparency rules. The revised transparency rules came into effect on 18 June 2024. See CCMO website.

### 7.4.3 ECTR application assessment

CCMO is responsible for the CTR assessment. A National Clinical Trial Office (in Dutch: Landelijk Bureau) within CCMO is responsible for the:

- validation of application dossier (complete and within scope of CTR): initial application and substantial modifications;
- selection process of the reporting Member State (multinational clinical trials);
- assignment of the clinical trial to an accredited Medical Research Ethics Committee (MREC) or CCMO for assessment;
- administrative support in preparing the assessment report Part I and communication about assessment with the applicant and concerned Member States (multinational clinical trials for which Netherlands is reporting Member State (rMS));
- administration CTIS (administrator and support);
- coordination of the assessment of SUSARs and annual safety reports;
- collection of fees and payments to MREC.

The clinical trial application consists of part I (same documents for all Member States Concerned (MSC)) and part II (national documents per MSC). In case of multinational clinical trials, Part I application will be jointly assessed by MSC with one conclusion valid for all MSC. A reporting MS (rMS), one of the MSC, will be appointed to coordinate and consolidate the joint assessment. Part II application will be a national assessment with a conclusion only valid in this MS. Each MSC will issue a decision which is the result of the conclusion part I and part II.

- Part 1: the assessment of the medical scientific method and of the product. In the case of multinational clinical trials, the concerned member states jointly conduct the assessment of Part 1. Per study proposal one member

state is the so-called reporting member state. This member state, in agreement with the reviewing committees in the other concerned member states, establishes the assessment report regarding Part 1. The approval of Part 1 applies to all the concerned member states. There is the option for a multinational trial to start the application as a national clinical trial and to add one or more member states at a later stage via the procedure Addition of MS (CTR, article 14). Addition of MS can start only after the trial has been authorized in at least one member state.

- Part 2: the national issues such as the information letter for research subjects, insurance and privacy aspects. Part 2 also includes the remunerations to research subjects and investigators and the suitability of investigators and site facilities. The approval of Part 2 applies to all the participating centers in the concerned member state.

### 7.4.4 Full, staggered or mixed application

The developer is allowed to submit a full initial application (part I and part II at the same time), a staggered initial application (first part I followed by part II) or a mixed initial application. For a staggered initial application the following rules apply:

- A part II application cannot precede a part I application.
- A part II application can be submitted after assessment part I has been concluded.
- A part II application has to be submitted within two years after conclusion part I. If a part II application is not submitted within two years after conclusion part I, the application part I will be lapsed.
- The part II application shall be accompanied by a statement from the sponsor in which he declares that he is not aware of any new substantial scientific information that would change the validity of any item submitted in the application on the aspects covered by Part I of the assessment report.

The following additional rule apply for mixed initial application in a multinational clinical trial:

- The developer can submit a whole application (Part I and II) to some Member States concerned (on the basis of Article 5 ECTR) and at the same time an application limited to Part I only (on the basis of Article 11 ECTR) to other Member States concerned.

### 7.4.5 Decision

Part I and part II are both assessed and two decisions will be published. Possible outcomes are:

- Both part I and II conclusions are acceptable or acceptable with conditions ➜ the application is automatically authorised.
- Part I conclusion is acceptable or acceptable with conditions and part II conclusion is not acceptable or lacking ➜ the application is automatically authorised.
- Part I conclusion is not acceptable and part II conclusion is acceptable or acceptable with conditions, not acceptable or lacking ➜ the application is automatically not authorised.
- Part I conclusion is lacking and part II conclusion is acceptable or acceptable with conditions, not acceptable or lacking ➜ the application is automatically still under evaluation.

In case of a positive decision a MSc can opt out. In case of a negative decision, this decision is applicable for all countries and the study is not authorized.

If CCMO came to the negative decision, the interested party may lodge a notice of objection to CCMO within six weeks after the day on which the decision was reached. According to national Dutch law, it would be possible to lodge an administrative appeal or objection against a negative decision based on a negative conclusion of part I by the rMS. However, this appeal or objection will be declared inadmissible, because this decision is taken at international level. Resubmission of the clinical trial as a new clinical trial with adjustments is possible.

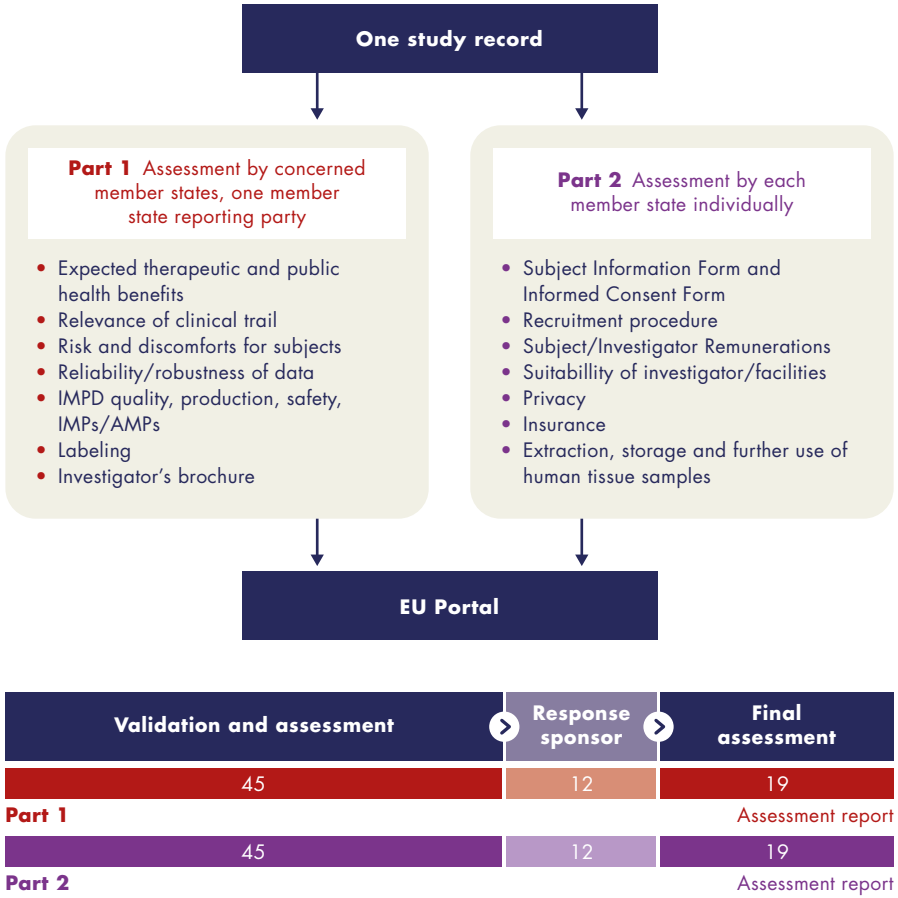
### 7.4.6 Timelines

The assessment period starts from the date of validation and is max. 45 days with the possibility to extend this by another 31 days (12 days for the sponsor and 19 days for the MS) in case the rMS send a request for information (RFI). The sponsor shall submit the requested additional information within the period set by the rMS (maximum 12 days). The timelines for the assessment of part I and part II are normally similar except:

- in case of clinical trials involving ATMPs, the rMS can extend the assessment period by an additional 50 days for consulting with experts;
- in case of sequential part II submission, there is no validation phase.

The extension of the timelines for the assessment of part II is not provided for by the legislation. This may result in part I having extended timelines compared to Part II and leading to particularly complex outcomes. Therefore, sponsors may consider applying Article 11 of the CTR in cases of complex applications, thereby submitting part II separately from Part I. Timelines are presented in figure 11.

*Figure 11: Simplified overview Clinical Trial Application*




Source: Simplified representation is based on various sources.

### 7.4.7 Assessment by Ministry of Infrastructure and Water Management (IenW)

For gene therapy research, a permit application must be submitted to the Ministry of Infrastructure and Water Management (IenW) via the GMO Office. Applicants should note that the permit's scope is primarily determined by the 'breadth' of the application. The goal is to draft the final decision in a way that, if applicable, allows for multiple clinical protocols to be conducted under a permit. It is recommended to consult the GMO Office beforehand for an informal discussion on the options for such a broader permit application.

An important point to note is that the Dutch administrative court (Raad van State, afdeling bestuursrechtspraak) has ruled in a previous decision that the permit holder is legally required to maintain full control over all activities conducted under their permit. This means that in the Netherlands, the sponsor cannot serve as the permit holder; only the legal entity where the activities take place, such as medical centres or hospitals, can hold the permit.

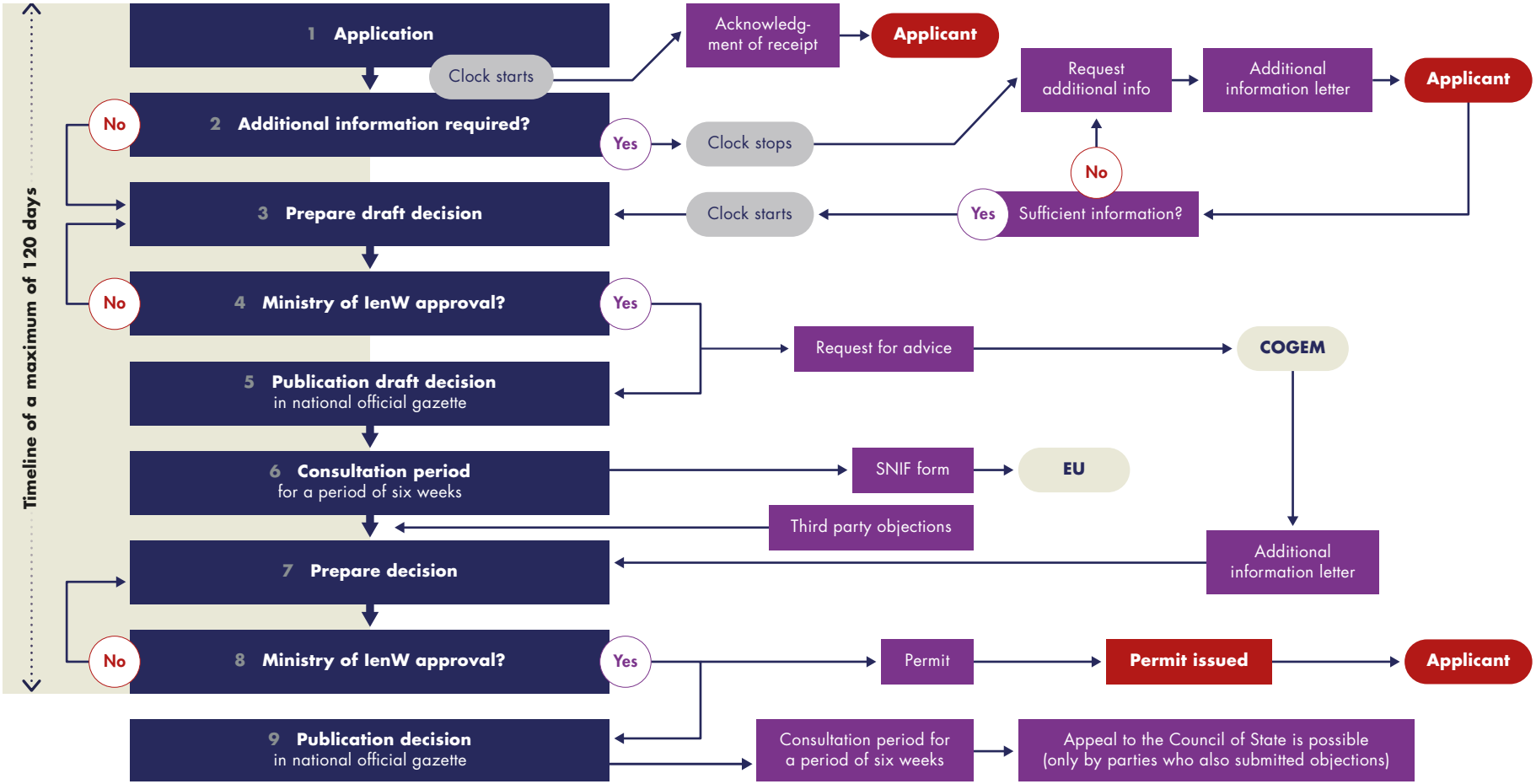
The standard permit procedure for gene therapy research submitted to Ministry of IenW, c/o GMO Office takes a maximum of 120 days. For this procedure, a draft decision is prepared, which, once approved by the Ministry of IenW, is made available for perusal along with the public part of the dossier. The notice is published in the national official gazette (Staatscourant). Thereafter, third parties can then submit objections to the proposed permit for a period of six weeks. During this time, COGEM will also provide advice on the application. After the consultation period has ended, the received objections and the COGEM advice will be incorporated into the final decision. As part of the formal notification, applicants are required to submit a SNIF (Summary Notification Information Format) form through the E-Submission Food Chain Platform (ESFC) system of the European Commission. This informs other Member States of the European Union of the proposed work and the decision of the Dutch Ministry of IenW.

The final decision is signed by the Ministry of IenW no later than week 17. This decision takes effect immediately. Notification of this decision is sent to the investigator before publication in the official national gazette (Staatscourant). If any objections to the permit are lodged, the Council of State (administrative court) informs the applicant and the Ministry of IenW. After the permit comes into effect, a description of the proposed work must be submitted before said work can be started. Since this description must be in accordance with the provisions of the permit, individual clinical protocols do not require approval from the Ministry of IenW. Figure 12 represents the assessment procedure and timelines.

In addition to this standard permit procedure, a simplified and shortened is available for specific categories of GMOs. This shortened procedure, which results in a permit with fixed terms (known as "vergunning onder vaste voorwaarden" or VoV), has a maximum duration of 56 days. If additional conditions are met, the process can be further shortened to a maximum of 28 days. The procedure begins as soon as the application is received and contains clock stops.

Furthermore applications may be submitted for so-called broad(er) defined permits. This is possible under both regular permit conditions as well as for permits with fixed terms (VoV). Any (new) study or Investigational Medicinal Product Dossier (IMPD) that falls within the (broad) scope of such a permit does not need to be notified in advance to the Minsistry of IenW and thus a new permit is no longer necessary in those cases.

*Figure 12: Assessment procedure I&W*




Source: Loket Gentherapie

The GMO Regulation states that an environmental safety officer (ESO) must supervise all the work done under a permit on environmental release. This officer must be approved by the State Secretary for IenW. The legal basis, the ESO requirements, the tasks and the approval procedure are described on the website of the GMO Office. The ESO application can be sent directly to the GMO Office, and there you can also direct any questions you may have about the procedure. In order to submit a permit application, an ESO must have been appointed by the MS.

### 7.4.8 Role of CCMO Ministry of VWS (Health, Welfare and Sport) and IenW (Infrastructure and Watermanagement)

The assessment of ATMP research involves various combinations of legislation and regulations as well as a number of different bodies.

- The Central Committee on Research involving Human Subjects (CCMO). BCB (Besluit centrale beoordeling medisch-wetenschappelijk onderzoek met mensen) review by CCMO is obigatory, see here.
- The Ministry of Infrastructure and Water Management (IenW) is responsible for the regulations that protect people and the environment during activities involving GMOs and has the task of developing policy and regulations. Makes decisions on permit applications on the basis of the Genetically Modified Organisms Decree.
- The Office for Genetically Modified Organisms (GMO Office) is responsible for the administrative and technical-scientific implementation of permit granting on the grounds of the GMO Decree and for supporting the policies named therein. The GMO Office processes permit applications for contained use and deliberate release. For deliberate release into the environment and market applications (parts B and C of Directive 2001/18/EC), GMO Office takes care of all substantive preparations, including the risk assessment. In addition, GMO Office is the point of contact for all parties involved in work with GMOs and supports the Ienw in their policy. The GMO Office promotes the link between policy and regulations on the one hand and signals from practice on the other hand and provides information.
- The Commission on Genetic Modification (COGEM) offers advice to the Ministry of IenW with regard to the environmental risks of the manufacture and application of GMOs, and on the safety measures that must be taken to protect people and the environment. With regard to GMO ATMP applications, COGEM does not advise on the possible risks for patients. The commission provides advice with regard to the risks of infection and transmission of GMOs to the wider environment including family members and others. Another of COGEM's tasks is to inform the ministers involved about the ethical and social aspects of activities with GMOs. For permit applications relating to the deliberate release of GMOs (including ATMPs), in most cases the Minister of IenW will request advice from COGEM in the draft decision phase.

**Key Take-Aways:**

- Right documentation and study design is crucial and determines the success rate of an trial application. Developers have access to different supportive meetings throughout the lifecycle of the product. Success rate of applications increases when SMEs and academia use these support meetings and align early in process with EMA and national bodies.
- For cell processing, only the Body Materials (Safety and Quality) Act is applicable not GMP. Depending on part of the process, different paragraphs in GMP certificate are needed.
- Make sure all parties are trained in Risk Management Program (RMP), Product training, Safety training (regarding patient safety), Cell chain training (including identity log).
- When training will take place in other countries/outside EU, check Dutch CGR hospitality obligations.
- In case of development within commercial company: company compliance policies often require additional training of physicians & distributors before contracts can be signed. Make sure training starts early on in process.
- Technical certificates for apheresis, cell collection, cell modification are required. NB these are company- specific requirements, can differ between companies and are not always fitting Dutch regulations.
- Some companies require an independent on-site inspection by the Joint Accreditation Committee of the EBMT and ISCT (JACIE) to comply to the International Standards for Cellular Therapy Collection, Processing and Administration, developed by FACT and JACIE. JACIE is supported by the European Group for Blood and Marrow Transplantation (EBMT) and the International Society for Cellular Therapy (Europe) (ISCT)). All Dutch centres performing allogenic SCT are JACIE certified.
- For apheresis, GMP is not required however this might be part of JACIE inspection (and some commercial companies oblige a JACIE inspection).
- For GMO applications, if an investigator is not directly employed by the license holder (e.g., a hospital, ZBC, or research institute), an employment contract, such as a zero-hours contract, must be arranged with the license holder to carry out work under the license. Final responsibility remains (by contract) with license holder, also for non-clinical procedures carried by other parties outside institution in question. Although draft contracts are accepted in the application process, permits can only be provided when signed contract is received. This might cause a delay.
- The GMO Regulation states that, an ESO must be appointed. This officer must be approved by Ministry of IenW. If an ESO is not be employed in the preparatory phase of the trial application, it is important to start the process early by training and appointing a suitable staff member.

**Support:**

- The CCMO has established a National Clinical Trial Office ('Landelijk Bureau') that offers administrative support to the MRECs involved in the assessment of multinational studies for which the Netherlands is the reporting member state. administrative support in preparing assessment report Part I and CTIS administration support.
- Engage in joint consultations with the GMO office and COGEM during preliminary meetings. These preliminary meeting are informal discussions between the investigator and the bodies that decide or advise on the application. This is not mandatory, but especially for academia and SME's strongly advised. The aim of the preliminary meeting is to exchange information so that, when submitting the application, the investigator submits the correct data with the correct degree of detail and knows which aspects the different bodies focus on during assessment.
- For the Netherlands specific there's a possibility to consult the CBG Wetenschappelijk en regulatoir advies | College ter Beoordeling van Geneesmiddelen (cbg-meb.nl).

# 8. Marketing Authorisation

## 8.1 Introduction

As by the ATMP Regulation (EC) No 1394/2007 and Regulation (EC) No 726/2004, all ATMPs should be centrally authorized by the EMA. They benefit from a single evaluation and authorisation procedure. The primary responsibility for the scientific evaluation of MAAs for ATMPs lies with the CAT. The CAT appoints a rapporteur and co-rapporteur based on objective criteria. These (co)rapporteurs draft an opinion on the quality, safety, and efficacy of each ATMP. The CHMP then conducts the final review and approval. The CHMP's recommendation is forwarded to the European Commission, which issues a decision that is binding across all Member States.

The CAT also provides recommendations on post-authorization activities for ATMPs to the CHMP. The Pharmacovigilance Risk Assessment Committee (PRAC) is responsible for advising the CHMP and the coordination group on pharmacovigilance activities and risk management systems related to ATMPs and for monitoring the effectiveness of these systems (as per Article 56(1) of Regulation (EC) NO 726/2004). The same principles that apply to the MAA evaluation procedure also extend to post-authorization activities (e.g., variations, renewals) according to the established timelines for each relevant procedure.

For the evaluation of an initial MAA for an ATMP, two assessment teams are appointed:

- The first team consists of the CAT Rapporteur, the CHMP Coordinator, and a PRAC Co-Rapporteur.
- The second team consists of the CAT Co-Rapporteur, the CHMP Coordinator, and a PRAC Rapporteur selected from the members and alternates of the PRAC.

Each assessment team should include assessors experienced in in the evaluation of Quality, Safety, Efficacy, Pharmacovigilance and ERA for ATMPs. Peer reviewers (at least one from the CAT and one from the CHMP) may be appointed from amongst the members or alternates from both Committees, if appropriate. If a CAT Rapporteur is also a CHMP Member or alternate, no additional CHMP Coordinator is nominated in the team. Each Committee is responsible for the appointment of its own Rapporteurs. For initial ATMPs applications, the chairs of the CAT, CHMP and PRAC will discuss and agree on the appointment of Rapporteurs, CHMP Coordinators and peer reviewers.

## 8.2 Roles and responsibilities of all interested parties involved in the evaluation procedure for ATMPs

### 8.2.1 General Principles

The lead responsibility for the assessment of MAAs for ATMPs (and by analogy also post-authorisation activities such as variations, renewals, etc.) is with the CAT. The milestones for the product discussion during the evaluation of a MAA for an ATMP takes place at the CAT. This includes:

- the adoption of the Day 120 List of Questions (LoQ);
- the adoption of the Day 180 List of outstanding issues (LoOI);
- and oral explanation (where required).

The CHMP Coordinators joins the CAT discussion for the product to ensure adequate interaction and information flow between the CAT and the CHMP. Similarly, the PRAC (Co-)Rapporteurs join the CAT discussion to facilitate the information flow between the CAT and the PRAC.

Any comments of the other committees regarding the assessment of the MAA should be submitted to the CAT including the comments to the Day 120 LoQ or Day 180 LoOI from the CHMP, PRAC, involved Working Parties (WP), Scientific Advisory Groups (SAGs), Inspections and Notified Bodies, as applicable. After adoption by the CAT, the Day 120 LoQ and Day 180 LoOI are sent to the applicant.

The CHMP is informed by the CHMP coordinators and/or CAT (Co-) Rapporteurs of the major objections and key scientific issues as discussed by CAT. In the exceptional case that the CHMP identifies major issues with the Day 120 LoQ or Day 180 LoOI (e.g. identification of de novo important scientific questions), these will be added to the LoQ/LoOI in collaboration with the CAT Chair and the CAT (Co-) Rapporteurs. The updated LoQ/LoOI will be circulated to the CAT for information and sent to the applicant.

When discussing the LoOI, the CAT will consider the need for an oral explanation. The oral explanation for an ATMP takes place before adoption of the draft opinion by CAT. The CHMP Coordinators attend the oral explanation at CAT, when possible. The CHMP Chair may also attend the oral explanation before the CAT. In the rare event that the CHMP opinion differs from the CAT draft opinion (e.g., a change in the outcome or conditions of the MA), an oral explanation will take place during the CHMP meeting, upon request or agreement of the CHMP, before a final decision is made. In such case, the applicant can only present or refer to data that have been previously assessed by the CAT. In case of an oral explanation for the CHMP, the CAT Chair and the CAT (Co-)Rapporteurs are expected to attend the oral explanation to support the discussion.

The CAT (Co-)Rapporteurs join the CHMP discussions on the draft opinion submitted by the CAT. This discussion may be also be attended by the CAT Chair/CAT Vice-Chair. When the CHMP identifies major concerns on the draft opinion adopted by the CAT, a clarification meeting shall be organised by the EMA in advance of the CHMP plenary meeting. The CAT and CHMP chairs, the CAT (Co-)Rapporteurs, the CHMP Coordinators and the CHMP members and where applicable the PRAC members, who raised major concerns, participate to help resolve any emerging disagreements before the final CHMP opinion is adopted.

### 8.2.2 Committee for Advance Therapies

The CAT holds the primary responsibility for evaluating MAA for ATMPs and managing post-authorization tasks, including variations and renewals. This includes:

- leading the assessment of the product during re-examination;
- determining the need to involve or consult working parties, scientific advisory groups, notified bodies, or inspections, and proposing questions to the experts;
- adopting key documents such as the Day 120 LoQ, Day 180 LoOI, the draft opinion, and making decisions regarding the applicant's request for a clock-stop.

### 8.2.3 CAT (Co-)Rapporteurs

To carry out a scientific assessment, usually an EMA committee appoints a CAT rapporteur to prepare an assessment report, which the committee will consider and eventually adopt as part of a scientific opinion or recommendation. For certain procedures, a 'co-rapporteur' also prepares an assessment independently from the rapporteur. The role of the CAT (Co-) Rapporteurs is to:

- perform the scientific evaluation of ATMPs;
- lead the discussions at the CAT;
- prepare the assessment report, the LoQ, the joint assessment report and the LoOI and circulate them to the CAT, CHMP and PRAC members according to the timetable agreed for the evaluation procedure and taking into account the timeframe laid down in the relevant legislation;
- inform and liaise with the CHMP coordinators, to ensure a consistent flow of information and to facilitate discussions between the committees. Similar, for the PRAC (Co-)Rapporteurs as necessary;
- identify the need for consultation with WP/SAG/Notified Bodies/ Inspections involvement at Day 80/Day 150 in preparation of the Day 120 LoQ/Day 180 LoOI;
- consider comments received from PRAC regarding the pharmacovigilance plan and the risk minimisation measures of the Risk Management Plan (RMP).

In case a medicinal product for human use contains or consists of GMO, the CAT (Co-)Rapporteurs shall take into consideration comments received from the consultations with national competent authorities designated under Article 4(4) of Directive 2001/18/EC (GMO competent authority).

In case of a combined ATMP, the CAT (Co-)Rapporteurs shall take into consideration comments received from the consultation with the Notified Bodies (where applicable).

### 8.2.4 Committee for Medicinal Products for Human Use

The CHMP is informed during its plenary meeting of the major objections and key scientific issues raised during the evaluation (at Day 120 LoQ/Day 180 LoOI) of the ATMP under review. The LoQ and LoOI will be circulated to the CAT for information and sent to the applicant. The CAT sends the draft opinion for final approval to the CHMP. The CHMP adopts the final opinion. In case the CHMP opinion is not in accordance with the draft opinion adopted by the CAT, the CHMP shall annex to its opinion a detailed explanation of the scientific grounds for the differences.

When a request for re-examination is received, the CHMP is responsible for the re-examination of the CHMP opinion. The re-examination of the CHMP opinion shall be based on the (new) draft opinion adopted by the CAT. In case the CHMP opinion is not in accordance with the (new) draft opinion adopted by the CAT, the CHMP shall annex to its opinion a detailed explanation of the scientific grounds for the differences. All dossier requirements for pharmaceutical products are also applicable under DIRECTIVE 2001/83/EC Annex I, but the assessment is performed by the CAT.

## 8.3 Optional Classification Procedure

The criteria for ATMPs are set out in Article 17 of Regulation (EC) No 1394/2007. In case of questions or borderline cases, applicants have access to an optional procedure which is the CAT scientific recommendation for the classification of ATMPs. The procedure will determine whether or not the referred product falls within the scope of the definition of ATMP in the EU and will address questions of borderline cases as early as possible. It provides clarity on the development path and scientific-regulatory guidance. **For submission procedure/formats and timelines *see Chapter 3*: Classification of ATMPs and *Chapter 11*: support for developers.**

## 8.4 Optional Certification Procedure (applicable for SME'S)

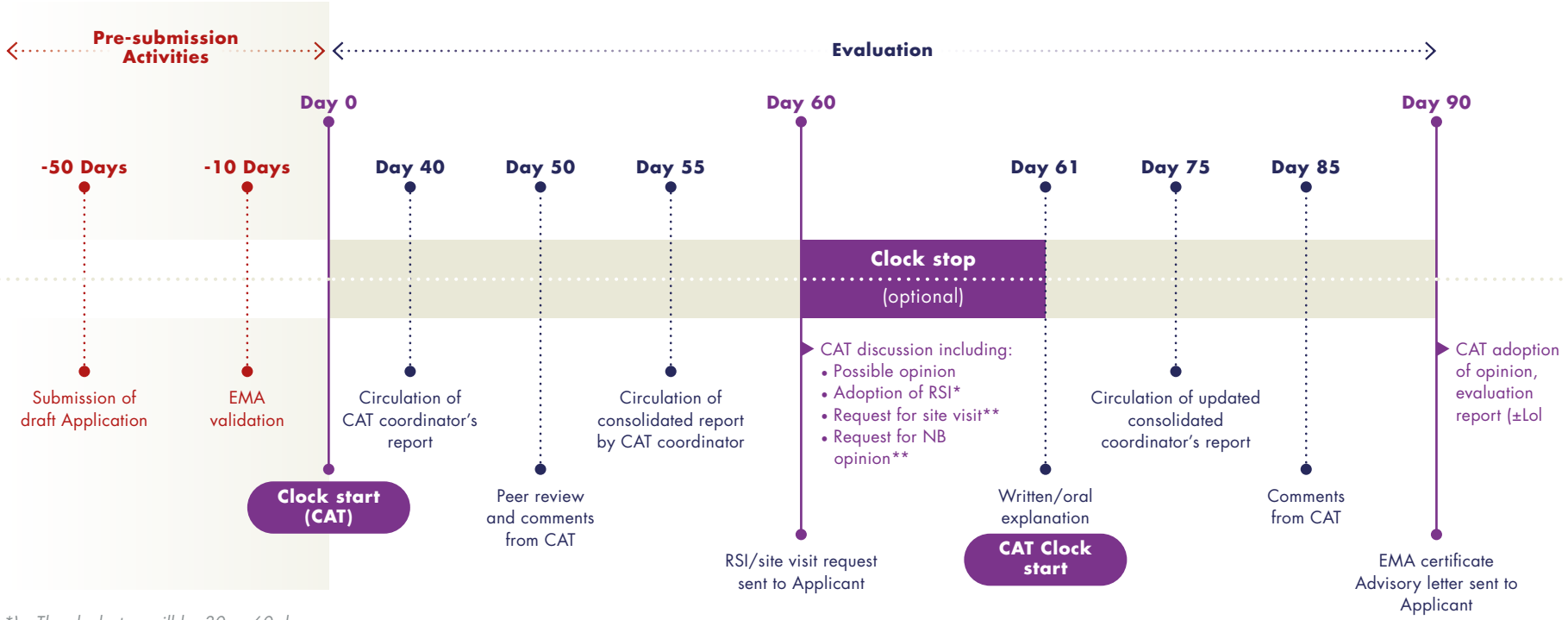
The EMA CAT provides a certification procedure for ATMPs under development by SMEs as defined in Article 18 of Regulation (EC) No 1394/2007. This certification procedure involves the scientific evaluation of quality data and, when available, non-clinical data that SMEs have generated at any stage of the ATMP development process. It aims to identify any potential issues early on, so that these can be addressed prior to the submission of a MAA.

***Note:*** EMA assumes the provided (clinical) data is correct and won't assess the robustness of the data or manufacturing procedures. The applicant should be aware that these aspects will be tested in the final registration assessment and new critical comments can occur. After assessment, the CAT may recommend issuing a certification confirming the extent to which the available data comply with the standards that apply for evaluating a MA.

Figure 13 presents the following timeline which is applicable to the certification procedure SME:

- Developers Applicants have to submit a pre submission form intent to submit at least 70 days before submission, specifying the intended submission date, the background information relating to the ATMP product and the type of data (quality or quality and non -clinical).
- For submission the pre-submission request form should be addressed to: PA-BUS@ema.europa.eu.
- If the applicant, EMA Coordinator or CAT Coordinator requires a pre-submission meeting, this take place approx. 40 to 20 days before the start of the procedure.
- The draft certification application (dossier) should be submitted approx. 50 days before start of the procedure.
- The final certification dossier should be submitted 10 days before start of the evaluation procedure. Required data is mentioned in Guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products and in line with Articles 8 – 11 of Directive 2001/83/EC and modules 3 and 4 of Annex I to Directive 2001/83/EC and Regulation (EC) No 668/2009.
- Timetables are published on the EMA website.
- The procedure will take 90 days, however the submission of the 'intention for a pre submission request' has to take place 70 days before the start of the procedure.

***Figure 13:*** *Activities and timelines for the Certification procedure for SME's*




**) The clock stop will be 30 or 60 days*
***) In case of site visit/consulation of NB clock stop is until site visit report/NB opinion is made available*

Source: EMA website

## 8.5 EMA pre-submission interactions

Applicants have the opportunity to interact with EMA to discuss procedural or regulatory issues in relation to the upcoming submission, and to establish contacts with EMA staff that will be involved with the application. Not all pre-submission interactions will require a dedicated meeting. Check the EMA pre-submission guidance for more information. Based on the pre-submission interactions form and relevant annexes, the EMA Process Lead will review and discuss the questions and background documents received with the EMA Product team members. A set of consolidated written responses to the questions raised by the applicant will be sent by EMA to the applicant within 3 weeks from receipt of these documents. The applicant may request a teleconference with the EMA if additional clarification is needed regarding the written responses already provided. It is anticipated that in some complex cases, a tailored pre-submission meeting with relevant members of the EMA product team may be required. Within the written responses, EMA will inform the applicant if such meeting is deemed necessary.

## 8.6 The Application Dossier, Requirements, submission and validation

Data generated from pharmaceutical tests, non clinical and clinical tests and trials with the medicinal product concerned, as well as other information required by the EU legislation, need to be provided to EMA and all CHMP members for evaluation. All applications have to be submitted in English. The application dossier for medicinal products for human use must be presented in accordance with the EU-CTD presentation outlined in Volume 2B in the electronic Common Technical Document (eCTD) format. The latest version of the ICH M2 eCTD specification can be found on the ICH website. The use of the eSubmission Gateway is mandatory. The use of the Electronic Application Form (eAF) is mandatory for all procedures in the EU. The forms and all related guidance documents are available on the eAF website and in the PLM Portal. The eAFs should always be submitted as a part of the submission dossier within the eCTD sequence. For the product information, EMA provides the applicant with a template of what must be included in these documents.

EMA will check if the application meets all relevant legal and procedural EU requirements ('validation') before the start of the scientific evaluation. Applicants should be aware that for medicinal products for human use, a compliance check for paediatric requirements may be necessary. SMEs should indicate the SME status and provide a valid SME number. Further information for human medicines can be found on section 4 of the pre-authorization guidance. **Applicants are encouraged to use the dossier validation checklist to ensure that the dossier complies with requirements and issues are avoided during validation**. EMA will issue an invoice on the date of the notification of the administrative validation to the applicant, and fees will normally be payable within 45 days of the date of the said notification. For SME applicants, the fee payment may be deferred.

## 8.7 Evaluation of application

### 8.7.1 Normal assessment procedure

Once the application is validated, EMA starts the evaluation procedure at the monthly starting date (published on the EMA website). EMA will ensure that the evaluation is finalised within 210 days (assessment time not including clock-stops for the applicant to provide a response to questions from the CHMP). The different steps and timelines are presented in figure 14.

*Figure 14: Timeline EMA MA procedure*

| Day | Action | |
|---|---|---|
| 1 | Start of the procedure | For ATMPs the scientific evaluation is carried out primarily by the CAT, which prepares the draft opinion on the quality, safety and efficacy for final approval by the CHMP. In the first evaluation phase, the rapporteur and co-rapporteur prepare assessment reports on the application within 80 days. The assessment reports are sent to all other CHMP members for comments and to the applicant for information. Following discussion of the assessment reports, the CHMP adopts a "list of questions", identifying 'major objections' and/or 'other concerns', which will be sent to the applicant by day 120. |
| 80 (85 Vet) | Receipt of the assessment report(s) from rapporteur and co-rapporteur by CHMP/CVMP members of the CHMP/CVMP. | |
| 100 | Rapporteur, co-rapporteur, other CHMP/CVMP members and EMA receive comments from members of the CHMP/CVMP. | |
| 115 | Receipt of draft list of questions (including the CHMP/CVMP recommendation and scientific discussion) from rapporteur and co-rapporteur. | |
| 120 | CHMP/CVMP adopts the list of questions as well as the overall conclusions and review of the scientific data to be sent to the applicant by EMA. Clock stop. | |
| 121 | Submission of the applicant's responses, including revised product information in English.<br><br>Restart of the clock. | The applicant is expected to respond within an agreed timeframe (usually 3 months from the date of receipt of the questions). Applicants may request an additional 3-month period. If the applicant cannot respond within the given timeframe, careful consideration should be given to withdrawing the application and resubmitting it later, if necessary, after obtaining scientific advice and when all required information is available. |
| 150 (160 Vet) | Joint response assessment report from rapporteur and co-rapporteur received by CHMP/CVMP members and EMA. Sent to applicant for information only. | In the second phase, the rapporteur and co-rapporteur assess the responses and submit their joint assessment for discussion to the CHMP. Based on the conclusions of this debate, the CHMP prepares a final assessment report which also includes the draft product information. The CHMP will adopt the report along with a list of outstanding issues, which may require an oral explanation. The CHMP will then provide their favourable or unfavourable opinion regarding authorization.<br><br>During the assessment, the CHMP may consult scientific advisory (SAGs) or ad-hoc expert groups in connection with the evaluation of specific types of medicinal products or treatments, to which the committee may ask for expert's views on a number of points. Scientific advisory or ad-hoc expert groups are established by the relevant committee. They consist of European experts selected according to the particular expertise required on the basis of nominations from the CHMP or EMA |
| 170 | Deadline for comments for CHMP/CVMP members to be sent to rapporteur and co-rapporteur, EMA and other CHMP/CVMP members. | |
| 180 | CHMP/CVMP discussion and decision on the need to adopt a list of "outstanding issues" and/or an oral explanation is needed, the clock is stopped to allow the applicant to prepare the oral explanation. Clock stop. | |
| 181 | Restart of the clock and oral explanation (if needed). | Applicants should normally respond (or prepare for an oral explanation) within one month. In exceptional circumstances an extension may be granted if scientifically justified |
| By 210 | Adoption of CHMP/CVMP opinion + CHMP/CVMP assessment report (and timetable for the provision of product information translations) | EMA will prepare a "summary of opinion" (for favourable as well as unfavourable opinions) in liaison with the applicant. This summary is published on the EMA website after the adoption of the CHMP opinion. If during the assessment procedure an applicant decides to withdraw its application before an opinion is adopted, EMA will publish the withdrawal and the assessment report. |

### 8.7.2 Accelerated assessment

In exceptional or well-justified cases, the timeline of assessment procedures can be shortened in an accelerated assessment. To meet patient expectations and keep pace with the rapid advancements in science and therapies, it is possible to obtain a MA via an 'accelerated assessment procedure.' This process allows for approval within up to 150 days instead of the standard 210 days, particularly for products of significant public health interest, especially those offering therapeutic innovation. Any request for accelerated assessment should be made as early as possible, but at least two to three months before the actual submission of the MAA. A pre-submission meeting six to seven months before submission to prepare for evaluation under accelerated assessment is strongly recommended. An accelerated assessment request should elaborate on the major benefits expected and present the arguments to support the claim that the medicinal product introduces new methods of therapy or improves on existing methods, thereby addressing to a significant extent the greater unmet needs for maintaining and improving public health. PRIME products are also expected to benefit from an accelerated assessment, which will be confirmed at the time of MAA. For further details visit Accelerated assessment.

## 8.8 Pharmacovigilance

### 8.8.1 General Legislation

The Pharmacovigilance legislation is concerned with the safety monitoring across Europe. Many of the challenges in safety monitoring of medicines stem from the limited amount of information available from clinical trials at the time of authorisation. See for more information chapter 4.4.5.

### 8.8.2 The Pharmacovigilance Risk Assessment Committee (PRAC)

The PRAC provides recommendations to the CHMP on any question relating to pharmacovigilance activities and on risk management systems including the monitoring of their effectiveness. In addition, the PRAC is responsible for assessing all aspects of risk management of human medicines, including:

- the detection, assessment, minimisation and communication of the risk of adverse reactions, while taking the therapeutic effect of the medicine into account;
- design and evaluation of post-authorisation safety studies;
- pharmacovigilance audit.

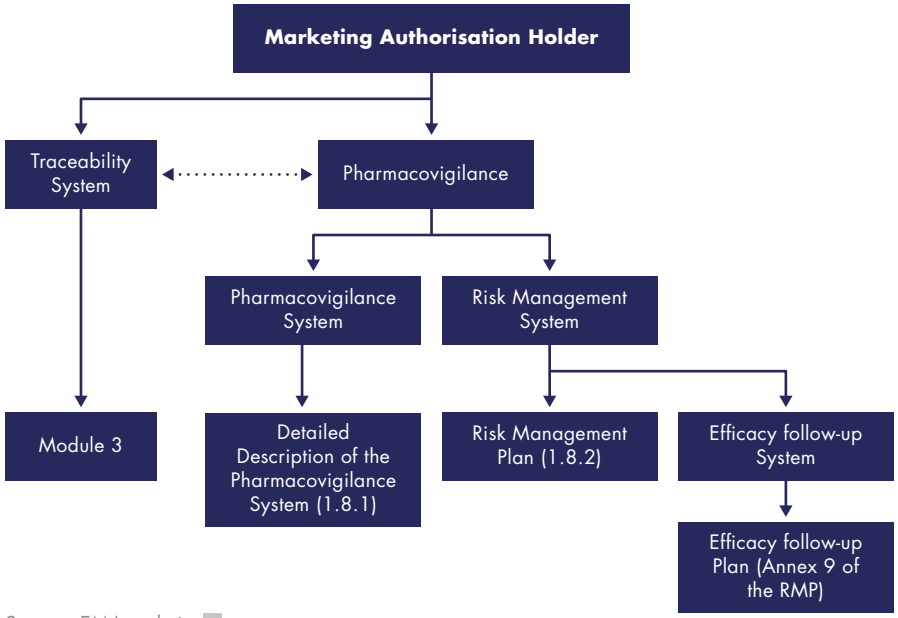
### 8.8.3 Pharmacovigilance system master file (PSMF)

MAHs are required to maintain a PSMF which includes an overview of the MAH's current pharmacovigilance system related to one or more products. The PSMF is not part of the MA dossier and is maintained independently from the MA. The MAA contains only a reference to the location and a summary of the applicant's pharmacovigilance system. For more information see chapter 4.4.6.

## 8.9 Post Authorisation Obligations

The EMA may grant market authorisation under special conditions or can impose certain post-authorisation measures. These can include letters of commitments; follow-up measures; conditional approvals or approvals under exceptional circumstances with specific obligations and their annual re-assessments. Additionally, there are a number of reporting obligations, such as expedited and periodic reports, EU-RMP updates, various special reports requested by regulators, and sunset clause reporting. Figure below illustrates the consistency between soft and hard (legally enforceable) regulations in the area of post-authorization surveillance.

*Figure 15: Post authorisation surveillance of ATMP*




Source: EMA website [20]

### 8.9.1 Risk Management Plan

The RMP is a stand-alone document which summarises the known safety information about the product and outlines how the applicant or MAH will monitor, further investigate, and manage the associated risks. Guidance on RMP is provided in GVP module V. Additional guidance is available on the EMA website.

All applicants submitting an initial MAA are required to submit an RMP in the application dossier. An RMP (or an update, if one already exists) is also required where there is an application involving a significant change to an existing MA or at the request of the Agency or national competent authority. Once a product has an RMP it needs to be updated throughout the lifecycle of the product. Summaries of RMPs will be made public by the Agency. **SMEs and academia are advised to contact the competent authorities to discuss the RMP in advance of its submission.**

Based on the existing tools and feasible approaches to risk minimisation, the following should be considered to reduce particular risks for ATMPs:

- Limitation of the use of the product to adequately trained and experienced clinicians only, possibly including a controlled distribution system to specialised (accredited) centres only. Selection and accreditation of centres by MAH and/or member states authorities, possibly in cooperation with an appropriate medical organisation might also be part of the risk minimisation plan.
- Specific risk communication (patient alert cards; patient ID cards; risk communication components of the educational programs; informed consent forms; protocols and mechanisms ensuring that any recipients who have received treatment prior to the age of consent or in need of information at a later stage will receive risk communication; guidance for recipients on how to communicate risks to close contacts and offspring where they could be at risk).
- Introduction of barriers to errors (design of the product, cross checks, double patient identification, second opinions, dedicated teams.). Some of these may be implemented by MAH alone (product design), some needs co-operation of healthcare establishments. When a need is identified,

requirement to implement these barriers may be part of the accreditation of healthcare establishments for the use of the product.

- Training of healthcare professionals in respect of procurement, storage, handling, administration, clinical follow-up, and their protection based on the environmental risk assessment.
- Education of support personnel, family and caregivers – for instance indicative symptoms of important identified or potential adverse reactions, clinical follow-up procedures, protection based on the environmental risk assessment etc.

### 8.9.2 Additional RMP and PharmacoVigilance reguirements for ATMPs

The EU Risk Management Plan (EU RMP) and the Detailed Description of the Pharmacovigilance System (DDPS) have additional requirements for ATMPs. Because of their novelty, complexity and technical specificity, they may bring along new, explored risks to public health and to individual patients. See chapter 4.4.7.

### 8.9.3 Periodic Safety Update Reports (PSURs)

Periodic Safety Update Reports (PSURs) and their assessment reports should discuss ongoing cumulative efficacy and safety data. A specific new chapter in the PSUR assessment report might be introduced for this purpose. This chapter should also discuss safety data relating to donors and close contacts. The PSUR is a document which provides an evaluation of the risk-benefit balance of a medicinal product at defined time points after its authorisation. It includes a comprehensive and critical analysis of the risk-benefit balance of the product taking into account new or emerging safety information in the context of cumulative information on risk and benefits. Guidance on the content and format of a PSUR is published in GVP module VII. MAHs are legally required to submit all PSURs14 to the central PSUR repository using the eSubmission Gateway or the eSubmission (Syncplicity) Web Client. Use of the PSUR repository is mandatory.

### 8.9.4 Post-Authorisation Safety Studies (PASS)

The ability to require and enforce PASS has become part of the EMA's toolkit for improving the benefit-risk monitoring of medicines. A PASS is a study of an authorised medicine which aims at identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicine, or measuring the effectiveness of risk management measures during its lifetime. Such studies provide information to support regulators in decision-making on the safety and benefit-risk profile of a medicine. A PASS may be imposed as a legal requirement on the conditions of a MA and may be a requirement of an RMP or conducted voluntarily by an MAH. Guidance on PASS is provided in GVP module VIII. Additional guidance is available on the EMA website.

### 8.9.5 Post-Authorisation efficacy studies (PAES)

To support a benefit-risk for a medicine, evidence of benefit must be demonstrated through trials that are properly designed and conducted in line with applicable guidelines. A PAES may nevertheless be needed to increase the understanding of therapeutic efficacy. For human medicines, delegated Regulation (EU) No 357/2014 provides details on PAES that may be imposed at time of, or after the MA of centrally authorised medicinal products (CAPs) and nationally authorised medicinal products (NAPs). Guidance on PAES within or outside the scope of Delegated Regulation (EU) No 357/2014 is available.

## 8.10 Authorisation under special conditions

### 8.10.1 Conditional marketing authorization (MA)

For certain categories of medicinal products, in order to meet unmet medical needs of patients and in the interest of public health, it may be necessary to grant MAs on the basis of less complete data than is normally required. In such cases, the granting of a conditional MA may be recommended subject to certain specific obligations to be reviewed annually. This may apply to medicinal products for human use that fall under Article 3(1) and (2) of Regulation (EC) No 726/2004. A conditional MA can be granted if:

- The benefit of the immediate availability on the market of that medicinal product outweighs the risk inherent in the fact that additional data are still required.
- The benefit-risk balance of the medicinal product is favourable and the applicant is likely to be able to provide comprehensive data in the near future.
- The applicant will fulfil specific obligations which will be reviewed annually by the Agency for the first three years and every two years thereafter.
- The applicant, as part of the specific obligations will complete ongoing studies, or conduct new studies, with a view to confirming that the benefit-risk balance is favourable.

The provisions for the granting of such an authorisation are laid down in Commission Regulation (EC) No 507/2006. An initial conditional MA is valid for one year, on a renewable basis for the first three years after granting the authorisation and every two years thereafter. When the specific obligations have been fulfilled the Commission may, following an application by the MA holder (MAH), and after having received a favourable opinion from the Agency, grant a unconditional MA.

For further information on conditional MAs, see question 50 of the pre-submission procedural guidance questions and answers: 'Could my application qualify for a conditional marketing authorisation?'.

### 8.10.2 Authorisation under exceptional circumstances

In exceptional circumstances where an applicant is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, the Commission may, by derogation to Article 6, grant an authorisation under Article 13, subject to specific conditions, where the following requirements are met:

- The applicant has demonstrated, in the application file, that there are objective and verifiable reasons not to be able to submit comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use based on one of the grounds set out in Annex II to [revised Directive 2001/83/EC].
- Specific conditions are included in the decision of the Commission, in particular to ensure the safety of the medicinal product as well to ensure that the MAH notifies to the competent authorities any incident relating to its use and takes appropriate action where necessary.

This MA under exceptional circumstances is valid for 2 years and thereafter a risk-based reassessment shall be conducted.

### 8.10.3 Variations Regulation

Commission Regulation (EC) No 1234/2008 of November 2008 (the Variations Regulation) outlines the procedure concerning the examination of variations to the terms of MA. This regulation was amended by Commission Regulation (EU) No 712/2012. Article 4(1) of the Variations Regulation

mandates the European Commission to establish guidelines detailing the various categories of variations, the procedures for their submission, and the required documentation. For more information on these guidelines see New variations regulation: Regulatory and procedural guidance.

### Key Take-Aways

Application validation issues occur in 90% of initial MAAs. They create additional workload and potential delays at a critical moment for the timely start of the procedure. To make the validation process more efficient, predictable and easier to navigate, EMA is encouraging applicants to:

- Plan pre-submission meetings (approximately 7 months prior to the anticipated date of submission of the application). They are a vital opportunity for applicants to obtain procedural, regulatory and legal advice from the EMA. The product team is available to address any questions MAHs may have regarding their pre-authorisation application.
- Use the pre authorisation guidance information.
- Use the dossier validation checklist.
- Start engagement early in the development process and stay in contact with the EMA team during the application and evaluation process.

# 9. Hospital Exemption

## 9.1 Introduction

The preferred route for bringing a product to the market is generally trough MA. However, ATMPs may follow an alternative route under hospital exemption (HE) with approval from IGJ. This exemption from the central MA requirement for ATMPs, outlined in Article 3(7) of Directive 2001/83, is applicable when obtaining an MA is not feasible or physicians need to treat patients outside of clinical trials. EU Member States are required to implement this exemption, though it is applied differently across the EU and is only valid within the state of approval. In the Netherlands, the HE is implemented through Article 40(3)(d) and Article 40(8) of the *Geneesmiddelenwet* (Gnw).

## 9.2 The Hospital Exemption application requirements and procedure

### 9.2.1 HE and clinical trials

An HE exemption cannot be used for the purpose of conducting a clinical trial. Clinical trials involving ATMPs, including investigational products, must be reviewed under the Medical Research (Human Subjects) Act (Wet medisch-wetenschappelijk onderzoek met mensen; WMO) and fall outside the scope of the Gnw. Therefore, the HE option cannot be applied to ATMPs in the preparation for clinical trials. However, in exceptional cases, it is possible to conduct a clinical trial and have an HE in parallel for the same medicinal product, if there is a need to treat certain patients with an ATMP outside the scope of the clinical trial.

### 9.2.2 Requirements

The manufacturing/preparation and use of an ATMP under HE within the Netherlands requires a prior approval from the CBG and IGJ. CBG and IGJ will assess the application together after which IGJ decides whether HE will be granted. Approval will only be granted if the legal entity that is responsible for the manufacture of the ATMP, has submitted a completed Application form HE ATMP for an ATMP under HE (under exclusive professional responsibility of the medical expert). This HE application can only be submitted by the legal entity responsible for the actual preparation of the ATMP. This can either be the board of the manufacturer (if the product is prepared under a Manufacturing and Importation Authorization (MIA) by the manufacturer) or the board of the hospital (if the product is prepared under a MIA within the hospital).

The ATMP must be manufactured or prepared at a manufacturing site having a valid MIA. The application should specify the site or location where the product is prepared (whether at the manufacturer or hospital pharmacy) and where the patients will be treated, noting that:

- The manufacturing site does not necessarily have to be the same as the site for patient treatment.
- There can be more than one site for patient treatment, although production and application has to be done within the same member state.

The administration of ATMPs under HE to patients should adhere to the following requirements:

- Manufactured under equivalent quality standards of ATMPs with a MA, complaint with GMP (see Guidelines on GMP for ATMPs and Chapter 4.4.3).
- They must be used in a hospital with a valid prescription.
- Each specific patient must be registered with a "Doctor's Declaration for the use of an ATMP under HE."

Approval for HE can only be obtained for a limited number of patients and a limited period in the Netherlands. But there's no guidance or limits provided by the Gnw regarding scale and the regularity/frequency of the preparation of an ATMP under HE. According to the IGJ website, approval can be granted for a preparation made for max. 10 treatments, for max. 1 year. Renewal of the HE is possible for 1 year.

### 9.2.3 Pre-submission consultations with IGJ

TThe IGJ advises to conduct preliminary consultations with the IGJ. A request for such pre-submission consultations can be made via email: atmp@igj.nl. Such a request should contain at least:

- a brief description of the ATMP;
- information on how the product will be used (circumstances);
- a brief description of the manufacturing/preparation of the ATMP;
- contact details, such as the applicant's name, company/hospital, department, address, phone number, email address.

***Note:*** Developers who would like to prepare and administer the ATMP to the patient which they expect may come within the HE are encouraged to ask advice at an early stage from the IGJ.

### 9.2.4 Application form & process

To apply for a Hospital Exemption (HE) for an Advanced Therapy Medicinal Product (ATMP), applicants must complete the Application form HE ATMP specifically designed for this purpose. The application process involves several critical steps, and applicants should ensure that all necessary documentation and information are provided to facilitate a thorough and efficient review.

## 9.3 Reporting requirements

### 9.3.1 Pharmacovigilance requirements

While pharmacovigilance requirements for ATMPs under HE are not the same as those for ATMPs with a MA, they must be equivalent in the following key aspects:

- A qualified person responsible for pharmacovigilance should be appointed.
- An RMP must be submitted and implemented, detailing the system in place to monitor efficacy, as well as to identify, characterize, and minimize any risks associated with the product. The plan should also specify the follow-up period.
- Reporting of adverse events: All unexpected serious adverse reactions and serious adverse events have to be reported immediately, within 48 hours, by email to the IGJ (atmp@igj.nl).

- The IGJ requires a Periodic Safety Update Report (PSUR) that include information on any (serious) adverse reactions, unexpected adverse reactions (including their frequency), safety data analysis, and information on the body that has reviewed this analysis.
- In addition to complying with Dutch regulations and IGJ policies, any suspected serious adverse events and reactions potentially linked to cells must be reported to the IGJ.

Furthermore, Dutch hospitals and tissue establishments use the notification system 'Transfusion and Transplantation Reactions in Patients' (TRIP). TRIP's mission is to receive and analysis reports of adverse reactions and adverse events associated with blood transfusion or with the application of human tissues or cells. TRIP also promotes hemovigilance and biovigilance in the widest sense, throughout the chain from donor to recipient, in order to contribute to improved safety of transfusion and transplantation in the Netherlands.

### 9.3.2 Traceability requirements

Traceability requirements for ATMP under HE differ from those for ATMPs with a MA. However, they must be equivalent and compatible with the traceability standards set by the Tissues & Cells Directive and the Blood Directive. Specifically:

- *Appointment of a responsible person:* A designated individual must be appointed to oversee traceability.
- *Traceability system:* A system must be in place to ensure traceability between each recipient of an ATMP, the final product, the active substance, and the starting materials used in the manufacturing. This information should be retained for at least 30 years after the product's expiration date and must be compatible with the traceability requirements of the Tissues and Cells Directive (Directive 2004/23).

Additionally, data retention requirements may be longer for ATMPs containing GMOs.

### 9.3.3 Report to IGJ after HE expiration

The HE is granted for a limited number of patients and a specific time period. Applicants are required to submit a report to the IGJ under certain circumstances: when the approval period has expired or the maximum number of approved treatments has been reached, when the applicant wishes to renew or extend the HE, or when treatments have been prematurely stopped. This report must include key information such as the number of patients treated with the ATMP under the HE, details of any adverse reactions or unexpected outcomes, and notable events that occurred during the manufacturing or preparation of the ATMP. Additionally, the report should provide efficacy, safety, and pharmacovigilance data.

If the applicant seeks to renew or extend the HE, additional information must be submitted, particularly a justification explaining why the renewal should be granted. In all cases, applicants should consider the size and characteristics of the patient population affected by the disease and the availability of alternative treatments, whether through clinical trials, compassionate use programs, or products with a marketing authorization. Currently, there is no public national database for Hospital Exemptions, though this may change in the future.

## 9.4 The relationship between HE and other exemption schemes

In addition to the HE scheme, other exceptions for medicines are available, such as ‘compassionate use’ (typically reserved for compassionate use programs within the meaning of Article 83 of Regulation 726/2004) or ‘named patient bases’ (Article 5 of Directive 2001/83, implemented into Dutch law through Article 40(3)(c) Gnw) and pharmacy preparations (Articles 3(1) and 3(2) of Directive 2001/83). Compassionate use is handled through the CBG and is intended for exceptional cases involving a specific number of patients for whom no registered alternatives are available. Use of a medicinal product via named patient bases (also known as a 'doctor's declaration') must be approved by the IGJ and is on an individual basis. In exceptional cases, an ATMP without MA may be produced abroad and administered in the Netherlands under a doctor's declaration. However, these routes are not specific to ATMPs.

# 10. Reimursement of EMA Registered Medicinal Products

## 10.1 Introduction

After a medicinal product receives EMA market authorization MA, physicians can prescribe it for the approved indication (on-label use). However, EMA approval does not automatically guarantee reimbursement at the national level. Each Member State is responsible for defining its own health policy, including the organization, funding, and delivery of healthcare. In other words, the decision to reimburse a medicinal product is made at the national level after EMA authorization, which can result in differences in reimbursement and patient access between countries.

*This chapter focuses on the reimbursement of EMA-authorized medicinal products. Products produced under the Hospital Exemption or other healthcare products are not covered here.*

## 10.2 National Legislation regarding reimbursement

### 10.2.1 Legislation & Roles and responsibilities

In the Netherlands, the routes to reimbursement are set out in legislation based on Articles 2, 10 and 11 of the Healthcare Insurance Act, (Zorg-verzekeringsWet, Zvw). Patients entitled to receive the care they require, as defined in the Healthcare Insurance Decree (Besluit Zorgverzekering, Bzv). Detailed rules on the types of care to which patients are entitled are set out in the Health Insurance Regulation (Regeling Zorgverzekering, Rzv). The totality of the forms of care is commonly referred to as 'the basic package (het basispakket, reimbursed care).

The Health Care Market Regulation Act (Wet marktordening gezondheidszorg, Wmg) applies to all care or services defined by the Zvw (Article 1(b) Wmg). This extends to services ('prestaties') and tariffs ('tarieven') related to extramural pharmaceutical care and inpatient treatments with medicinal products.

Key roles in the reimbursement process:

- The Ministry of Health (MoH) decides what is included in (or excluded from) the basic package.
- The Health Care Institute (Zorginstituut Nederland 'ZIN') advices the MoH what should be included in the basic package (HTA).
- The Health Care Insurer (HCI) are obliged to offer (and reimburse) care from the basic package as long as it meets the criteria of Scientific & Clinical Practice. To guarantee this care HCIs and health care providers negotiate and agree upon arrangements about what each treatment entails, the quality and the price that can be charged.

### 10.2.1 Two reimbursement routes for medicinal products

In the Netherlands there are two reimbursement systems for medicinal products.

- medicinal products used in an outpatient setting (outpatient pharmaceutical care or 'farmaceutische zorg');
- medicinal products used for treatment in hospital setting/intramural (medical care, or 'geneeskundige zorg'). This category contains also products used in oncology and most rare diseases.

All medicinal products used in outpatient setting require an HTA performed by ZIN before the MoH can decide on their inclusion in the basic package. Once a product is approved, it is added to the positive reimbursement list (Geneesmiddel Vergoeding Systeem, GVS). If the cost-effectiveness is deemed unfavourable or the product has a high budget impact, the MoH may mandate price negotiations with the MAH.

For intramural products, a risk-based assessment system applies:

- Products with an expected yearly maximum budget impact (BI) > 20 million or the threshold of 10 million and a cost per patient per year of 50K or more require an HTA performed by ZIN and the Office Financial Arrangements Medicines (Bureau Financiële Arrangementen Geneesmiddelen, BFAG) of the MoH can require a negotiation when the cost benefit ratio is not cost effective or the budget is too high. When the assessment, sometimes followed by a negotiation is successful finalized, reimbursement is granted. This is called the Central or Lock Procedure.
- All other intramural (no high risk) products will be assessed by a coordinated group of HCI's; the Commission of Assessment Add on Drugs (Commissie Beoordeling Add on Geneesmiddelen, CieBAG). The CieBAG assesses whether a product meets the criteria of established medical science & medical practice (SW&P). When this assessment is positive the product is reimbursed. However, individual HCIs may still negotiate specific conditions, such as the selection of treatment centres or price reductions.

*Most ATMPs are used in intramural setting with costs exceeding the 50K per patient per year. For that reason we focus on the intramural reimbursement route with an HTA assessment performed by ZIN.*

### 10.2.2 Horizon Scanning performed by ZIN and decision on reimbursement route

To keep all stakeholders—such as the MoH, ZIN, HCIs, health professionals, and patients—well-informed of upcoming developments and their potential impact on the macro budget, assessment capacity, healthcare, treatment and hospital budgets, ZIN publishes a Horizon Scan twice a year.

ZIN collects information from various sources, including data provided by the pharmaceutical industry, publicly available resources (such as EMA, MEB, clinical studies, and pipeline overviews), and expert opinions. Eight expert groups, organized by disease areas, review, refine, and validate the gathered information. The Horizon Scan provides a comprehensive overview of new medicines and indications or line extensions expected within the next two years, along with their potential budget impact. It covers anticipated new medicines, related indications, volumes, U.S. prices, and forthcoming line extensions of existing products, as well as alternatives (biosimilars, generics) and patent expirations. Based on this scan, ZIN advises the MoH on which products should be placed under the Central Lock procedure.

### 10.2.3 The Central Lock Procedure

Although the MoH and ZIN can identify potential candidates for the Central Lock procedure based on the Horizon Scan, the formal decision to initiate the procedure is made after a positive opinion from the CHMP and no later than one month after the product receives its MA. Depending on the outcome of the advice of ZIN and negotiations between the MoH and developer, the product can either be placed out of the Central Lock (successful negotiations) or remain in the Lock.

Although assessments of products in the Lock procedure are prioritized, there are no strict timelines. The average time for products placed in the Lock, based on the formal Lock decisions as published in the Government Gazette ('*Staatscourant*'), is currently > 12 months but for ATMPs this is substantial longer. Figure 16 presents the procedural steps in the Lock procedure in relation to the Joint Clinical assessment of the EU.

## 10.3 ZIN's HTA Process for Medicine Reimbursement

### 10.3.1 Key Steps and Stakeholder Involvement

For a medicine to qualify for reimbursement, a HTA by ZIN is mandatory. The Scientific Advisory Board (Wetenschappelijke Advies Raad, WAR) of ZIN reviews the following required documents submitted by the MAH[21]:

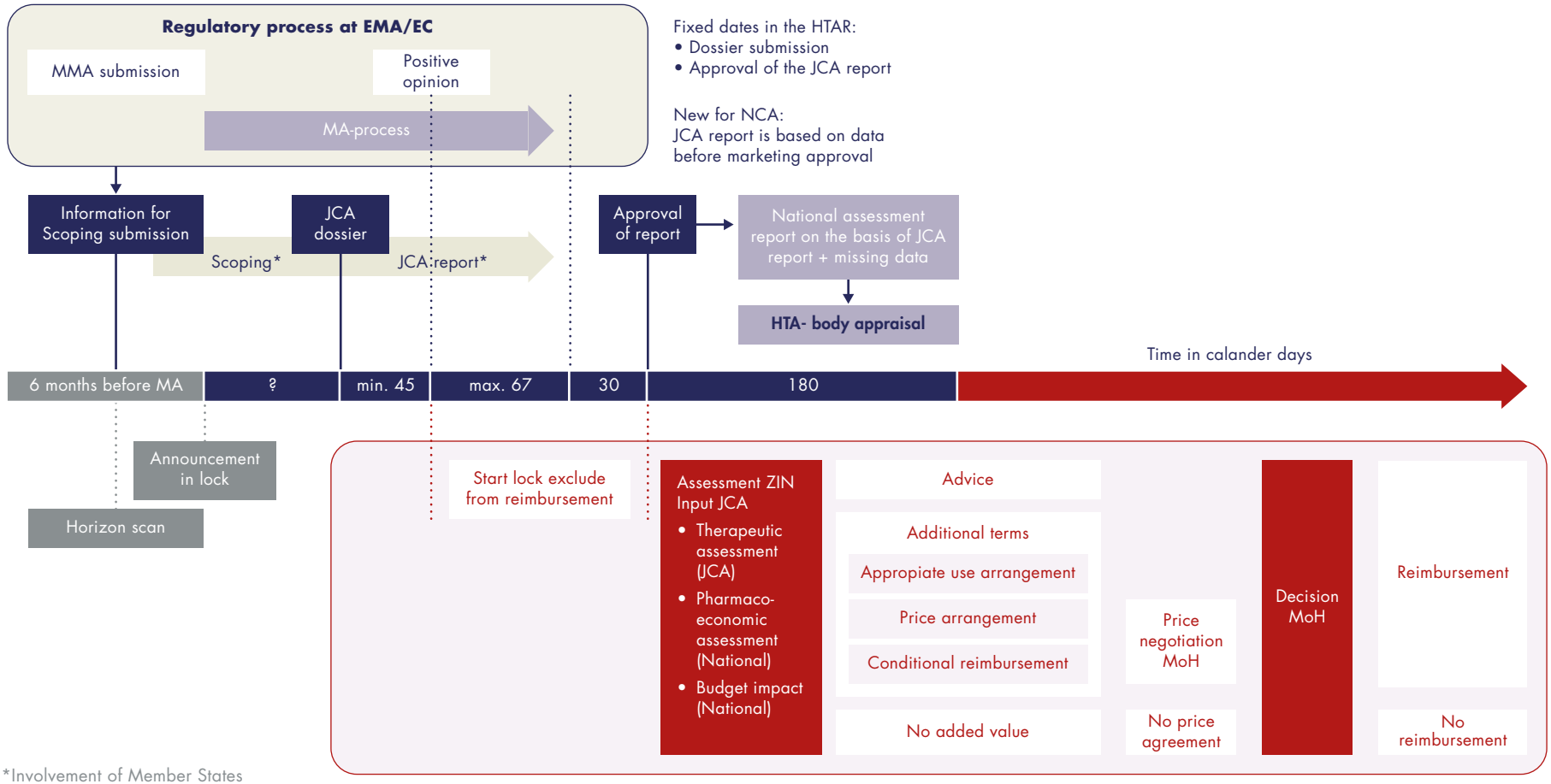
- Pharmacotherapeutics[22]
- Budget impact analysis[23]
- Pharmaco-economic file.[24]

Following discussions within the WAR, draft reports are prepared and sent confidentially to the MAH and other relevant stakeholders for feedback. These stakeholders include scientific professional associations (expert groups), patient associations (general and possibly specific), and a committee of HCI's (CieBAG of ZN). The MAH and stakeholders have at least five working days to submit comments or to provide additional information. If the deadline is missed, the assessment process is extended by a minimum of 30 days. The MAH may also request a clock stop of up to 90 days. Responses and comments are discussed in a second WAR meeting, after which final reports are drafted. Ideally, this occurs within a month of the first meeting. This can only be done if the responses of the stakeholders are received in a timely manner. ZIN therefore always mentions a deadline for response.

If a medicine is deemed to meet the SW&P criteria and involves a social consideration, ZIN consults the Package Advisory Committee (ACP), which holds public meetings monthly. The ACP assesses relative effectiveness, cost-effectiveness, necessity, and feasibility, and questions if reimbursement is justifiable from a societal perspective (*appraisal*). Although the MAH may express their views during these public meetings, they are not part of the decision-making process. ZIN will incorporate its own assessments and the ACP's considerations in its final recommendation to the MoH. The possible outcomes of this advice include:

- Inclusion in the package because the medicine complies with the SW&P, is cost-effective with a reasonable budget impact.
- No inclusion in the package due to insufficient data on effectiveness as a result of the EU JCA (ZIN may advise to collect additional data during a conditional admission process, i.e., Voorwaardelijke toelating weesgeneesmiddelen, "Conditionals", "Exceptionals" and/or Subsidieregeling Veelbelovende Zorg (VEZO).
- No inclusion in the package based on weighting of the four package criteria.
- No inclusion in the package based on the cost effectiveness or budget impact, unless a Financial Arrangement is concluded with the MoH and/or Appropriate Use agreements are made. In this case, the medicine does comply with SW&P, but has not proven to be cost-effective, has too great a budget impact or too high a risk of inappropriate use.

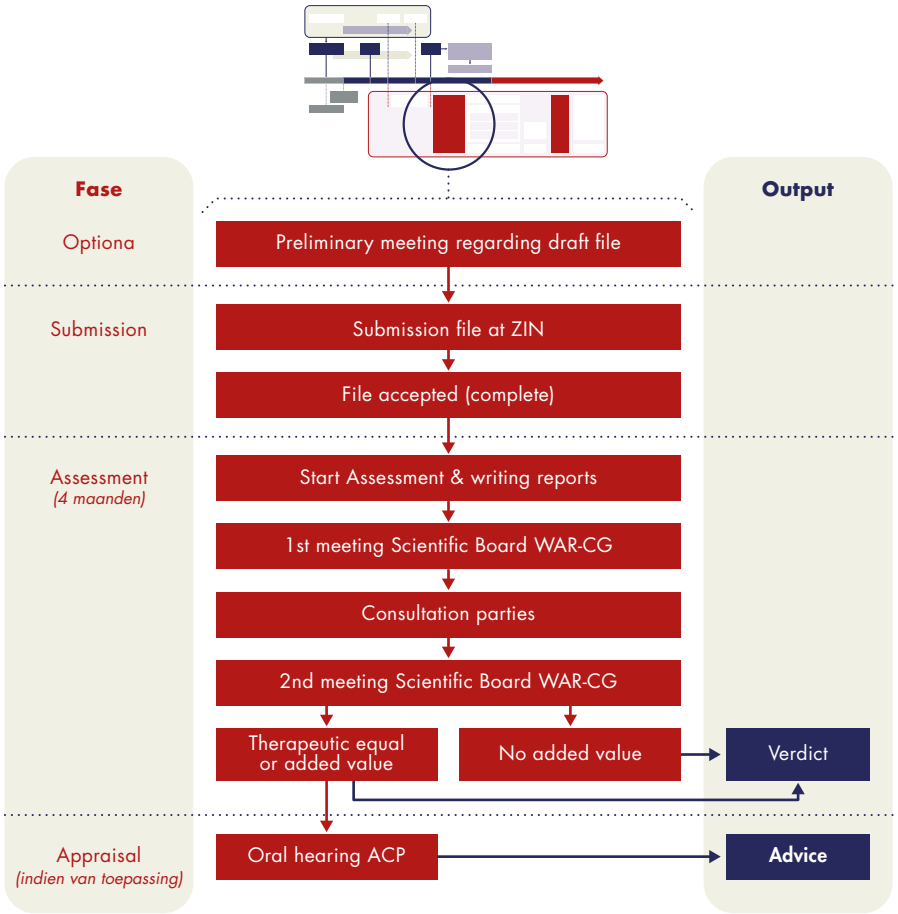
*Figure 16: JCA and National assessment and negotiation*




*Involvement of Member States

Source: FAST figure based on presentation Dr. Stephanie Said (Webinar 05 May 2023) [25] and Zorginstituut NL

*Figure 17: details of national HTA and Budget impact assessment ZIN*




Source: FAST figure adapted from Zorginstituut NL.

### 10.3.2 Joint Clinical Assessment

Developers often face the difficulty of submitting the same information, data, analyses and other evidence to different Member States, often at different times. This duplication of submissions, coupled with varying submission timelines across Member States, creates a substantial administrative burden for developers. It can also contribute to impeding and distorting market access, leading to a lack of business predictability, higher costs and, in the long run, negative effects on innovation. To address this, a Joint Clinical Assessment (JCA) will be introduced under the EU HTA Regulation in January 2025: Regulation (EU) 2021/2282 (EN)

Starting on January 12, 2025 this JCA will be implemented via a stepwise approach, with ATMPs and oncology products being the first for which JCA is the mandatory procedure in the EU:

- January 2025, for medicinal products with new active substances for which the applicant declares in its application for MA submitted to the EMA that it contains a new active substance for which the therapeutic indication is the treatment of cancer and medicinal products which are regulated as advanced therapy medicinal products pursuant to Regulation (EC) No 1394/2007 of the European Parliament and of the Council (15);
- January 2028, for medicinal products which are designated as orphan medicinal products pursuant to Regulation (EC) No 141/2000 of the European Parliament and of the Council (16);13 January 2030, for medicinal products.

The EU HTA Regulation focuses on clinical aspects of HTA, i.e. the relative clinical effectiveness and relative clinical safety of a new health technology compared with existing technologies. Member States' HTA bodies will conduct

JCA of new medicines and will also engage in Joint Scientific Consultations to advise developers on clinical study designs that generate appropriate evidence. Moreover, horizon scans will identify, at an early stage, promising health technologies, to help health systems prepare for them.

ZIN is obliged to consider the results of the JCA in their own assessment procedure. However, ZIN might perform additional clinical analyses, such as those related to national disease epidemiology or the specific national healthcare context. Additionally, ZIN will perform their own economic analyses, including budget impact and cost-effectiveness analyses. ZIN remains responsible for formulating the overall value and reimbursement advice. The MoH remains responsible for pricing and reimbursement decisions.

### 10.3.3 Pharmaco-economic Assessment, Budget Impact Analysis and Pharmacotherapeutic Assessment

ZIN is responsible for assessing the relative cost-effectiveness and budget impact of a health technology, with specific requirements for the submission of these dossiers and models.[26] All dossiers must be submitted in Dutch, and models should be in R, with formats available on ZIN's website. However, ZIN does not conduct the pharmacotherapeutic assessment, as the EU-HTA Regulation stipulates that Member States:

- Do not carry out a clinical assessment or an equivalent assessment process on a health technology included in the List of Assessed Health Technologies or for which a JCA has been initiated.
- Apply JCA reports, in their HTA's at Member State level.

From 2025 onward, the therapeutic value of health technologies will be assessed through the JCA procedure. In this process, the European Coordination Group will appoint an assessor and co-assessor, who will request the required documentation from the developer, perform the assessment, and draft a report. The draft JCA report, along with a summary, will then be shared with the developer for comments within a set time frame. Other stakeholders, such as patients and clinical experts, will also have the opportunity to provide feedback during the preparation of the draft report. The Coordination Group will finalize the JCA report and summary, ideally through consensus, or if necessary, by a simple majority vote among Member States. The conclusions of the JCA report will be restricted to:

- an analysis of the health technology's relative effects on the patient-relevant outcomes chosen for the assessment;
- the level of certainty regarding the relative effects based on available evidence.

If the Coordination Group finds that the product does not meet the required standards, the developer will requested to provide additional information. Should the Commission determine that the revised JCA report and summary still fail to meet both substantive and procedural requirements, it will decline to include the name of the health technology to the List of Assessed Health Technologies. The Commission will inform the Coordination Group, who will inform the submitting developer and a summary information on the negative assessment reports will be included in the Commission's annual report.
For health technologies included in the List of Assessed Health Technologies, the Commission will publish the approved JCA report and summary on the IT platform referred to in Article 27, making these documents available to the developer no later than 10 working days after their inclusion.

### 10.3.4 Transparency and Accessibility of HTA Reports and Meetings

The final assessment report of the JCA is made publicly available. Additionally, ZIN's assessment reports are published on the ZIN website for transparency. While the meetings of the WAR are conducted privately, relevant portions of the meeting minutes are published alongside the final assessment reports on the ZIN website. In contrast, the meetings of the Package Advisory Committee (ACP) are open to the public, and their reports are also published on the ZIN website. The MAH files remain confidential and are not publicly accessible, except under the provisions of the Open Government Act (Woo) or its predecessor, the Government Information (Public Access) Act (WOB), prior to May 1, 2022.

### 10.3.5 Early Dialogue in the Joint Clinical Assessment & National Preliminary Advice

Within the JCA procedure, developers have the option to request a joint scientific consultation from the Coordination Group. These consultations, commonly referred to as 'early dialogues', allow developers to seek guidance from HTA authorities and bodies on the data and evidence likely needed for a potential future JCA. The Coordination Group will conduct a specified number of these consultations annually, based on its work program and available resources. When considering a request for a joint scientific consultation, the Coordination Group will evaluate several criteria:

- the likelihood that the health technology under development will be the subject of a JCA in accordance with Article 5(1);
- unmet medical needs;
- potential impact on patients, public health, or healthcare systems;
- significant cross-border dimension;
- major Union-wide added value;
- the available resources.

The Coordination Group will respond to a request for a joint scientific consultation within 15 working days, indicating whether the request will be accepted. If accepted, a sub-group will be designated to oversee the preparation of the consultation report. This sub-group will request the necessary documentation from the developer and appoint an assessor and co-assessor, selected for their relevant scientific expertise.

Within 15 working days after receipt of the request, the Coordination Group shall inform the requesting health technology developer whether or not it will engage in the joint scientific consultation. If accepted, the Coordination Group shall designate a sub-group to oversee the preparation of the joint scientific consultation report on its behalf.
This sub-group will request the necessary information, data and evidence from the developer and appoint an assessor and co-assessor from its members based on their relevant scientific expertise.

The assessor, supported by the co-assessor, will draft the joint scientific consultation report. If additional evidence is needed any stage in the preparation of the draft joint scientific consultation report, the assessor may request the sub-group to suspend the time period set for the preparation of the report and request the additional information from the developer.
The assessor shall provide the draft joint scientific consultation report to the submitting health technology developer and set a time-frame in which the developer may submit comments. The designated sub-group shall ensure that stakeholders, including patients and clinical experts are given an opportunity to provide comments during the preparation of the draft joint scientific consultation report and set a time-frame in which they may submit comments.

If the joint scientific consultation carried out in parallel with scientific advice from the EMA, the assessor will coordinate with the Agency to ensure consistency in conclusions. After incorporating comments from the sub-group and stakeholders, the final draft of the report will be submitted to the Coordination Group by the assessor, with the assistance of the co-assessor. The report must be approved by the Coordination Group, ideally by consensus or, if necessary, by a simple majority of Member States, within 100 days from the start of its preparation. These reports will be accessible to developers but are not binding for the developer nor the Member States at the time of JCA.

In the current national assessment procedure, MAHs can request Preliminary Advice, which **is strongly advised for ATMPs**. This preliminary advice can be complemented by a concept file that includes all 3 parts of the final file, i.e. the Pharmaco-economic Analysis, Budget Impact Analysis and the Pharmacotherapeutics. From 2025 onwards, the Pharmacotherapeutics will not be part of this file, as it should be submitted at the European level. Preliminary consultations address potential issues and shortcomings, with written feedback provided within two weeks. However, no legal rights can be derived from the preliminary consultation. From 2025 onwards, it is anticipated that Joint Early Dialogues will replace national preliminary consultations for clinical assessment topics, though Pharmaco-economic and Budget Impact discussions will continue at the national level.

### 10.3.6 Joint Clinical Assessment Scoping meeting

To ensure that all relevant information is available for a proper and timely assessment of a JCA, the starting point is defining the research questions and the relevant parameters for the assessment scope. This will be done in a JCA Scoping meeting, initiated by the designated subgroup. The assessment scope shall be inclusive and reflect Member States' needs in terms of parameters and of the information, data, analysis and other evidence to be submitted by the developer. The assessment scope shall include all relevant parameters for the assessment in terms of:

- Population: the Patients or population(s) in which the intervention under assessment should be used.
- Intervention: The therapeutic diagnostic or preventative intervention under assessment (including setting).
- Comparator: the alternative interventions under assessment should be compared.
- Outcome: The outcomes of interest (if relevant include minimum follow-up time).

The JCA aims to include a broad range of perspectives and address as many PICO (Population, Intervention, Comparator, Outcome) questions as possible, as defining these research questions is an important step in the JCA process. At this stage, patients can capture patient relevant issues as well as variations across countries. Patients who contribute to the JCA scoping can offer advice on comparators that could be considered, relevant outcomes and share their national needs. The scoping of a JCA, happens before, but parallel to, the granting of MA via the EMA and European Commission.

### 10.3.7 National ZIN Scoping meeting

The ZIN offers scoping meetings at the national level, with the procedure depending on the number and nature of the questions raised. It remains uncertain whether these national scoping meetings will still be necessary after the introduction of the scoping process under the EU/HTA Regulation. Currently, relevant parties that may be invited to these meetings include:

- the patients (general and/or specific patient association/representatives);
- the Scientific Professional Association;
- representatives of centers of expertise (if applicable);
- insurers (ZN, often afterwards a few representatives);
- representatives of hospitals (NVZ) (if applicable);
- The MoH (if applicable).

When ZIN deems a scoping meeting necessary, they inform the relevant parties. Registration holders or their interest groups are not invited to attend these meetings. The discussion topics during the scoping meeting include:

- an explanation of the process;
- the role of the various parties in the process;
- discussing the (pathophysiology and clinical aspects of the) condition;
- the current treatment and the impact of the future treatment(s);
- place of the drug (and possibly other future drugs) in the treatment algorithm;
- defining the patient population;
- relevant outcome measures and clinical relevance limits.

## 10.4 Conditional reimbursement

To address the complex decision-making involved in reimbursing advanced health technologies, the Dutch government has implemented a conditional reimbursement framework. This system includes a mandatory re-evaluation and is applicable to:

- Orphan medicines (for more information see chapter 4.3.5).
- Medicines that have been authorised to the market with certain conditions (so-called conditionals) (for more information see 8.10).
- Medicines that have been authorised under special circumstances (so-called exceptionals) (for more information see 8.10).

Certain ATMPs may also qualify under these conditional reimbursement rules. To apply for this scheme, MAHs with a eligible product must submit an application to the Dutch Healthcare Institute (ZIN) and include a research proposal in collaboration with professional groups, patient organizations, and an (independent) research institute. Applications can be made at two key stages: Prior to a drug assessment by ZIN and after a negative recommendation or position from ZIN due to insufficient evidence required to answer the package criteria.

The following conditions must be met when submitting a file for conditional reimbursement:

- The medicinal product is registered by the EMA with the status of orphan medicinal product, conditional or exceptional for the relevant indication on the basis of which conditional reimbursement is requested.
- There is an unmet medical need (unmet treatment need) according to the current definition of the EMA.

- The main applicant is the MAH. Professional associations, patient associations and an (independent) research institute are co-applicants.
- It must be plausible that a package decision can be taken at the end of the research period based on the data collected. The entire process from research up to and including (renewed) drug assessment by ZIN can be completed within the period of conditional admission. This period is a maximum of 7 or in exceptional cases 14 years. The MAH must record the duration of the process when submitting the file. An interim extension of the conditional admission is not possible.

Applicants should complete and submit an application form for conditional reimbursement of orphan medicines, conditionals, and exceptionals via email to VTgeneesmiddelen@zin.nl. If the medicine is designated by the Minister as a potential candidate, a model agreement will be required. Detailed procedures are described in Rapport Conditional reimbursement of health care and in 'Procedure for starting conditional reimbursement of orphan medicinal products, conditionals and exceptionals'.

Once ZIN selects a medicine for conditional reimbursement, the MoH will negotiate with the MAH to establish a price agreement for the duration of the conditional admission for which a certain level of Public net price transparency is required. If all conditions are met, the product will be reimbursed for the agreed period (max. 7-14 years). The MAH is responsible for funding the research and trial costs during this conditional reimbursement phase.

Furthermore, all parties involved—including the MAH, professional groups, and patient organizations— obliged to draw up a covenant with each other. This agreements contains the (minimum) outcome measures of the study, information dissemination to patients, and criteria for starting, stopping, or phasing out treatment. Cooperation is also required if the medicine is negatively assessed by ZIN after the conditional authorization period ends, in which case it will not be included in the basic health package.

## 10.5 Subsidy scheme promising care

The Promising Care ZIN and Promising Care Regulation aims to accelerate patient access to potentially promising treatments by including them in the basic healthcare package. This scheme provides temporary funding for treatments that show potential in terms of (cost) effectiveness but are not yet covered under the basic package due to insufficient proof of effectiveness. The scheme requires that high-quality research data be collected during the subsidy period to evaluate the new treatment's effectiveness and cost-effectiveness compared to standard care or usual treatment in the Netherlands. After evaluation of the research results, ZIN will review the data within six months to determine if the treatment meets the required SW&P and if the (additional) costs are justifiable. This scheme is also open to non-registered ATMPs as outlined in Article 2.4 of the Healthcare Insurance Decree. The following applications criteria apply:

- The reason for the treatment not being reimbursed under the basic package should be the absence of research demonstrating that it is at least as effective as the standard care or treatment available in the Netherlands.
- The safety and efficacy of the treatment to be investigated has to be demonstrated. This must be substantiated with (among other things) data from clinical research and a CE-marking or market registration.
- The risk to the patient must be reasonable in relation to the anticipated health benefits.
- The treatment must address a market failure.

An annual budget of approximately €69 million is allocated for this subsidy scheme, with an initial funding ceiling of €40 million for the first round of the year. If the ceiling is not reached, the remaining funds will be carried over to the second round within the same calendar year. A project subsidy is granted for a maximum of six years.

The primary applicant must be an administrative representative of a health-care provider, such as a hospital or physiotherapy practice in line with the OCW, SZW, and VWS subsidies framework. Collaboration with relevant patient associations, professional groups, and possibly the owners of the intervention is also required.

## 10.6 Assessment by Health Care Insurers

### 10.6.1 Add-On Integration and SW&P Compliance for Medicinal Products in Hospitals

Medicinal products used within hospitals that have not undergone the Central Lock procedure are automatically considered part of medical care and included in the insured package following EMA registration, as long as they meet the SW&P criteria. This process is known as "open inflow." HCIs are legally required to verify that these products comply with the SW&P criteria. However, during this verification, no reimbursement is provided.

The assessment process by health insurers regarding SW&P compliance begins with an application for an add-on claim title. Although the add-on claim title is for financial administrative purposes, this application and allocation process is used as a starting point for the SW&P assessment; Typically, hospitals charge HCIs for providing treatments (DRG 'diagnose behandel combinaties' or 'DBC'), and are responsible for purchasing the necessary medicinal products to provide state-of-the-art care. However, if a medicinal product is costly (>1000 euros per patient per year), the physician association and an insurer can request an add-on title from the Dutch Healthcare Authority (NZa). Once granted, hospitals can charge HCIs separately for the cost of the add-on medicine used to treat patients with the expensive product. This is why healthcare providers and hospitals often equate the add-on with reimbursement. An add-on is a combination of a performance description and a maximum tariff, allowing hospitals and HCIs to negotiate a price below the NZa maximum tariff for the add-on medicine.

In most cases, the MAH prepares the add-on application in collaboration with a clinical expert. Add-on titles are relevant for all expensive intramural products, but for products assessed by HCIs, the add-on application also serves as the basis for the SW&P assessment conducted by HCIs.

### 10.6.2 Reimbursement application at the CieBAG

A delegation from CieBAG conducts the SW&P assessment of add-on applications based on the completed questionnaire and then presents it to the entire CieBAG. Prior to the assessment, CieBAG consults with the Physician Association. If the Physician Association does not provide guidance on therapeutic value, placement in treatment algorithms, start-stop criteria, patient numbers, or center selection, CieBAG will either make these determinations independently or request the ZIN to establish the SW&P. Ultimately, CieBAG will determine the SW&P.

The outcome of the CieBAG assessment depends on the opinion of the physician association and can be following:

- Negative opinion on SW&P of the physician association. This may result in one of the following reimbursement outcomes:
  - A negative decision and HCIs will not grant the add-on application and reimbursement. The medicine can be prescribed, but there is no entitlement or reimbursement (and may not be financed from the hospital budget). The reimbursement status remains at NO. An individual reimbursement can be requested by the specialist, and can in specific situations honoured.
  - A negative opinion on population level, however reimbursement on patient level within an (Orphan) Drug Access Scheme ((O)DAP) scheme. In this scheme the MAH will provide the therapy free of charge for the first months. After proven efficacy at patient level (response at 4 months in oncology, response at disease specific moment in hematology and in rare diseases) the insurers reimburse the therapy. This protocol is still a pilot for orphan medication and does not seem applicable for one off treatments like CAR-T.
- Unsure opinion on SW&P of the physician association. This may result a proposal of the HCI's to start a conditional reimbursement application at ZIN.
- Positive opinion on SW&P of the physician association. This may result in one of the following reimbursement outcomes:
  - Adoption of the positive advice and reimbursement without additional conditions or negotiations. From that moment on, HCIs will set the entitlement status to YES.
  - Adoption of the positive advice, however based on the cost per patient/ budget impact, additional criteria (start-stop criteria, center selection) are required. The entitlement status is set to YES, but there's limited access.
  - Adoption of the positive advice, but reimbursement only after successful price negotiations with the Clean Team of the insurers. After a positive interpretation of the SW&P, the add on declaration title will have to be set to entitlement status YES. However, until the price negotiations with the Clean Team have been completed, insurers can individually pursue a very restrictive purchasing policy, which means that in practice the medicine will not be used very often.

Since deviations from the basic insurance package are not permitted, insurers evaluate the SW&P collectively within the CieBAG. All insurers are represented in CieBAG, which consists of 14 members (advising doctors and pharmacists employed by insurers) and a technical chairman (a policy officer from Zorgverzekeraars Nederland (ZN)). The CieBAG meets twice a month.

### 10.6.3 Price negotiating at the Clean Team of insurers

Once CieBAG determines that a product meets the SW&P criteria, reimbursement is granted. If the costs per patient or the impact on the overall budget are expected to be high, CieBAG will advise individual HCIs to initiate a joint price negotiation. Each individual HCI can decide whether to follow this advice and participate in the joint negotiation. In such cases, the MAH is requested to start the negotiation with the Clean Team of Insurers. There are no official procedures, thresholds, or timelines for these negotiations.

During the negotiation, the medicinal product is reimbursed based on CieBAG's conclusion. However, individual HCIs may restrict the reimbursement by strict center selection, additional conditions and a reduction on the reimbursed add on tariff. As a result, hospitals may prescribe these medicinal

products infrequently unless the MAH compensates for the difference between the price and the reimbursed add-on tariff.

Given that many ATMPs are one-time treatments, price discussions can be extra complex. Therefore, it is crucial to begin discussions on sustainable funding early in the process with HCIs, supported by your TTO. Additionally, consult the COGEM publication on the value of gene therapy, which, despite being in Dutch, offers valuable insights into affordability scenarios.

## 10.7 Reimbursement of ATMPs within Hospital Exemption

There are no specific rules regarding the reimbursement of ATMPS under hospital exemption. Under the Dutch Healthcare Insurance Act (reimbursement) and the Health Care (Market Regulation) Act (financing of reimbursed care), ATMPs, including hospital exemption products, will likely be considered as 'medical specialist care' or hospital care. This implies that the reimbursement tariff will be determined/negotiated by the health care insurers. As per 2019, ATMPs under hospital exemption may be able to qualify for a subsidy under the regulation of Promising Care ZIN and Promising Care Regulation (see 11.5).

### Key Take-Away

In case a price negotiation is foreseen, explore in an early phase (for academia together with the TTO) possibilities and consider sustainability of the funding (in case of research or development grants/subsidies) and affordability from academic or organizational (SME/pharmaceutical companies), but also societal perspective.

For academia and SMEs consider consulting the IP and health technology experts of DARE-NL.

When discussing different models with payers keep their needs in mind: addressing issues uncertainty (long term efficacy) end the discrepancy between long term effects and high costs in 1st year.

***See annex 4* for possible pricing performance or data related schemes.**

# 11. Support for Developers of ATMPs

## 11.1 Introduction

Developers of ATMPs must be aware of the legislation governing different stages of the medicine development process, including GMP, GCP and GLP) requirements. The EMA and on a local level College ter Beoordeling van Geneesmiddelen (CBG), Inspectie Gezondheidszorg en Jeugd (Dutch Health and Youth Care Inspectorate - IGJ) and also DARE-NL, offer a wide range of advisory services and incentives to support the development of ATMPs throughout the different phases. The most relevant are presented in the table below. Some of these supporting tools or dialogues are described in more detail in one of the sections below.

| Type of support | Provider | Link | Related section |
|---|---|---|---|
| ***Training, Guides & Tools*** | | | |
| *General* | | | |
| EMA's interactive tool describes the journey of a medicine authorised via the Agency, from initial research to patient access in the EU, and how EMA works. | EMA | Link | 4-8 |
| EMA's report (and interactive timeline) outlines the entire journey of a medicine, from initial research to patient access, and provides insights into how the EMA supports development, assesses benefits and risks, and monitors safety. | EMA | Link | 4-8 |
| The European Consortium for Communicating Gene and Cell Therapy Information (EuroGCT) provides information about the use of cells and genetic material to treat disease and information on the practical steps needed for cell and gene therapy development) | EuroGCT | Link | 4-8 |
| EuroGCT Detailed information per pathway | EuroGCT | Link | 4-8 |
| DARE-NL Course directory offers a wide range of courses relevant for ATMP development | DARE-NL | Link | |
| Guidelines for Socially Responsible Licensing | FAST | Link | |
| *(Pre) Clinical trials* | | | |
| EMA guide for clinical trials | EMA | Link | 7 |
| The steps from fundamental to pre-clinical and clinical research underpinning the development of innovative gene and cell therapies. | | Link | 5-7 |
| Online training of EUPATI regarding the different phases of clinical development | EUPATI | Link | 6-7 |
| Guide for developers for Clinical trial application (CTR): from start to finish | CCMO | Link | 7 |

| Type of support | Provider | Link | Related section |
|---|---|---|---|
| Guidance for developers to generate robust quality data packages for their MA applications in the EU. It covers medicines containing chemical, biological or biotechnologically derived substances and ATMPs | EMA | Link | 4-8 |
| Guidance on scientific guidelines adopted at ICH and EU levels, and in the Notice to applicants (NTA) which includes guidance on the common technical document (CTD) | EMA | Link | 5.3 |
| Quick interactive guide to IRIS registration process | EMA | Link | |
| *Regulatory* | | | |
| EMA's guide for micro, small and medium-sized enterprises provides details about the regulatory processes involved in a MA and is aimed at developers which are unfamiliar with the regulatory framework (also for Academia) | EMA | Link | |
| Guidance on Classification of ATMPs | EMA | Link | 3.2 |
| Guidance on how to obtain Scientific Advice and Protocol assistance | EMA | Link | 3.3 |
| Guidance on how to obtain procedural advice on orphan medicinal product designation | EMA | Link Link | 4.3.5 |
| Guidance for priority medicines PRIME | EMA | Link | 5.7 |
| Toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME and certain MAA targeting an unmet medical need | EMA | Link | |
| Preparatory Meeting | EMA | | 4.4 |
| Quality Innovation Group, Forum with explanations regarding manufacturing and regulatory requirements | EMA | | 4.5.3 |
| *Patient involvement* | | | |
| Patient Engagement Resource Centre for training materials, guidance and formats to support patient involvement during the lifecycle of ATMP | PERC | Link | 2 |
| *On national level* | | | |
| Scientific Advice CBG | CBG | Link | 5.3.2 / 11.3.2 |
| Support for Clinical trials from start to finish | CCMO | Link | 5.3.2 / 11.3.3 |
| DARE-NL: Knowledge and expertise center. An online training tooland regulatory roadmap are expected on the website in 2nd half of 2024 | DARE-NL | Link | 11.10 |

| Type of support | Provider | Link | Related section |
|---|---|---|---|
| *Support for micro, small and medium enterprises (SME) & Academia* | | | |
| User guide for micro and small medium size enterprises | EMA | Link | 11.5 |
| EMA support for SME´s via the EMA SME office | EMA | Link | |
| Overview of certification procedures for advanced therapies under development by micro-, small- and medium-sized enterprises (SMEs) and the support provided by the EMA service desk and SE office | EMA | Link | |
| SME briefing meetings | EMA | | |
| Guidance on clinical data publication | EMA | Link | |
| Support/assistance (free of charge) with the translation of the Product Information in all European languages (excl. Icelandics and Norwegian) via the translation Centre | EMA | Link | |
| Different events to inform, engage or train SMEs on relevant topics. | EMA | Link | |
| Overview of training materials, reports and presentations | EMA | Link | |
| Support for academia and non-profit organisations (temporary pilot): guidance throughout the regulatory process, from manufacturing tot clinical development and follow up planning on efficacy or safety issues. | EMA | | |
| The Innovation Task Force this is a forum for informal dialogue between EMA and developers of ATMPs in the early stages of the medicine development process. | EMA | Link | 11.5.3 |
| Support via academic partners in the paediatric-medicine field within the EMA European network of pediatric Research (Enpr-EMA) | Enpr- EMA | Link | |
| The ATMP Engage PPI Directory contains patient and public involvement (PPI) resources for developers of cell and gene therapies, including toolkits, guidelines, advice, templates and case studies. | Euro GCT | Link | 2 |
| *Reduction in EMA fees* | | | |
| Developers of ATMPs can obtain reductions in EMA fees. Fees for scientific advice varies depending on the scope of the advice. Reductions per types of medicines or applicant: 65% fee reduction for a request for scientific advice for ATMPs (90% for SMEs); 90% fee reduction for the certification procedure; 75% fee reduction for medicines for orphan medicines. | EMA | Link | 5-8 |
| Reduction for academia and non-profit organizations and SMEs: full waiver for medicines intended to treat, prevent or diagnose a declared public health emergency; free of charge briefing meetings; free of charge support for translation of the product information; academic sector get free protocol assistance for developing orphan medicines. | | | |

## 11.2 The ATMP classification procedure

The ATMP classification procedure is introduced by the CAT. It provides clarity on the development path and scientific regulatory requirement. The ATMP classification procedure initiates early engagement with regulators. This procedure can be requested at any stage of product development, is voluntary (not obligatory) but strongly advised, free of charge and non-binding (for both). The applicant submits the following two documents according to the templates provided:

- Administrative information ATMP classification and the administrative information sheet can be found here;
  The following information need to be submitted:
  - Information on the product (e.g. on active substance, finished product, mechanism of action and proposed use);
  - Information on the development of the product (including element of the manufacturing, quality aspects and outline of the non-clinical and clinical development) relevant for the ATMP classification;
  - Applicants should also substantiate their positions on the classification of their product.
- Classification request form and briefing information can be found here.

Submission dates are published on the EMA website. The procedure takes 30 days (60 days when additional information is required when the European Commission (EC) has major comments. See also chapter 3.4 and figure 10 for the timelines.

## 11.3 Scientific Advice, regulatory advice and protocol assistance

### 11.3.1 Scientific Advice and protocol assistance EMA

Developers can request scientific advice or protocol assistance from the EMA at any stage of a medicine's development, this includes advice on best methods and study designs to generate robust data on a medicine's efficacy and safety. This support is available regardless of whether the medicine is eligible for the centralised authorisation procedure. Developers can request scientific advice or protocol assistance from the EMA during the initial stages of development before submitting a marketing authorisation (MA) application, and later, during the post-authorisation phase.

Scientific advice helps in ensuring that developers conduct the necessary tests and studies, thereby reducing the likelihood of major objections during the evaluation of the MA application. This approach also helps prevent patients from participating in studies that may not yield useful evidence. Starting January 12th, 2025, a Joint Scientific Advice as part of the new EU Health Technology Assessment (HTA) regulation will also be available (see 10.3.2). While the detailed advice given during development and assessment phases remains confidential, this information is made available once a medicine receives MA.

Questions during **scientific advice** can relate to:

- quality aspects (e.g. manufacturing, chemical, pharmaceutical and biological testing of the medicine);
- non-clinical aspects (e.g. toxicological and pharmacological tests designed to show the activity of the medicine in the laboratory);
- clinical aspects (e.g. appropriateness of studies in patients or healthy volunteers, selection of endpoints, i.e. how best to measure effects in a study, post-authorisation activities including risk management plans);

- methodological issues (e.g. statistical tests to use, data analysis, modelling and simulation);
- overall development strategy (e.g., conditional MA, bridging strategy for generics, safety database), significant benefit for maintaining orphan designation, and paediatric developments.

For developers working on **orphan medicines for rare diseases**, protocol assistance offers additional support. This special form of scientific advice helps developers navigate the specific challenges of bringing orphan medicines to market. The EMA provides protocol assistance to discuss critical compliance criteria such as demonstrating 'significant benefit' within the designated orphan indication and resolving issues of 'clinical superiority' over existing medicines. This is relevant if other orphan medicinal products exist that might be similar to the product concerned and which have market exclusivity in the same indication. To further encourage the development of orphan medicines, the EMA waives fees for academic applicants when they seek protocol assistance.

*Scientific advice and protocol assistance are particularly beneficial when:*

- developing an innovative medicine and there appears to be no or: insufficient relevant detail in EU guidelines or guidance documents, or in Pharmacopoeia monographs, including draft documents or monographs released for consultation;
- developing new or repurposed medicines targeting (re)emerging pathogens for which there is an unmet medical need but insufficient or no guidance is available;
- choosing to deviate from scientific guidelines in its development plan;
- not/less experienced in the medicine regulation, such as some academic groups or micro, small and medium sized enterprises (SMEs).

Developers should use EMA's secure online IRIS platform to request scientific advice, protocol assistance or qualification of novel methodologies for medicine development. The IRIS platform provides a single space for applicants and EMA to submit requests, communicate, share information and deliver documents concerning a scientific advice procedure. Steps to be taken:

- Registration: developers need to be registered in IRIS Quick interactive guide to IRIS registration process. A research product identifier (RPI) will be granted (formerly the unique product identifiers (UPIs)).
- Upload a draft briefing document introducing the medicine under development and the applicant's questions. It is mandatory to use the Committee for Medicinal Products for Human Use (CHMP) scientific advice/protocol assistance briefing document template.

Developers can get assistance in putting their scientific advice or protocol assistance requests together through preparatory meetings. Preparatory meetings are particularly important for first-time users of these procedures, for academia, micro-, small- and medium-sized enterprises (SMEs), and for companies seeking general advice on specific types of medicinal products or therapies. The information provided by the applicant provides the basis for the meeting discussion. The opinions expressed by the EMA participants are individual views and do not represent the final opinion of the Stichting Werkgroep Antibiotica Beleid (SWAP) or CHMP.

### 11.3.2 Scientific and regulatory advice CBG

The CBG provides detailed scientific and regulatory advice to ensure the efficient and responsible development of medicines. This advice may cover regulatory or scientific strategies for all aspects of the registration dossier, including chemical-pharmaceutical, pharmacological-toxicological/

pre-clinical, pharmacokinetic, clinical, or pharmacovigilance components. The advice can address the entire product lifecycle, from the preclinical research phase to post-marketing modification proposals.

Scientific advice cannot replace a marketing authorization application and does not preempt the final judgment of the CBG or the CHMP. The CBG will not conduct preliminary assessments of results or data outside the context of the entire dossier, nor will it make statements about the benefit/risk profile. Additionally, the CBG does not address medical-ethical questions, which fall under the jurisdiction of the Central Committee on Research Involving Human Subjects (CCMO) or local medical-ethical review committees.

Any party involved in the development of a medicine, from large pharmaceutical companies to small (academic) research institutions, can request scientific and/or regulatory advice. The CBG treats all submitted data with strict confidentiality.

*Categories of Advice include:*

- *Simple Advice:* Focuses on regulatory matters, pharmaceutical, or preclinical aspects, often used for less complex issues or follow-up consultations.
- *Partially Multidisciplinary Advice:* Primarily clinical advice concerning the efficacy and safety of a medicine, potentially combined with pharmaceutical or preclinical advice.
- *Fully Multidisciplinary Advice:* Addresses clinical, preclinical, and pharmaceutical aspects, often for more complex product developments.
- *Tailored Advice:* Aimed at startups, small enterprises, and academic groups, focusing on early-stage development, Phase I clinical research, or new uses for existing medicines. It also includes guidance on the 'regulatory roadmap' and may involve a preliminary consultation.

To request advice, complete the application form, where you can select the most appropriate type of advice. It is important to ask specific questions and provide your perspective on these questions. You can choose between oral or written advice in the form. Written advice is typically used for less complex topics, while oral advice facilitates effective exchange of insights through a meeting. The process for requesting advice is as follows:

- Applicants can request advice via a specific application form, selecting between written or oral formats depending on the complexity of their inquiries (the application form can be found here).
- After receipt, the application is validated. Within three weeks, you will be informed whether the application will be processed and the applicable fee.
- Written advice is provided within seven weeks of receiving all necessary documentation.
- For oral advice, a meeting is scheduled within six weeks to three months after application acceptance, allowing for an in-depth exchange between applicants and CBG experts.

CBG also participates in a pilot for simultaneous national scientific advice, where applicants can seek advice from multiple EU member states at once. For more complex cases, CBG offers a joint advisory service with the ZIN, addressing both registration and reimbursement requirements within a single procedure. All advice is strictly confidential, and CBG handles all submitted data with the highest discretion.

### 11.3.3 Pilot program scientific advice CCMO

In 2024, the CCMO launched a pilot program to assess the feasibility of offering scientific advice as a new service. This pilot will also explore how this advice integrates with existing national and European scientific advisory services. The pilot will run until at least January 31, 2025.

*In the pilot, advice can be requested on the following topics:*

- Early phase studies (design, quality pre-clinical data prior to starting a first-in-human trial).
- Investigational Medicinal Product Dossier questions (IMPD-Q) in the context of a planned clinical trial application.
- Clinical trials on rare diseases with an unmet medical need.
- Complex clinical trials / platform trials (methodology and CTIS submission);
- Regulatory and procedural questions related to clinical trials or trials where both the CTR as well as Chapter VI of the Medical Devices Regulation (MDR) and In Vitro Diagnostics (IVDR) apply (the so called combined studies).
- Clinical trials with minors.
- Medical-ethical issues.

*The scientific advice does not concern the following areas:*

- Questions related to studies with medical devices/IVDs where only the MDR/IVDR apply.
- Questions related to marketing authorization (MAA) of a medicinal product. This falls under the remit of the Medicines Evaluation Board (MEB).

The number of scientific advice during the pilot has been maximised to 10. The requests will be processed in the order of receipt. In the pilot, the advice is free of charge. More information on this pilot program including the application procedure can be found here.

## 11.4 EMA Support for Small and Medium Enterprises & academia

ATMPs are frequently developed by Small and Medium Enterprises (SMEs) and academia. While their success rate for MAAs is improving, it remains below the average. One of the primary reasons for the refusal or withdrawal of these applications is the need for additional clinical data to support the MAAs. The quality of documentation remains another significant challenge for many SMEs. **To ensure that the appropriate studies are performed and that there are no major objections regarding the study design at the time of the evaluation of the MAA, academia and SMEs are particularly encouraged to seek scientific advice from EMA**. EMA emphasizes the value of early interaction to prevent major objections during the evaluation of the MAA. Additional support is available specifically for SMEs and Academia.

Support is available for SMEs through SME@ema.europa.eu. Enterprises are eligible for SME status if they meet the following criteria: (I) they must be established in the European Union (EU) or European Economic Area (EEA), (II) have a limited enterprise's size (including partnership):< 250 employees, and (III) have an annual turnover of less than €50 million or an annual balance-sheet total of less than €43 million.

Support is also available for academic institutions through Academia@ema.europa.eu, which addresses the needs of developers from the academic sector. This platform aims to facilitate communication and help academic developers navigate the regulatory framework. Academic institutions can request support from the SME office, and all the support available to SMEs is also extended to academia.

The EMA recommends that both SMEs and academic developers consult the dedicated user guide, which provide an overview of the regulatory requirements and incentives available throughout a medicine's product lifecycle. This guide helps developers better understand the procedures that support research and development activities and clarifies what is needed to obtain a MA.

### 11.4.1 SME and Academic briefing meetings

SMEs and academia often operate with limited resources, which can result in a lack of experience or familiarity with the regulatory approval process. Opening up early dialogue with EMA during development during the pre-submission phase of MA application, can be challenging due to limited capacity or experience in navigating the regulatory landscape. EMA offers briefing meetings, which provide a platform for a EMA or academia to discuss their planned regulatory strategy with the agency. These meetings are valuable to find out about available procedures, guidance and incentives and to engage in an early dialogue with an EMA multidisciplinary team (e.g. scientific advice, PRIME, regulatory affairs, orphan medicines or quality offices) depending on the questions raised. **SMEs and academia are encouraged to approach the EMA to request a briefing meeting at any stage of their product development**. One to two months prior to the meeting, the applicant should provide the EMA with background information on the product, mechanism of action, stage of development, previous interactions with authorities or EU funding scheme (when applicable) and questions to be addressed. The EMA will review the request to determine the best way to address it, may request additional information if needed and will set up an SME briefing meeting as appropriate. **Briefing meetings are provided free of charge by EMA.**

### 11.4.2 Certification of advanced therapy

As an incentive to develop ATMPs, SMEs or academia can submit the results of studies conducted to demonstrate the quality and non-clinical safety of ATMPs to the EMA pior to any MAA. They can request evaluation and certification of the data, independently of any MAA. While this certification is not legally binding, it is designed to facilitate the evaluation of future applications for clinical trials and MA.

### 11.4.3 Translating the product information into all EU official

Translations of product Information are required in all EU official languages (including Norwegian and Icelandics). These translations can pose a significant financial and administrative challenge for SMEs and academia. To alleviate this burden, the EMA offers free translation services for the product information and relevant opinion annexes required to grant an initial EU MA. The EMA initiates these translations through the Centre de Traduction (CdT) in Luxembourg at the time of the CHMP opinion. The national competent authorities in the member states then review the translations. For a SME to be eligible for this translation assistance (see LINK) they must hold a valid SME status when the translation process begins. It is important to note that the developer is responsible for providing translations into Norwegian and Icelandic.

## 11.5 Innovation Task Force

The Innovation Task Force (ITF) at the EMA provides a multidisciplinary platform designed for early dialogue on innovative medicines, methods, and technologies. ITF is available to all types of developers, including academia, micro enterprises, SMEs and large pharmaceutical companies. ITF brief meetings should held at much earlier stage of the development than the scientific advice and provide developers with the opportunity to discuss regulatory, technical, and scientific challenges at the earliest stages of development. Experts attending ITF meetings include EMA staff with relevant expertise, members of EMA Committees and Working Parties, and European experts who provide scientific expertise to EMA's activities. Depending on the need, additional expertise may be brought in, including international regulators such as the Food & Drug Administration (FDA), Swissmedic, or Health Sciences Authority (HSA) Singapore.

These **free of charge** meetings can provide advice on a wide array of topics, from scientific issues like pre-clinical development, manufacturing, and quality aspects, to regulatory questions such as how to proceed when no existing guidance is available. Legal topics can also be addressed, for example, determining whether a product qualifies as a medicinal product under current legislation. EMA's ITF also provides advice to medicine developers on eligibility to EMA procedures relating to the research and development of borderline products. These meetings are designed to be informal brainstorming sessions, allowing for the exchange of ideas and guidance that complement existing formal EMA procedures **(e.g. scientific advice, ATMP certification)**. General queries can be sent to ITFsecretariat@ema.europa.eu

## 11.6 Orphan designation

'Orphan' medicinal products are those intended to diagnose, prevent or treat life-threatening or serious and debilitating conditions that are rare and affect not more than 5 in 10,000 persons in the European Union. To check whether a product is fitting the requirements see the flowchart to an orphan designation. 'Orphan' medicinal products can benefit from incentives such as protection from competition once on the market. Developers seeking orphan designation are encouraged to request a pre-submission meeting, which, although not mandatory, significantly improves the success rate of applications. These Pre-submission meetings are useful as the evaluation process has a fixed duration of 90 days with no extensions allowed to accommodate for the lack of data or other omissions in the application. Pre-submission meetings usually take place via teleconference, unless the applicant has a strong preference to come to EMA in person. During the application for orphan medicinal product designation the Committee for Orphan Medicinal Products (COMP) will determine whether the applicant has established the designation criteria, i.e.:

- the life-threatening or debilitating nature of the condition;
- the medical plausibility of the proposed orphan indication;
- that the prevalence of the condition in the European Union is not more than five in 10,000 or that it is unlikely that marketing the medicinal product in the European Union, without incentives, would generate sufficient return to justify the necessary investment;
- that no satisfactory method of diagnosis prevention or treatment exists, or if such a method exists, that the medicinal product will be of significant benefit to those affected by the condition.

An in depth guide on the application process and regulations can be found here.

## 11.7 PRIME: priority medicines

PRIME is a voluntary scheme run by the EMA and offers support for the development of medicines that target an unmet medical need (unmet medical need defined: no treatment option exists or where there's a major therapeutic advantage over existing treatments). It offers **early and proactive support to optimise the generation of robust data** on a medicine's benefits and risks and enable accelerated assessment of medicines applications.

*The scheme provides scientific and regulatory support:*

- Early appointment of a rapporteur from the scientific committees.
- Assignment of a dedicated EMA contact point.
- Dedicated meeting with the rapporteur and experts to provide guidance on the development plan and regulatory strategy ('kick off meeting').
- Scientific advice involving stakeholders such as health-technology-assessment bodies and patients as applicable (see section 11.4), including parallel EMA-FDA advice for products developed for both the EU and the US market.
- Submission readiness meeting approximately 1 year before the MAA submission date to discuss development status and maturity of the dossier in view of the planned type of MAA.
- Eligibility to additional SME fee reductions for scientific advice.

PRIME builds on the existing regulatory framework and tools already available such as scientific advice and accelerated assessment. Developers of a medicine that benefited from PRIME can expect to be eligible for accelerated assessment at the time of application for a MA. **SMEs and applicants from the academic sector may be granted Early Entry PRIME status if they demonstrate proof of principle**.

To be accepted for PRIME, a medicine must demonstrate the potential to address an unmet medical need to a significant extent. Therefor applicants must provide any available data showing a meaningful improvement of clinical outcomes, such as:

- Impacting the prevention, onset and duration of a given condition.
- Improving the morbidity or mortality of a disease.

Applicants from academia and SMEs, who generally have less experience of the regulatory landscape, may submit an eligibility request for Early Entry PRIME status if:

- Compelling non-clinical data in a relevant model provide early evidence of promising activity, or proof of principle.
- First-in-human studies indicate adequate exposure for the desired pharmacotherapeutic effects and tolerability.

Applicants receive the evaluation outcomes, via letter, following their adoption by CHMP. CHMP also adopts an overview of outcomes, which is then published in the CHMP meeting highlights. It contains limited information on the type of product, intended indication, level of data supporting the request, and type of applicant (SME, academia or other). CHMP publishes the name of the active substance/international non-proprietary name (INN) for products with a positive outcome and therefore deemed eligible to PRIME. This is not the case for negative outcomes. More information on PRIME can be found here.

Guidance for developers to generate robust quality data packages for their MA applications in the EU is available here. It covers medicines containing chemical, biological or biotechnologically derived substances and ATMPs.

## 11.8 Quality Innovation Group (QIG)

The Quality Innovation Group (QIG) is an operational expert group set up to support the translation of innovative approaches to the design, manufacture and quality control of medicines, to bring new therapies and help improve the supply of existing medicines to patients. These include innovative technologies, novel materials and devices, and digitalisation in manufacturing, in line with EMA's Regulatory science strategy to 2025.

The QIG can support the development and registration of innovative technologies and products, by clarifying the regulatory requirements for manufacturing and control early on for stakeholders. The group's work helps to avoid regulatory barriers and adapt regulatory guidance while ensuring products meet the required quality, safety and efficacy standards.

The QIG holds listen-and-learn focus group meetings with stakeholders from industry, academia and international regulators to hear about the regulatory challenges developers face in relation to innovative products, processes, control strategies and facilities, and to identify potential solutions together.

The QIG aims to provide coherent advice to developers during the product development lifecycle. It can do this during:

- Regulatory procedures, such as scientific advice or protocol assistance, initial MAAs or post-authorisation procedures.
- Informal information-sharing meetings with individual developers, which can help identify potential regulatory issues in development programmes.

QIG support is available through: qig@ema.europa.eu

## 11.9 Joint advice with EU HTA bodies

The EMA offers consultations in parallel with the European Network for Health Technology Assessment (EUnetHTA) 21 consortium. This allows medicine developers to obtain feedback from regulators and Health Technology Assessment (HTA) bodies in EU Member States on their evidence-generation plans to support decision-making on marketing authorisation and reimbursement of new medicines at the same time. Consultations can take place before or after the product is placed on the EU market. The objective is to help generate optimal and robust **evidence** that satisfies the needs of both regulators and HTA bodies.

Interactions between medicine developers, regulators and HTA bodies or other stakeholders to discuss the development plan enable evidence to be generated to meet the needs of respective decision-makers as efficiently as possible. This facilitates patient access to important new medicines and benefits overall public health. The main benefits of the parallel joint scientific consultation (JSC) procedure include:

- streamlined procedure for applicants;
- increased mutual understanding and problem-solving ability between EMA and HTA bodies through a more structured interaction;
- improved coordination with, and greater participation of HTA bodies in parallel consultations through EUnetHTA 21's Committee for Scientific Quality & Consistency in its configuration for Joint Scientific Consultations (CSCQ JSC).

Applicants wishing EUnetHTA21 to take part in a parallel JSC procedure should respond to an EUnetHTA21 open call for joint scientific consultation, in line with the latest version of the joint guidance. For the latest information on open calls for joint scientific consultation (JSC), see the EUnetHTA 21

website. Developers will be able to apply for parallel advice until January 2025 when Regulation (EU) 2021/2282 on health technology assessment will become fully applicable. From then European cooperation between medicine regulators and HTA bodies will be governed by this new regulation; EMA will collaborate with the secretariat of the Member State Coordination Group on HTA (HTACG) to support this group's clinical assessments.

## 11.10 DARE-NL

The development of ATMPs often starts in close collaboration with or within academic centers. For (very) rare disorders, these centers can play a crucial role in integrating treatments into clinical practice. However, these centers often lack the resources and infrastructure needed for further development beyond clinical trials, including navigating the registration process and securing reimbursement. The translation from preclinical research to clinical trials and the implementation in clinical practice presents significant challenges). To address these challenges and accelerate clinical testing of novel ATMPs for cancer patients while ensuring timely and sustainable access, The 'Dutch platform for cancer-specific ATMP research' (DARE-NL) was established.

DARE-NL wants to establish a national infrastructure and connect all relevant stakeholders (e.g. scientists, clinicians, pharmacists, regulatory agencies, patient advocates) in the oncological ATMP development cycle. It bundles the high-quality but fragmented knowledge in the Netherlands with the aim of harmonizing and thus accelerating ATMP research into clinical implementation. To achieve this, all Dutch university medical centres, the Netherlands Cancer Institute-Antoni van Leeuwenhoek, Princess Máxima Center, Sanquin and Utrecht University share knowledge, expertise and resources and enter into a joint dialogue with all stakeholders. The consortium forms a central voice from academic ATMP development towards other parties such as regulatory and supervisory bodies All academic developers are welcome to (actively) join DARE-NL.

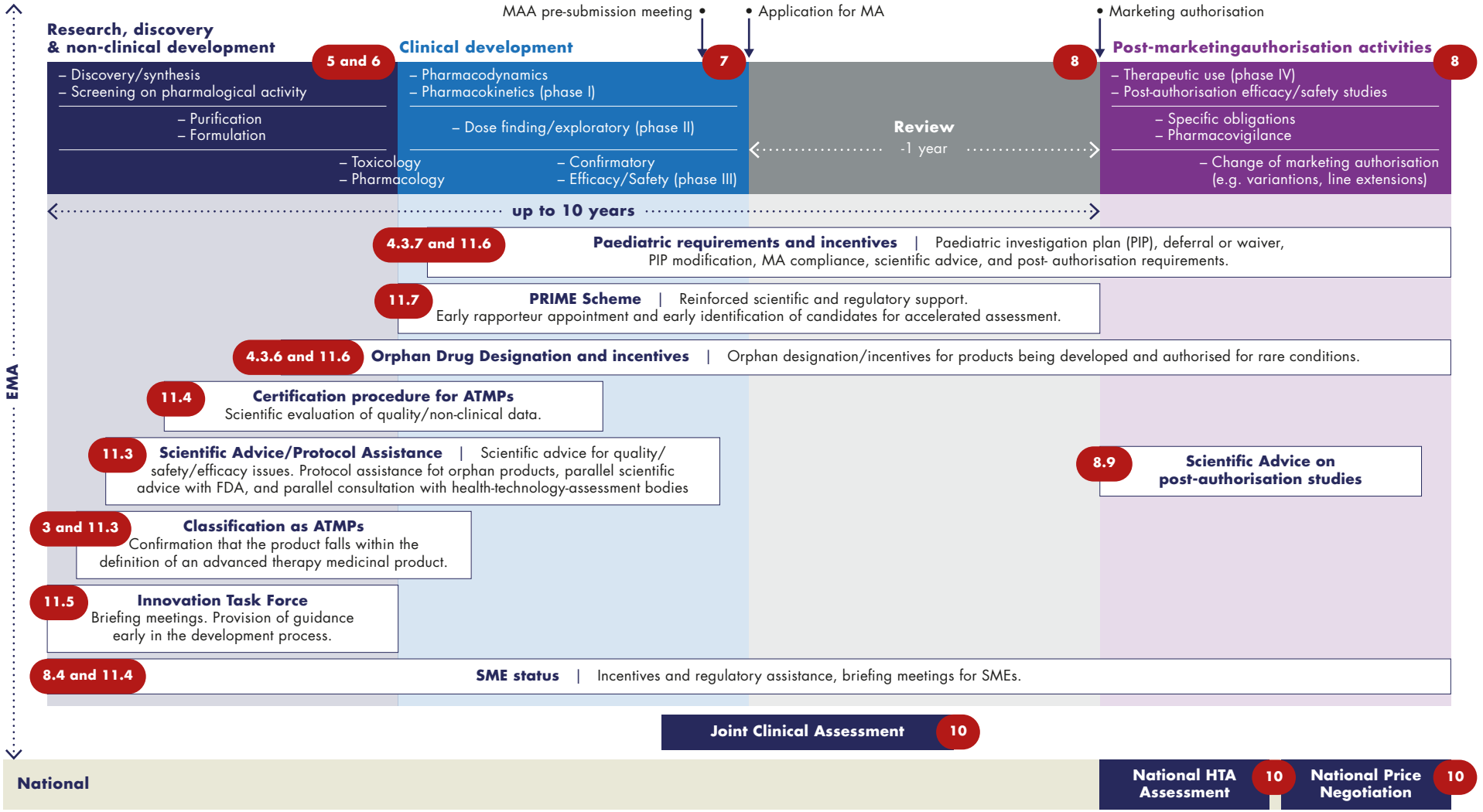
*Table 1: Dare-NL prioritised activities based upon following challenges*

| Issue | DARE-NL |
|---|---|
| Fragmentation of knowledge as the ATMP field encompasses many different disciplines (e.g. research, pharmacy, healthcare, regulation, inspection, fees, rights, valorisation, commercialisation and advocacy) and various medical centres, research and healthcare institutes. | Facilitates knowledge exchange and continuous dialogue between all stakeholders and experts through the knowledge platform, meetings and workshops. In addition, DARE-NL has connections with relevant knowledge networks such as the Dutch-Belgian ATMP working group. |
| Highly skilled personnel with a combination of biological, technological, and pharmaceutical knowledge are scarce, expensive, and time-consuming to train. | Setting up an education programme to (re)train (future) translational ATMP experts |
| Lack of IP-related expertise at an early stage of development, which is necessary for sustainable ATMP developments. | Oncode Institute is involved in DARE-NL as an advisor. In addition, DARE-NL has set up an IP management committee to support social discussions in this area with representatives of technology transfer offices, business developers and IP-experts van alle partners. |
| The laws and regulations for medical technological developments are a patchwork of procedures, quality controls and administration. | Harmonize protocols and assays for ATMP production and quality control to make the trajectories transparent for both researchers and control authorities. And the creation of overviews of production and regulatory processes, so that developers have the necessary information easily available for every part of the process to registration. |
| There's a limited amount of certified producers of certified materials (i.e. viral vectors) what will drive the price | Establishment of a Dutch platform for central and uniform production of viral vectors and other biological raw materials certified for clinical trials. This includes new technologies such as genetic modification, non-viral engineering and artificial intelligence. |
| Uncertainty about ATMP development and registration processes for the formulation and interpretation of guidelines | DARE-NL has scientific expertise in the field of regulation. These regulatory experts draw up overview maps to provide insight into where a developer can go in each step of the development and registration process of different types of ATMPs. In addition, they facilitate a continuous joint dialogue between developers, regulatory and controlling authorities in order to provide insight into suitable routes towards registration and tools. |
| Little insight into production costs and treatment reimbursements due to the complexity of realistic value propositions related to, among other things, the many production and development costs, the required characterization and safety analyses, and the uncertainties about the potentially long-term clinical activity. | DARE-NL has expertise in the field of health economics and health technology evaluation and will work closely with organisations involved in reimbursement, such as the National Health Care Institute (ZIN), for knowledge of market access and collection of evidence, including economic evidence, at an early stage of development. By means of an ATMP cost instrument, DARE-NL creates insight into the ATMP production and development costs to maximize the cost efficiency of new therapies and thus accelerate reimbursement. |

Source: Punt et al, 2024

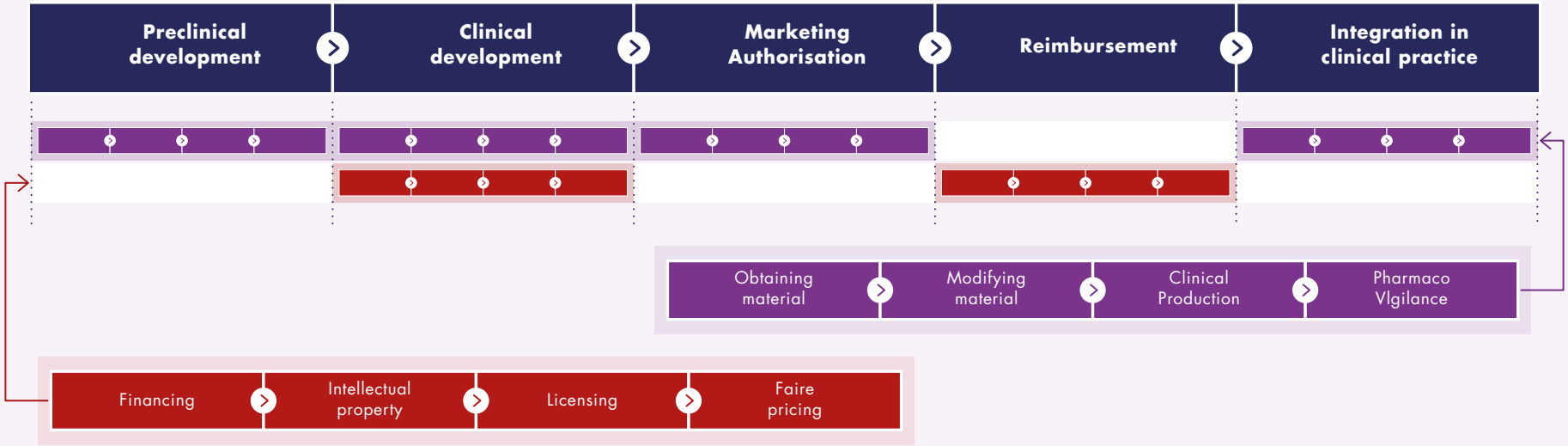
**Recommendation**: Right documentation and comply to the (pre)clinical requirements is crucial and determines the success rate of an application (trail and MA). Developers have access to different supportive meetings throughout the lifecycle of the product. Success rate of applications (clinical trials and MA) increases when SMEs and academia use these briefing and pre submission support meetings and align early in process with EMA and national bodies (CBG, CCMO). Use the EMA dossier validation checklist early in process to verify what´s lacking in your data package, process or organisation.

*Figure 18: Overview of medicinal products development, incentives and opportunities for dialogue*



# Annexes

## Annex 1: ATMP drug lifecycle



## Annex 2: Overview relevant Directives and Regulations in the ATMP drug lifecycle

| Pre Clinical Development | | Clinical Development | | Marketing Authorisation | | Reimbursement |
|---|---|---|---|---|---|---|
| Directive 2004/9/EC | | Regulation (EU) No 536/2014 | | Directive 2001/18/EC | | Council Directive 89/105/EC |
| Directive 2004/10/EC | | Directive 2001/20/EC | | Directive 2009/14/EC | | Regulation (EU) 2021/2282 |
| EMA GLP principles ATMPs | | Eudralex Volume 10 | | Directive 2002/98/EC | | **Dutch Legislation/Regulation** |
| | | Directive 2005/28/EC | | Directive 2009/120/EC | | Zorgverzekeringswet |
| | | Directive 95/46/EEC | | Directive 2010/53/EU | | Besluit Zorgverzekering |
| | | Regulation (EU) No 1901/2006 | | Regulation (EU) No 1394/2007 | | Regeling Zorgverzekering |
| | | Regulation (EU) No 1902/2006 | | Regulation (EU) No 726/2004 | | Regeling medisch specialistische zorg |
| | | Directive 2001/18/EC | | Regulation (EU) No 2017/745 | | Wet Geneesmiddelenprijzen |
| | | Directive 2009/14/EC | | Regulation (EU) No 141/2000 | | Wet marktordening gezondheidszorg |
| | | | | | | Beleidsregel prestaties en tarieven med-spec. zorg |
| | | | | | | |
| EMEA/CAT/852602/2018 | | EMEA/CAT/852602/2018 | | 3AB11a | | ZIN-Beoordeling SW&P |
| EMEA/CAT/486831/2008 corr | | EMEA/CHMP/QWP/805880/2012 rev 2 | | Ph.Eur: (2.7.23) | | ZIN-Richtlijn economische evaluaties |
| EMEA/CAT/418458/2008 rev | | EMEA/149995/2008/Rev 1 | | Ph.Eur: (2.7.28) | | ZIN-Beoordelingsprocedure |
| EMEA/CHMP/SWP/28367/07 Rev 1 | | CHMP/EWP/83561/2005 | | Ph.Eur: (2.6.21) | | ZIN-Ziektelast in de praktijk |
| EMA/CAT/80183/2014 | GTMP | CPMP/SWP/1042/99 Rev 1 Corr | | Ph.Eur (2.7.24) | | |
| EMA/CAT/GTWP/671639/2008 Rev 1 corr | GTMP | C(2019) 7140 final | | Ph.Eur: (2.6.27) | | |
| EMEA/273974/2005 | GTMP | EMA/502388/2020 | | Ph.Eur: (2.6.1) | | |
| EMEA//CHMP/GTWP/125459/2006 | GTMP | CPMP/ICH/375/95 | | Ph.Eur: (5.1.6) | | |
| EMEA/CHMP/GTWP/125459/2006 Rev 1, Corr 1 | GTMP | CPMP/ICH/137/95 | | Ph.Eur: (2.6.7) | | |
| EMEA/CHMP/ICH/318372/2021 | GTMP | CPMP/SWP/378/95 | | Ph.Eur: (2.6.14) | | |

| Pre Clinical Development | | Clinical Development | | Marketing Authorisation | | Reimbursement |
|---|---|---|---|---|---|---|
| EMEA/CHMP/ICH/449035/2009 | GTMP | CHMP/ICH/135/95 | | Ph.Eur: (5.2.12) | | |
| EMEA/CHMP/BWP/271475/2006 Rev 1 | sCTMP, TEP | CHMP/ICH/379/95 | | EMA/CAT/CPWP/686637/2011 | | |
| CPMP/BWP/328/99 | sCTMP, TEP | CPMP/ICH/291/95 | | EMEA/CHMP/SWP/4447/00 corr 2 | GTMP | |
| CHMP/ICH/731268/1998 | sCTMP, TEP | CPMP/ICH/2711/99 | | EMEA/CHMP/BWP/473191/2006 | GTMP | |
| EMEA/CHMP/410869/2006 | sCTMP, TEP | EMA/CAT/80183/2014 | GTMP | EMEA/CHMP/GTWP/125491/2006 | GTMP | |
| EMEA/CHMP/CPWP/83508/2009 | sCTMP, TEP | EMA/CAT/GTWP/671639/2008 Rev 1 corr | GTMP | EMEA/CHMP/QWP/396951/2006 | GTMP | |
| EMEA/CH,P/BWP/706271/2010 | sCTMP, TEP | EMA/CHMP/GTWP/587488/2007 Rev 1 | GTMP | EMEA/CAT/CHMP/158266/2021 | GTMP | |
| | | EMEA/CHMP/GTWP/60436/2007 | GTMP | | | |
| | | EMEA/CAT/190186/2012 | GTMP | | | |
| | | EMEA/CHMP/ICH/607698/2008 | GTMP | | | |
| | | CHMP/ICH/469991/2006 | GTMP | | | |
| | | CPMP/ICH/539/00 | sCTMP, TEP | | | |
| | | EMA/CAT/573420/2009 | sCTMP, TEP | | | |
| | | EMEA/CHMP/410869/2006 | sCTMP, TEP | | | |
| | | EMEA/CHMP/CPWP/83508/2009 | sCTMP, TEP | | | |

| Obtaining Material | | Modifying Material | | Clinical Production | | Pharmaco Vigilance |
|---|---|---|---|---|---|---|
| Directive 2004/23/EC | | Directive 2004/23/EC | | Directive 2003/94/EC | | Regulation (EU) No 1235/2010 |
| Directive 2002/98/EC | | Directive 2002/98/EC | | Eudralex Volume 4 | | Directive 2010/84/EU |
| | | Directive 2006/17/EC | | | | Regulation (EU) 1027/2012 |
| | | Directive 2006/86/EC | | | | Directive 2012/26/EU |
| | | | | | | Directive 2001/83/EC |
| | | | | | | Regulation (EC) No. 726/2004. |
| | | | | | | Commission Implementing Regulation No 520/2012 |
| EMEA/CAT/600280/2010 Rev 1 | | EMEA/CAT/852602/2018 | | EMEA/CAT/852602/2018 | | Good pharmacovigilance practices (GVP) modules |
| EMEA/410/01 rev 3 | | EMEA/CHMP/CVPM/ QWP/850374/2015 | | EMEA/CAT/486831/2008 corr | | |
| EMEA/CAT/571134/2009 | | EMEA/CAT/486831/2008 corr | | EMEA/CAT/418458/2008 rev | | |
| CHMP/BWP/245/03 | GTMP | EMEA/CAT/418458/2008 rev | | EMEA/CHMP/QWP/805880/2010 2 rev 2 | | |
| Ph.Eur.5.14 | GTMP | EMEA/CHMP/QWP/805880/2012 rev 2 | | CHMP/ICH/295/95 | | |
| EMEA/CHMP/410869/2006 | sCTMP, TEP | EMA/CHMP/ICH/82260/2006 | | CPMP/ICH/5721/03 | | |
| EMEA/CHMP/CPWP/83508/2009 | sCTMP, TEP | CHMP/ICH/295/95 | | EMA/CAT/499821/2019 | | |
| EMEA/CAT/CPWP/568181/2009 | sCTMP, TEP | CPMP/ICH/5721/03 | | CHMP/ICH/138/95 | | |
| EMEA/CH,P/BWP/706271/2010 | sCTMP, TEP | EMA/CAT/499821/2019 | | CPMP/ICH/4106/00 | | |
| Ph. Eur.2.7.29 | sCTMP, TEP | CHMP/ICH/138/95 | | CHMP/ICH/167068/04 | | |
| | | CPMP/ICH/4106/00 | | EMA/CH,P/ICH/24235/2006 | | |
| | | CHMP/ICH/167068/04 | | EMA/CHMP/ICH/214732/2007 | | |
| | | EMA/CHMP/ICH/24235/2006 | | EMA/CHMP/BWP/187338/2014 | | |
| | | EMA/CHMP/ICH/214732/2007 | | EMEA/22314/02 | | |

| Obtaining Material | Modifying Material | | Clinical Production | | Pharmaco Vigilance |
|---|---|---|---|---|---|
| | CHMP/BWP/245/03 | GTMP | EMA/CHMP/BWP/353632/2010 | | |
| | EMA/CAT/80183/2014 | GTMP | 3AB11a | | |
| | EMA/CAT/GTWP/671639/2008 Rev 1 corr | GTMP | Ph.Eur: (2.7.23) | | |
| | EMA/CHMP/GTWP/587488/2007 Rev 1 | GTMP | Ph.Eur: (2.7.28) | | |
| | EMA/CAT/GTWP/44236/2009 | GTMP | Ph.Eur: (2.6.21) | | |
| | EMEA/CHMP/410869/2006 | sCTMP, TEP | Ph.Eur (2.7.24) | | |
| | EMEA/CHMP/CPWP/83508/2009 | sCTMP, TEP | Ph.Eur: (2.6.27) | | |
| | EMEA/CH,P/BWP/706271/2010 | sCTMP, TEP | Ph.Eur: (2.6.1) | | |
| | Ph. Eur.2.7.29 | sCTMP, TEP | Ph.Eur: (5.1.6) | | |
| | CPMP/ICH/139/95 | sCTMP , TEP | Ph.Eur: (2.6.7) | | |
| | CHMP/ICH/294/95 | sCTMP , TEP | Ph.Eur: (2.6.14) | | |
| | CHMP/ICH/365/96 | sCTMP , TEP | Ph.Eur: (5.2.12) | | |
| | CHMP/BWP/157653/07 01/2008:50203 | sCTMP , TEP | CHMP/ICH/381/95 | | |
| | | | CHMP/BWP/245/03 | GTMP | |
| | | | EMA/CAT/80183/2014 | GTMP | |
| | | | EMA/CAT/GTWP/671639/2008 Rev 1 corr | GTMP | |
| | | | EMA/CHMP/GTWP/587488/2007 Rev 1 | GTMP | |
| | | | EM/CHMP/BWP/457920/2012 rev 1 | GTMP | |
| | | | EMA/CHMP/BWP/814397/2011 | GTMP | |
| | | | EMA/CHMP/BWP/532517/2008 | sCTMP, TEP | |
| | | | EMEA/CHMP/410869/2006 | sCTMP, TEP | |
| | | | EMEA/CHMP/CPWP/83508/2009 | sCTMP, TEP | |
| | | | EMEA/CH,P/BWP/706271/2010 | sCTMP, TEP | |

| Guidance | |
|---|---|
| CPWP/BWP/269/95, rev.3 | |
| CPMP/BWP/3354/99 | |

| Guidance |
|---|
| Pharmacovigilance legislation |
| Pharmacovigilance for ATMPs |

## Annex 3: Clinical Trial Information System (CTIS) Guide

There is one single point of entry for all clinical trials conducted in the EEA: the Clinical Trial Information System (CTIS). The EMA CTIS Sponsor Handbook addresses key questions on CTIS and provides a compilation and references to key guidance, technical information, recommendations, a CTIS training material catalogue and supportive documentation to facilitate the submission and assessment of CTAs and additional information during the lifecycle of a trial. It has been developed by the EMA in collaboration with representatives of industry stakeholders.

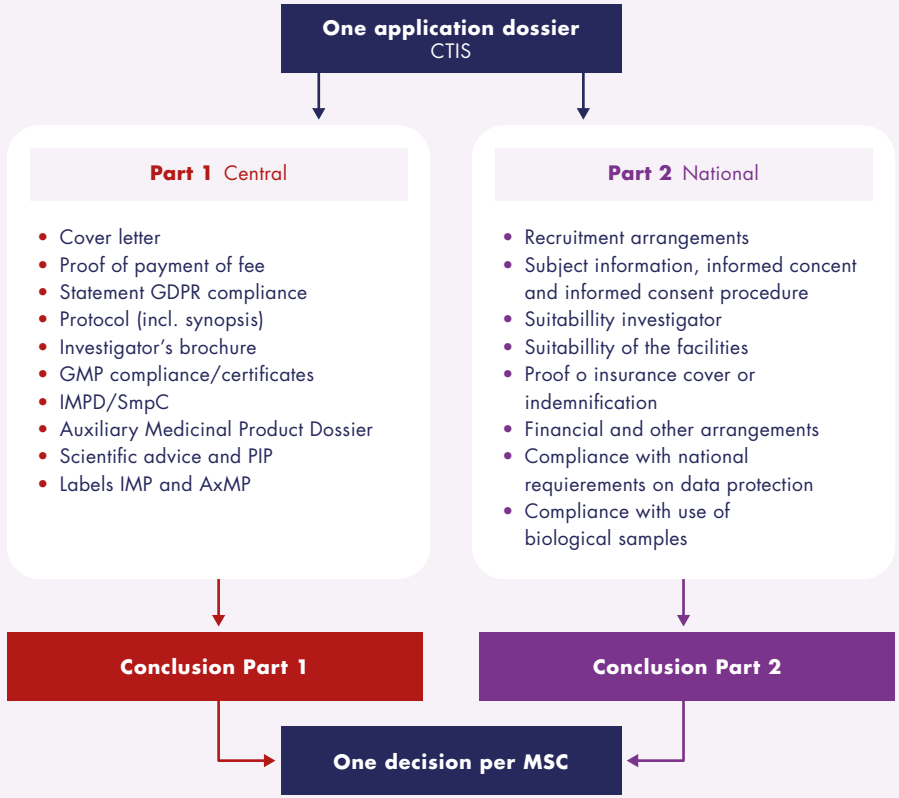
### Step 1: Preparation

The clinical trial application consists of part I (same documents for all MSC)) and part II (national documents per MSC).In case of multinational clinical trials, Part I application will be jointly assessed by MSC with one conclusion valid for all MSC. A reporting MS (rMS), one of the MSC, will be appointed to coordinate and consolidate the joint assessment. Part II application will be a national assessment with a conclusion only valid in this MS. Each MSC will issue a decision which is the result of the conclusion part I and part II.

A national clinical trial application also consists of a part I and a part II and is assessed by the MS concerned. This Member State is the rMS for this clinical trial by default.

See figure on the right with an overview of the components of part I and part II.

*Annex 3: Overview of the components of part I and part II*



### Note: full, staggered or mixed application

The sponsor is allowed to submit a full initial application (part I and part II at the same time), a staggered initial application (first part I followed by part II) or a mixed initial application. For a staggered initial application the following rules apply:

- A part II application cannot precede a part I application.
- A part II application can be submitted after assessment part I has been concluded.
- A part II application has to be submitted within two years after conclusion part I. If a part II application is not submitted within two years after conclusion part I, the application part I will be lapsed.
- The part II application shall be accompanied by a statement from the sponsor in which he declares that he is not aware of any new substantial scientific information that would change the validity of any item submitted in the application on the aspects covered by Part I of the assessment report.

The following additional rule apply for mixed initial application in a multinational clinical trial:

- The sponsor can submit a whole application (Part I and II) to some Member States concerned (on the basis of article 5 CTR) and at the same time an application limited to Part I only (on the basis of article 11 CTR) to other Member States concerned.

*Important*

For mixed initial applications (full and staggered) in a multinational clinical trial: the "slowest" MS drives the process: the sponsor can only submit a substantial modification or an additional MSC if all MSC which were part of the initial application have authorized the clinical trial.

*Full or staggered application in the Netherlands*

In the Netherlands, the assessment of national and multinational studies is done by the CCMO.

*Important*

For certain clinical trials, the RMS can extend the assessment period part I by max 50 days for the consulting of experts. In that case, the timeline for part I may be longer than for part II which may result in complex applications. Therefore, the sponsor might consider a staggered applications for these type of clinical trials:

- clinical trials with an ATMP;
- clinical trials with a medicinal product developed by means of biotechnological processes like recombinant DNA technology or controlled expressions of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells or hybridoma and monoclonal antibody methods.

## Step 2: Registration in CTIS, OMS and XEVMPD

**Clinical Trial Information System (CTIS):** Applicants should be registered in CTIS. Users already using other EMA applications (Eudralink, SPOR, IRIS, Eudravigilance, OMS) can use the same EMA account to access CTIS sponsor workspace. If one does not have an EMA account, one needs to create one by self registration on the EMA Account management page (IAM). The self registration process is described in module 03 of CTIS training material catalogue.

**Organization Management Service (OMS):** CTIS retrieves organization data OMS. Sponsors, co-sponsors, third party contractor (e.g. CRO) and MAHs need to be registered in OMS. Clinical trial sites (in the EEA) do not need to be registered first in OMS, but can be taken up in CTIS directly.
If an organization is not yet registered in OMS when starting to use CTIS, it is necessary to register the organization via a request in OMS. Access to OMS is on the EMA SPOR portal (SPOR: Substance, Product, Organization, Referentials management services). The registration process of a new organization in OMS takes from five to ten working days.

**Xtended EudraVigilance Medicinal Product Dictionary (XEVMPD):** The sponsors of clinical trials should ensure that the details of the medicinal products used in the clinical trial are registered in the XEVMPD. The dictionary includes all medicinal products that are authorised in the EU/EEA and also development products that are associated with clinical trials. A placebo can be added manually without resorting to a registration in XEVMPD necessarily. For each trial in CTIS, the sponsor has to associate at least one test product. Other product types that can be associated in CTIS are: comparator, placebo and auxiliary medicinal product. In CTIS, the product information is retrieved from XEVMPD and this is enabled by a search and selection process for an authorised product (product with a MA from the EU/EEA), development product, an active substance or an ATC code. For more information, see CTIS training module 10 including video: CTIS – M10 How to submit an initial CTA in the CTIS – Fill in the Product details of Part I section. See also chapter 5 of the CTIS Sponsor handbook on "Product management in CTIS".

## Step 3: Research Form and MSC in CTIS

The application dossier consist of a Part I and a Part II. The list of required documentation and information is set out in Annex I of the CTR. The documents in the clinical trial application should be in a searchable format and it is strongly recommended to adhere to the structure, the codes and filenames as given in the Document codes and titles in CTIS of the Clinical Trial Coordinating Group (CTCG). In the document Instruction on uploading, naming and changing documents in CTIS is specified how to change your clinical trial application in CTIS if an RFI requests new documents or document changes.

CTIS contains two sections (Form, MSC) that must be completed for an initial application.

### *Form: Initial application details*

- *Cover letter:* the template cover letter should be used.
- *Proof of payment of fee:* In the Netherlands no proof of payment of fee has to submitted. However, you must upload the invoice details.
- *Compliance with Regulation (EU) 2016/679:* the template statement should be used.
- *Deferral publication date:* Trial category 1,2 or 3 has to selected for the publication date of trial information, including a justification for the selected category (see transparency rules). Deferral of publication date is possible by indicating a new publication date.

### *MSC*

Overview of the member states concerned including the proposed reporting member state. Also an overview of the participating countries outside the European Economic Area.

## Step 4: Research dossier Part 1

Research dossier Part I consists of sections B-J of Annex I of the CTR and is the same for all member states concerned. The section characters B-J are not visible in CTIS. Instead there are several placeholders to complete the sections with trial and document identifiers and to upload the requested documents. Please note that all the documents in the clinical trial application should be in a searchable format.

### *Trial details*

- *Trial identifiers:* Full and public title, protocol code, secondary identifying number registries.
- *Trial information:* Justification low-intervention clinical trial (if applicable), medical condition, primary and secondary objectives, principal in- and exclusion criteria, primary and secondary endpoints, trial duration, source of monetary support, identifiers study population.
- *Protocol information:* Study design description including the different treatment groups ("study arms", including placebo group if applicable), use the template clinical trial protocol, synopsis of the protocol, patient facing documents, data safety monitoring committee charter (if applicable).
- *Scientific advice and Paediatric Investigation Plan (PIP):* use the template scientific advice (if applicable) and/or PIP (if applicable).
- *Associate clinical trials:* Trial number of associate clinical trial (EU CT number or EudraCT number) (if applicable).
- *References:* references to online publications (if applicable).
- *Countries outside the EEA:* to identify third countries where CT is will be conducted (if applicable).

### *Sponsors*

Sponsor identifier, contact point for EU and scientific and public contact point.

### *Products*

Description of investigational medicinal products (test and/or comparator), auxiliary medicinal products (if applicable) and placebo (if applicable). Following product-related documents are required:

- Investigator's Brochure.
- Investigational Medicinal Product Dossier (IMPD) contains data on the quality, production and control of the medicinal product being researched. The Quality section contains information on the active medicinal product, placebo and reference medicine (if applicable) IMPD-Quality. The Safety and Efficacy section contains a summary of data from all clinical and non-clinical studies, with an overall assessment of the risks and benefits IMPD-Efficacy & Safety: For this latter part, reference can also be made to the Investigator's Brochure (IB).
- Good Manufacturing Practice (GMP) for Investigational Medicinal Product: For products with no EU authorisation, or no authorisation from a third country that is a party to ICH, and not manufactured in the EU, a manufacturing and import authorisation (MIA) and a QP declaration of GMP equivalence is required. If a Mutual Recognition Agreement (MRA) is in place with the particular country which already provides for this equivalence the latter declaration is not required. The documentation required to show compliance with GMP is outlined in Annex 1, section F of the CTR (GMP certificates).
- Labelling IMP and AxMP: Investigational and auxiliary medicinal products should be appropriately labelled in order to ensure subject safety and the reliability and robustness of data generated in clinical trials, and in order to allow for the distribution of those products to clinical trial sites throughout the EU. Labelling requirements for IMPs and AxMP are set out in the CTR.

## Step 5: Research dossier Part 2 application in CTIS

Part 2 contains:
Trial sites: Register name and location of the clinical trial site plus the name of the investigator.

*Documents Part II:*

- Recruitment arrangements Unless described in the protocol, a separate document shall describe in detail the procedures for inclusion of subjects. Where the recruitment of subjects is done through advertisement, copies of the advertising material have to be submitted, including any printed materials, and audio or visual recordings. The NL template on recruitment arrangements is mandatory.
- Subject information and informed consent form: All information given to the subjects (or, where applicable, to their legally designated representatives) before their decision to participate or abstain from participation shall be submitted together with the form for written informed consent, or other alternative means according to Article 29(1) CTR for recording informed consent.
  In the Netherlands, several templates for the subject information sheet and informed consent form have been developed. Sponsors and/or investigators are strongly advised to use these templates. The CCMO and MREC will use this model as basis for their review. Only the Dutch version of the subject information sheet and informed consent form should be submitted in CTIS.
- Suitability of the investigator A recent CV and a declaration of interest from the principal investigator per investigational site must be submitted for review (and parts will be published because of the revised transparency rules. A CV template is available but not mandatory. The declaration of interest template is mandatory.
- Suitability of the facilities The CCMO guideline on Review Site Suitability [CCMO-richtlijn Toetsing Geschiktheid Onderzoeksinstelling] is applicable in the Netherlands. This guideline makes it mandatory for research with a medicinal product submitted on or after 1 November 2021 to submit a signed declaration suitability investigational site [Verklaring Geschiktheid Onderzoeksinstelling, VGO] of each participating centre to the review committee (accredited MREC or CCMO). The VGO and the procedure for local feasibility have been developed jointly by the Dutch Clinical Research Foundation (DCRF) with its affiliated partners and CCMO. More information on the VGO can be found on the DCRF-website and the procedure for local feasibility.
  Next to a signed VGO, a Clinical Trial Agreement (CTA) should be submitted. This standard agreement contains a paragraph stating that if the agreement is signed by the executive board/management before the review committee has approved the research, the executive board/management gives the researcher permission, subject to conditions precedent, to conduct the research in the centre. Templates for the CTA are available for industry-sponsored research and for investigator-initiated research.
- Proof of insurance cover or indemnification: two types of insurance must be taken out before the start of a clinical trial: WMO clinical trial participants insurance and liability insurance. In certain cases, exemption may be granted for the WMO clinical trial participants insurance. Cover by a liability insurance must always be guaranteed.
  - WMO clinical trial participants insurance: Subjects participating in a clinical trial must be insured against any potential damages incurred as a result of participating in the clinical trial. The insurance must comply with specific regulations stated in the Compulsory Insurance Decree in Medical Research Involving Human Subjects (dd 1 July 2015). If the research is carried out by a ministerial appointed institution, service or governmental organization, such as those which fall under the Ministry of Health, Welfare and Sport (VWS), or the Ministry of Defence, then a human subject insurance or a liability insurance is not needed (section 7, sub 10 WMO).

  - Liability insurance: The Dutch Act on medical scientific research with human subjects (WMO, article 7 sub 8-11) outlines rules regarding the liability of the sponsor or the executing party in medical research. These rules apply to all the clinical trials covered by the CTR. In general, a common liability insurance policy, for the whole research is sufficient.
- Financial and other arrangements: A description of the financing of the clinical trial, on financial transactions and compensation paid to subjects and investigator/site for participating in the clinical trial and on any other arrangements shall be submitted. The NL template on payment, compensation and funding is mandatory.
- Compliance with national requirements on data protection: There is a placeholder in CTIS for the submission of documentation related to GDPR compliance. Template is available and mandatory.
- Compliance with use of biological samples: There is a placeholder in CTIS for the submission of documentation related to the collection, storage and future use of biological samples. A template is available and mandatory.

## Timelines

Validation phase: max. 25 days including 15 days for the MS (10 plus an additional 5 in case of the rMS requests for information), and 10 days for the sponsor to complete the application dossier.

The assessment period starts from the date of validation and is max. 45 days with the possibility to extend this by another 31 days (12 days for the sponsor and 19 days for the MS) in case the rMS send a request for information (RFI). The sponsor shall submit the requested additional information within the period set by the rMS (maximum 12 days). The timelines for the assessment of part I and part II are normally similar except:

- in case of clinical trials involving **ATMPs**, the rMS can extend the assessment period by an additional 50 days for consulting with experts;
- in case of sequential part II submission, there is no validation phase.

The extension of the timelines for the assessment of part II is not provided for by the legislation. This may result in part I having extended timelines compared to Part II and leading to particularly complex outcomes. Therefore, sponsors may consider applying Article 11 of the CTR in cases of complex applications, thereby submitting part II separately from Part I.

## Decision

Part one and part two are both assessed and two decisions will be published. Possible outcomes are:

- Both part I and II conclusions are acceptable or acceptable with conditions ➜ the application is automatically authorised.
- Part I conclusion is acceptable or acceptable with conditions and part II conclusion is not acceptable or lacking ➜ the application is automatically authorised.
- Part I conclusion is not acceptable and part II conclusion is acceptable or acceptable with conditions, not acceptable or lacking ➜ the application is automatically not authorised.
- Part I conclusion is lacking and part II conclusion is acceptable or acceptable with conditions, not acceptable or lacking ➜ the application is automatically still under evaluation.

In case of a positive decision a MSc can opt out. In case of a negative decision, this decision is applicable for all countries and the study is not authorized.

If CCMO came to the negative decision, the interested party may lodge a notice of objection to CCMO within six weeks after the day on which the decision was reached (section 7:1 of the General Administrative Law Act).

According to national Dutch law, it would be possible to lodge an administrative appeal or objection against a negative decision based on a negative conclusion of part I by the rMS. However, this appeal or objection will be declared inadmissible, because this decision is taken at international level. Resubmission of the clinical trial as a new clinical trial with adjustments is possible.

## Annex 4: Managed Entry Agreements (MEA), Outcome Based Agreements (OBA) and Financial Based Agreements

Not all agreements are suitable for ATMPs. Based upon the characteristics of an ATMP a managed entry, outcome based or financial based agreement (might be opportune. Note that in general payers prefer simple arrangements without too much measurements and administrative burden.

When (long term) clinical efficacy is uncertain following constructs (or combinations) can be considered to create patient access:

- conditional reimbursement with the obligation to collect additional research/ data. This requires:
  - Patient selection;
  - Define start criteria (not always possible);
  - Define stop criteria (only applicable in long term treatment products);
  - Administer in specialized centers;
  - Registry requirements to collect efficacy data;
  - Measured efficacy is basis for re-assessment and reimbursement continuation.
- Reimbursement level related to level of evidence (national level)/ Step wise reimbursement based on additional data:
  - Proven safety and/or efficacy data in combination with robust data ➜ price legitimation.
  - Start reimbursement against discounted price.
  - Register and collect data, when agreed data is available the discount is decreased.
  - Enlarge patient population when treatment effects are proven.
- Outcome based:
  In an outcomes-based or performance based agreement, reimbursement would be adjusted based on whether a pre-specified health outcome is achieved. This model shares risk between the MAH and the payer. When the pre-specified outcome is not reached an agreed percentage of cost is refunded, retreatment or new patients are free of charge. There are many variations. It could be implemented based on population based measures or patient level measures. It could include outcomes-based money-back guarantees, discounts on future payments, indication-based pricing or general rebates.
  Example: Cure rate (OS) on population level is measured and based on this percentage an average discount is calculated 1) Use cure rate (OS) in clinical trial to calculate average discount, and 2) Measure cure rate in real life and agree on financial consequences in case of deviation
- Annuity models.
  - Under an annuity or installment payment model payments would be spread over a pre-determined time period. This model recognizes the long-term therapeutic durability of single-administration cell and gene therapies, matches the payment to the multiyear benefit and minimizes large up- front or annual costs for payers.
  - Fixed amount equally spread over max. x years (regardless of result).
  - Fixed amount but ascending/descending over max. x years (regardless of result).

  *Note: the current system of HCI funding is not supporting these models.*
- Delayed payment on patient level
  - Payment after certain clinical milestones are reached.
  - Pay 1st percentage at start treatment and a smaller percentages for every additional year (up to X years).

  *Note: the current system of HCI funding is not supporting these models.*

## Annex 5: List of experts

The following is a list of consulted experts, presented in alphabetical order.

- Antoni van Leeuwenhoekziekenhuis
- Centrale Commissie Mensgebonden Onderzoek (CCMO)
- College ter Beoordeling van Geneesmiddelen (CBG)
- CURE4LIFE
- Dutch infrastructure for cancer-specific ATMP Research (DARE-NL)
  Via DARE-NL Patient Advisory Board:
  - Stichting Melanoom
  - Hematon
  - Nederlandse Federatie van Kankerpatiëntenorganisaties (NFK)
  - Vereniging Kinderkanker Nederland (VKKN)
- Erasmus University Medical Center / ATMP facility
- Hollandbio
- Inspectie Gezondheidszorg en Jeugd (IGJ)
- Leiden University Medical Center / Center for Cell and Gene Therapy
- Leijnse Artz
- Ministerie van Infrastructuur en Waterstaat (ienW)
- Ministerie van Volksgezondheid, Welzijn en Sport (VWS)
- Nederlands Kanker Instituut (NKI)
- Netherlands Center for the Clinical Advancement of Stem Cell and Gene Therapies (NecstGen)
- Prinses Maxima Centrum
- Radboud University Medical Center
- Rijksinstituut voor Volksgezondheid en Milieu (RIVM)
- Sanquin
- University Medical Center Utrecht
- Utrecht University
- Vereniging Innovatieve Geneesmiddelen (VIG)
- Vereniging Samenwerkende Ouder- en Patiëntenorganisaties (VSOP)
- Zorginstituut Nederland (ZIN)
- Zorgverzekeraars Nederland (ZN)

## Annex 6: References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