ADVANCED THERAPY MEDICINAL PRODUCTS

A GUIDEBOOK FOR COMPANIES IN THE NETHERLANDS

FROM CLINICAL TRIALS TO MARKET ACCESS

Dutch Association
Innovative
Medicines

1 CONTENT

1 INTRODUCTION

Biological and technological advances lead to many new developments in gene modifying technologies. At this moment worldwide more than 1000 clinical trials with advanced therapy medicinal products take place. Of these nearly 100 are Phase III studies (30 gene therapies, 16 gene-modified cell therapies, 32 cell therapies and 16 tissue engineering therapies (Q2 2019; www.alliancerm.org/publication). In the Netherlands different clinical trials with ATMPs are open. At this moment 14 ATMPs have been approved by the European Medicines Agency (EMA), of which 10 are still on the market. However, in many countries patients still have only limited access to these therapies.
Because of the specificities of an ATMP, companies are faced with new challenges in the field of intellectual property rights, production, quality assurance, quality control, regulatory approvals, pricing and reimbursement, sales and marketing. However, not only pharmaceutical companies are experiencing these new challenges. Small developers, researchers (in hospitals), authorities in the field of licenses and quality and government and insurers seems to be surprised with new challenges in creating patient access to these new treatments.

In order to guarantee optimal patient access it is crucial to better understand the requirements in the field of regulation, quality and pricing and reimbursement in the Netherlands. The process differs per type of ATMP and will probably require continuously customization. However, lack of knowledge, misunderstandings and possibly fear among all stakeholders may lead to unnecessary delays in access. This report provides first of all an overview of different steps from development to patient access and the challenges companies experienced developing and launching ATMPs.

1.1 WHAT MAKES AN ATMP DIFFERENT FROM A CONVENTIONAL MEDICINE?

Although ATMPs are seen as medicines by the EMA from a regulatory viewpoint, it appears that many ATMPs have characteristics that are comparable to treatments, like blood transfusions, skin transplants and organ- or bone marrow transplantation. ATMPs are products that involve a certain level of engineering or re-use of cells or tissues, in which cells and tissues fulfil their natural function (again). This means that in many cases an ATMP is only administered once and there is an (assumed) curative (or long term) effect.

ATMPs must therefore be regarded much more from a treatment point of view, in contrast to conventional medicines.

ATMPs often require different formulations and methods for production procedures and methods compared to conventional medicines. The risk and costs of chemistry, production and controls for ATMPs are therefore often much higher than with conventional pharmaceutical or biopharmaceutical products. A marketing authorization holder is obliged to adjust the existing infrastructure and care provision in such a way that an optimal clinical result can be realized. This requires staff development, training, quality standards, permits and accreditation, and investments/adjustments in equipment, processes and procedures. Not only in the direct treatment, but also the supportive care before or after the treatment has to be adjusted and possibly adjusted. In contrast to conventional medicines, it are often therapies that have been specifically designed to be used once with the aim of a cure or a long-term effect. It is necessary to manage the complete therapy and the process more than with a medicine as we know it.

In the context of reimbursement discussions, a comparison with treatment as an organ transplant is more appropriate. After all, in contrast to conventional medicines, we speak of personalized (often cell/tissue-based) therapies that have been specifically designed to be used once with the aim of a cure or a long-term effect. These specific characteristic of ATMPs often do not fit in the current assessment frameworks and financing models, which often involve elaborate interventions and annually recurring costs. In addition, conventional upfront payment mechanisms will increase affordability concerns for the often high costs of ATMPs. Therefor ATMPs require an adapted assessment and financing framework.

This guide is intended as a guide for companies wishing to conduct ATMP clinical trials in the Netherlands or bring these products onto the market. We are aware that surroundings and procedures are subject to change. We therefore see this document as a way to increase the general level of knowledge about ATMPs. The Association will start discussions with other relevant stakeholders to jointly and proactively search for adequate solutions, to guarantee optimal patient access to these new promising therapies.

2 ATMP CLASSIFICATION

Key elements

- Each ATMP type has specific procedures and (registration/clinical study) requirements.
- Four types:
  - A gene therapy medicinal product.
  - A somatic cell therapy medicinal product.
  - A tissue engineered product. These contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue.
  - A combined ATMP. These products contain a medical Device as an integral part of the final product.
- The ATMP classification procedure of the EMA Committee Advanced Therapies (CAT) creates clearness and direct investigator/company to the right procedures & requirements. Free of charge, any point in time and takes 30-60 days.

2.1 CLASSIFICATION OF ATMPS

According to Article 2(1)(a) of Regulation (EC) No.1394/2007 any of the following medicinal products for human use will be classified as an ATMP.

- **A gene therapy medicinal product**
  These contain genes that lead to a therapeutic, prophylactic or diagnostic effect. They work by inserting 'recombinant' genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases. A recombinant gene is a stretch of DNA that is created in the laboratory, bringing together DNA from different sources.

- **A somatic cell therapy medicinal product**
  These contain cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body. They can be used to cure, diagnose or prevent diseases.

- **A tissue engineered product**
  These contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue.

- **A combined ATMP**
  These products contain as an integral part of the product a medical device.

Border line cases could appear where the classifications of drugs, ATMPs and medical devices overlap and a clear delineation between product types is not immediately obvious. However, since the regulatory requirements differ, the correct classification is critical and should be determined at an early stage of development. For a classification decision the concept of a product's intended use as well as the notions of pharmacological action and physical means are important criteria. This means, a decision will depend on whether a product is actually 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 with a view to achieving a medicinal purpose.

2.2 ATMP CLASSIFICATION PROCEDURE EMA

Due to the complex nature of these products, the limited data package at early stage in product development and the rapid evolution of science and technology, questions arise at the regulatory level. For that reason the EMAs Committee Advanced Therapies (CAT) introduced the ATMP classification procedure. It's free of charge, can be requested at any stage of product development, non-binding (for both) and helps the developer to clarify and facilitate most relevant criteria and procedures to be applied. Procedural advice on the provision of scientific recommendation on classification of advanced therapy medicinal products in accordance with article 17 of Regulation (EC) No 1934/2007.

A Request for a classification recommendation can submitted at any stage of product development. Deadlines for submission are published on the EMA website deadlines submissions request classification recommendation via a pre submission and a request form. Both forms need to returned to advancedtherapies@ema.europa.eu. The procedure will take approx. 30 days and 60 days in case major comments received from the EC.

Examples of scientific recommendations can be found on the EMA-website summaries of scientific recommendations as well as the information that need to be provided.

2.3 CLASSIFICATION CHARACTERISTICS OF ATMPS

Table 1 Classification of ATMPs

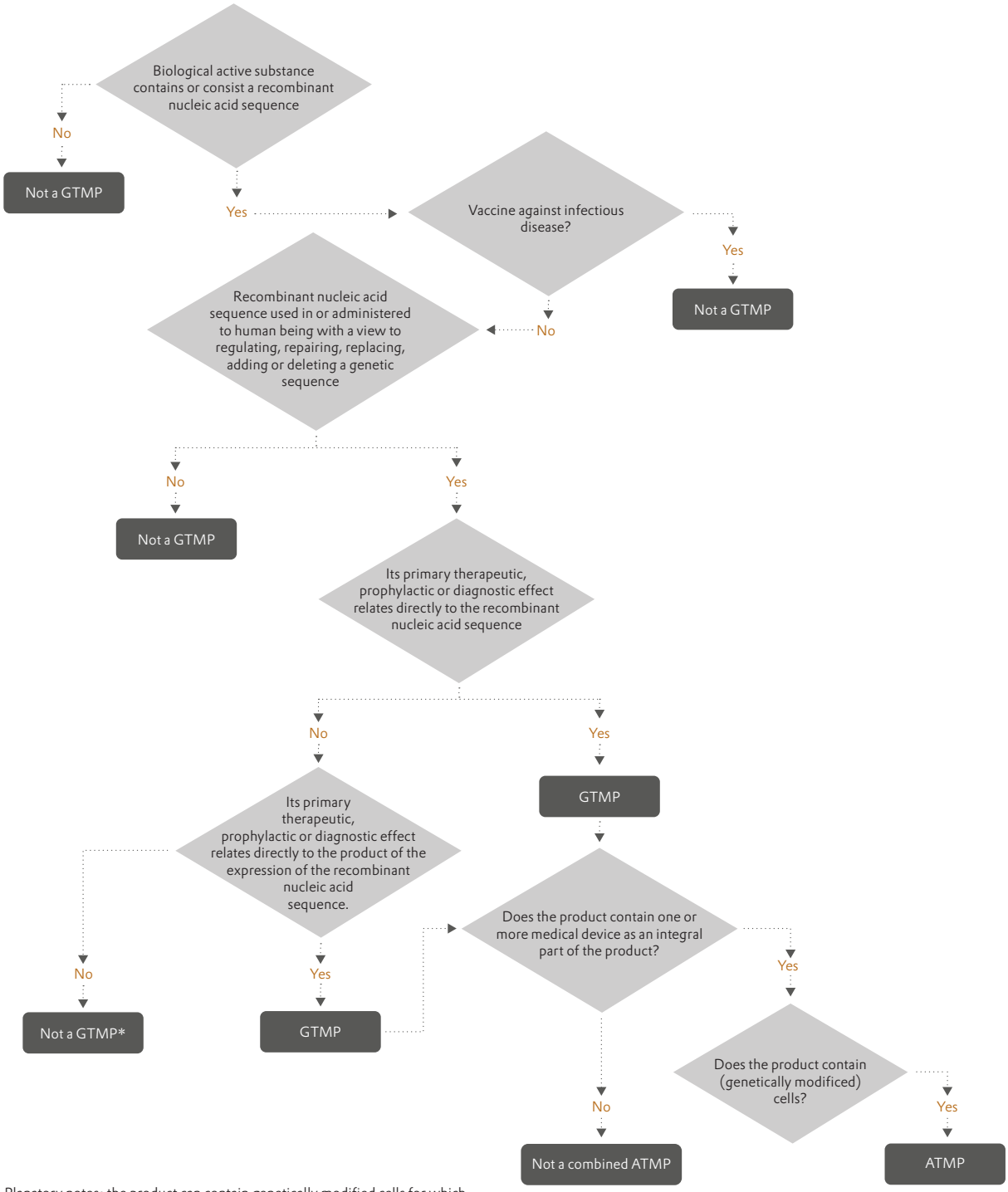
Type	2.1 Gene therapy medicinal product	2.2 Somatic cell therapy medicinal product	2.3 Tissue engineered product	2.4 Combined ATMP
Regulation	Part IV of Annex I to Directive 2001/83/EC.	Part IV of Annex I to Directive 2001/83/EC.	Article 2(1)(b) of Regulation (EC) No. 1394/2007.	Article 1(2)(a) of Directive 93/42/EEC Article 1(2)(c) of Directive 90/385/EEC Article 1(2)(a) of Directive 93/42/EEC or one Article 1(2)(c) of Directive 90/385/EEC
Purpose	Genes that lead to a therapeutic, prophylactic or diagnostic effect. They work by inserting 'recombinant' genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases. A recombinant gene is a stretch of DNA that is created in the laboratory, bringing together DNA from different sources.	Cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body. They can be used to cure, diagnose or prevent diseases.	Cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue.	Contain as an integral part of the product a medical Device or one or more active implantable medical devices.

Type	2.1 Gene therapy medicinal product	2.2 Somatic cell therapy medicinal product	2.3 Tissue engineered product	2.4 Combined ATMP
Characteristics	A biological medicinal product which has the following characteristics: a) 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. AND b) 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.	A biological medicinal product which has the following characteristics: a) 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 b) of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor. AND c) 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.	A product that: a) contains or consists of engineered cells or tissues, AND b) 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.	An advanced therapy medicinal product that fulfils the following conditions: a) 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 b) its cellular or tissue part must contain viable cells or tissues. OR c) 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.

Type	2.1 Gene therapy medicinal product	2.2 Somatic cell therapy medicinal product	2.3 Tissue engineered product	2.4 Combined ATMP
			Cells or tissues shall be considered 'engineered' if they fulfil at least one of the following conditions: a) 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. (substantial: change, cultivation, expansion, genetic modification). OR b) the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.	
NB	Gene therapy medicinal products shall not include vaccines against infectious diseases.		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.	

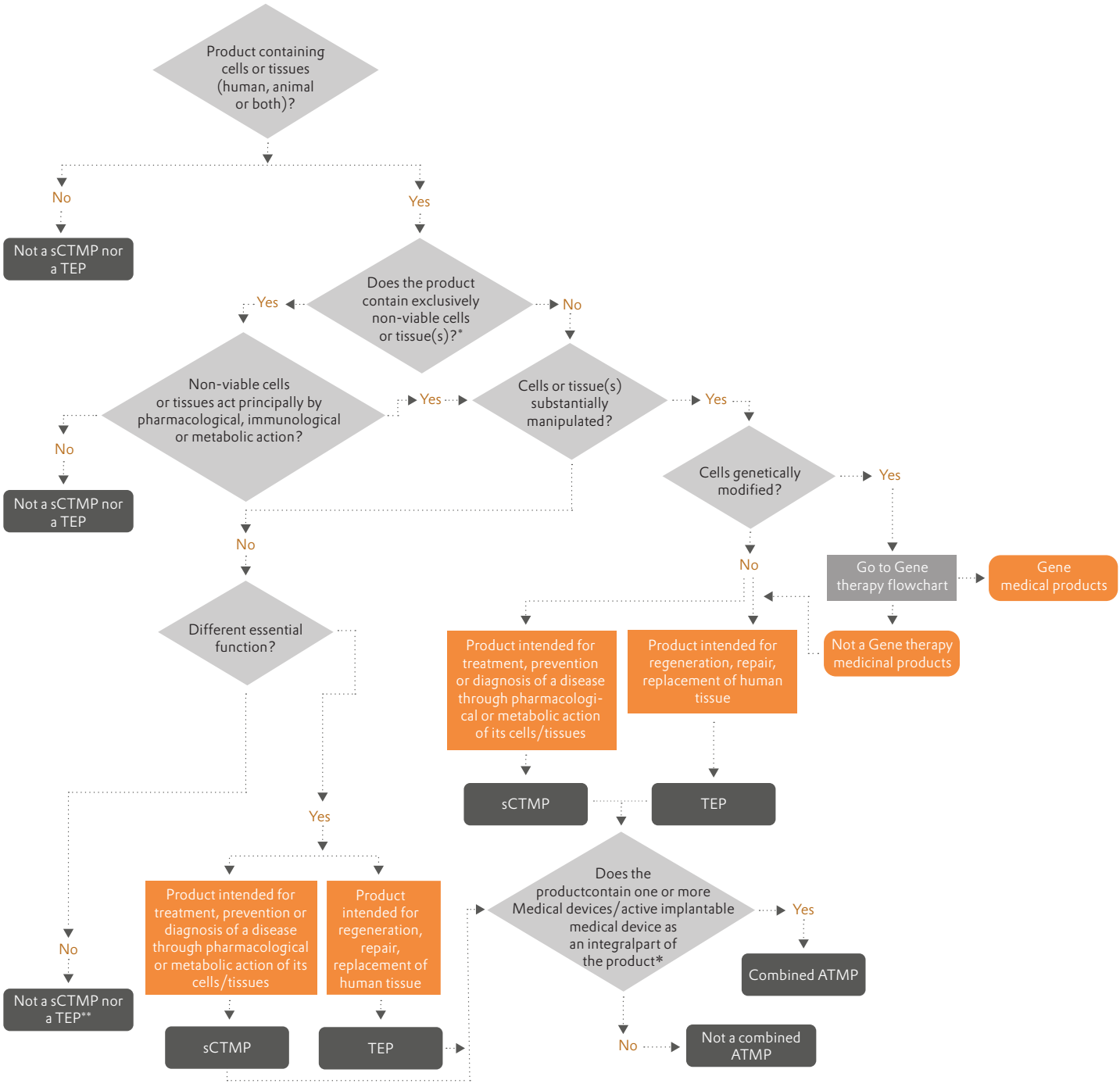
2.4 CLASSIFICATION DECISION TREES

Figure 1: Decision tree Gene Therapy Medicinal Product



Planatory notes: the product can contain genetically modified cells for which specific requirements should be followed (see 'Guideline on human cell-based medicinal products' (EMEA/CHMP/410869/2006)).

Figure 2: Somatic cell therapy medicinal products (sCTMP) and tissue engineered products (TEP)



3 CLINICAL RESEARCH REQUIREMENTS

Key elements

- Clinical trials with ATMPs require the same assessments as other studies within Human Subjects.
- Additional assessments by CCMO (instead of MREC), MoH and MoI&W are required for clinical trials with ATMPs or ATMPs containing a GMO (genetically modified organisms).
  - These assessments differ per member state (Office Gen Therapy coordinates application).
  - Assessment procedure can be finalised in 120 days, several clock stops (lacking information, required permits and even misunderstandings) can cause substantial delays.

Attention must be paid to:

- application procedure for all participating hospitals is required;
- lack of experience with these complex procedures within participating hospitals;
- low priority and coordination between participating physicians and Environmental Safety Officer (ESO);
- requirement of employment of Environmental Safety Officer (ESO) appointed by Ministry of I&W in hospital.
  - International company training & compliance requirements do not always fit Dutch legal framework & requirements.
  - Lack of clarity on procedure and required permits => advice: involve a national legal expert for specific licences early in process.

3.1 DEFINITIONS

Since there are specific additional requirements for Clinical Trials (CTs) with ATMPs and ATMPs containing a Genetically Modified Organism (GMO) following definitions are important.

- Cell therapy research: the administration of (autologous or allogenic) cells of human origin or xenogenic living, nucleated cells to humans, in situations in which the isolation, processing and/or administration involves individual living cells and where (processing and/or administration of) the cells are the subject of the research question.

- Gene therapy: a medicinal product which has been produced by means of a series of manufacturing techniques aimed at the in vivo or ex vivo transfer of prophylactic, diagnostic or therapeutic gene (a nucleic acid) to human or animal cells and the following expression in

vivo. The expression occurs during the gene transfer with the aid of an administration system, the so-called 'vector', which can have a viral or non-viral origin.
Gene therapy can be divided into somatic cell therapy and germ line gene therapy, depending on the cells in which the genetic material is altered. In the case of somatic gene therapy, the genetic make-up of human cells is altered. Such alterations cannot be genetically transferred. In the case of germ line gene therapy, the genetic material of gametes are altered. The alterations are transferred to the offspring and are therefore genetically transferred. This form of gene therapy is prohibited in the Netherlands.

- A Genetically Modified Organism (GMO): any organism of which the genetic make-up has been altered in a way that does not occur naturally through reproduction and/or natural recombination. An organism is defined as 'a micro-organism or other biological entity that can replicate or transfer genetic material'.

  Further to this definition, GMOs include organisms obtained by means of the following techniques:
  - recombinant nucleic acid techniques in which new combinations of genetic material are formed by the insertion of nucleic acid molecules produced outside of an organism into a virus, bacterial plasmid or other vector system and their inclusion in a host in which they do not occur naturally but in which they can be permanently multiplied;
  - techniques involving the direct introduction into an organism of heritable material produced outside the organism, including microinjection, macro injection and microencapsulation;
  - cell fusion (including protoplast fusion) or hybridisation techniques where live cells with new combinations of heritable genetic material are formed by the fusion of two or more cells using methods which do not occur naturally. With the exception of the organisms obtained by means of the following technique: (a) mutagenesis and (b) cell fusion, including protoplast fusion, of plant cells from organisms that can exchange genetic material using traditional breeding methods; both unless other recombinant nucleic acid molecules or genetically modified organisms are used than those produced using the techniques mentioned under a or b.

  Other relevant definitions under the GMO rules are:
  - vector: DNA or RNA molecule used to add genetic material to a host;
  - viral vector: a vector containing nucleic acid sequences from a virus infectious to plant or animal cells, and capable of adding that genetic material to eukaryotic cells, provided that the viral sequences involved may lead to replication of the vector or parts thereof, or to the integration of genetic information of the vector or parts thereof in the genetic material of the cell. A vector can be a GMO if the definition of GMO is met. Therefore a technical/ biomedical assessment is required.

3.2 LEGISLATION

3.2.1 GENERAL LEGISLATION FOR CLINICAL TRIALS INVOLVING HUMAN SUBJECTS ACT (WMO)

Clinical trials are subject to the Act on Medical Research Involving Human Subjects (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.

EU Regulation

Legislation & regulation for all Clinical Trials (incl. CT's with ATMPs/ATMPs containing GMO's).

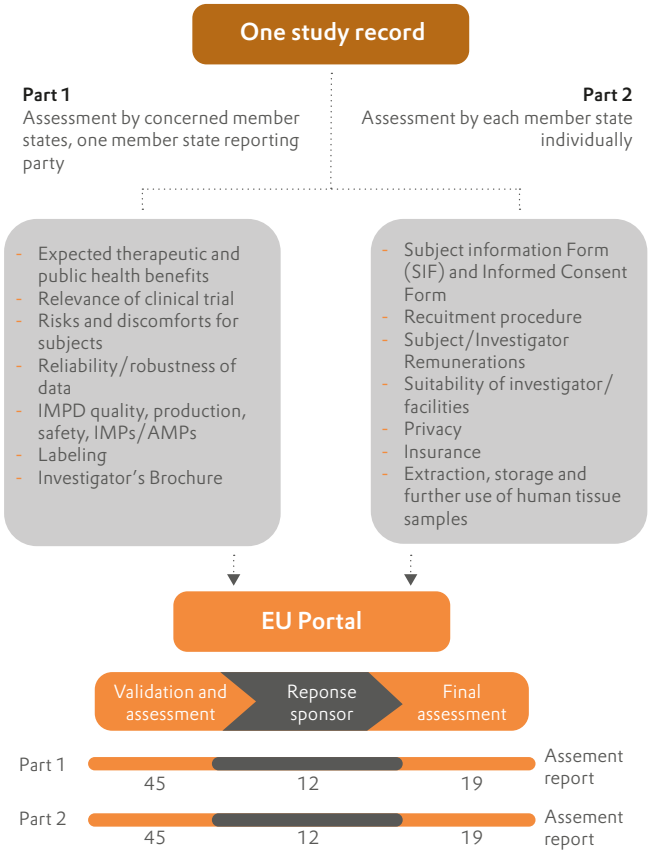
- The (WMO) was put in place to implement the EU Clinical Trial Directive 2001/20.
- In 2020 the European Clinical Trial Regulation (CTR) 536/2014 will become effective. This Regulation harmonizes the assessment, timelines and supervision processes for clinical trials throughout the EU. It will also apply to trials authorized under the previous legislation if they are still ongoing three years after the Regulation has come into operation (2023). The ECTR brochure provides more information.
- The General Data Protection Regulation (GDPR) is the privacy legislation which applies throughout the entire European Union. It stipulates the requirements that have to be met when processing (collecting, using and retaining) personal data and the rights of data subjects.
- EU Medical Device Regulation (MDR) (apply in 2020) and IVD Regulation (IVDR) (apply in 2022).

National regulation

- The Medical Research Involving Human Subjects Act (WMO).
- Requirements for submission in the Netherlands.
- Medicines Act.
- 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. Genetically Modified Organisms (Environmental Management) Decree.
- Medical scientific research involving substances covered by Articles 2 and 3 of the Opium Act, whereby the research takes place within the framework of treating addiction to these substances, must be reviewed by the "Centrale Commissie Mensgebonden Onderzoek', CCMO.

- The clinical trial assessment for CT's without ATMPs is done by accredited MRECs. All MRECs can review a study (company can choose) and use own rates. Information is available in the list of accredited MRECs. Administrative appeals against a negative MREC decision can be submitted at the CCMO. When the ECTR becomes effective (expectation 2020) this procedure will change and only part II is performed at national level.

Figure 3: Future review process of clinical drug trials in the EU



3.2.2 ADDITIONAL LEGISLATION FOR CLINICAL TRIALS WITH ATMP

For Clinical Trials containing ATMPs additional legislation/requirements are applicable.

EU Regulation

- Advanced therapy medicinal products (ATMPs) are gene therapy, somatic cell therapy, tissue manipulation products, or a combination thereof. European legislation applies to research involving ATMPs.

National regulation

- For cell therapy using living cells and/or gene therapy/medicinal products (with or without GMO) the CCMO (and not the MREC) will perform the clinical trial assessment.
- Research with a gene therapy or cell therapy medicinal product must undergo an extra, marginal review alongside the review by the reviewing committee (CCMO). This is carried

out by the competent authority. This is known as a dual reviewing system. Both reviews can take place simultaneously.

- Since July 2012 a prior license for cell therapy is no longer required for a medical center. Medical procedures involving ATMPs are considered "cell transplants' under the Special Medical Procedures Act (Wet op bijzondere medische verrichtingen; WBMV). The WBMV requires a prior license for cell transplants, but makes an exception for:
  - ATMPs with a marketing authorization (MA);
  - ATMPs under the hospital exemption (HE);
  - ATMPs without an MA used in the context of an authorized compassionate use program;
  - ATMPs used in scientific research authorized under the WMO;
  - Sometimes an ATMP does not meet the quality requirements as laid down in the specifications of the Investigational Medicinal Product File (IMPD). In that case there is an out of specification (OOS) ATMP. In exceptional cases, an OOS ATMP can still be administered to the subject. More information can be found under section D7. Out of specification (OOS) ATMP.

3.2.3 ADDITIONAL LEGISLATION FOR CLINICAL TRIALS WITH ATMP CONTAINING GMO

If an ATMP is either gene therapy or cell therapy products containing genetically modified cells (e.g. Alipogene tiparvovec, talimogene laherparepvec, Tisagenlecleucel), there are specific additional clinical trial requirements. In addition to the normal assessments and ATMP assessments; if the materials used within the context of a clinical trial with an ATMP are GMOs, such materials also fall under the scope of the GMO rules.

EU Regulation

- Directive 2001/18/EC on the deliberate release into the environment of GMOs.
- Directive 2009/41/EC on the contained use of genetically modified micro organisms.
- Regulation (EC) 1946/2003 on transboundary movements of genetically modified organisms.
- Regulation (EC) 1829/2003 on genetically modified food and feed.
- Directive (EU) 2015/412 amending Directive 2001/18/EC as regards the possibility for the Member States to restrict or prohibit the cultivation of GMOs in their territory.
- Regulation (EC) 1830/2003 concerning the traceability and labelling of genetically modified organisms and the traceability of food and feed products produced from genetically modified organisms.

National Regulation

- The GMO rules have been implemented in the Netherlands, in the Environmental Management Act (Wet milieubeheer), the Genetically Modified Organisms (Environmental Management) Decree (Besluit genetisch gemodificeerde organismen milieubeheer (BGGO), and the Genetically Modified Organisms (Environmental Management) Regulations (Regeling genetisch gemodificeerde organismen milieubeheer (RGGO).
- The assessment of gene therapy research involves various combinations of legislation and regulations as well as a number of different bodies. The following authorisations are required in order to start clinical gene therapy research:

- a positive decision from the CCMO;
- a declaration of no objection from the Minister of VWS (Health, Welfare and Sport);
- a permit from the Ministry of IenW Ministry of Infrastructure and Water Management.

- On the grounds of the Genetically Modified Organisms (Environmental Management) Decree a permit is required for work with genetically modified organisms (GMOs). These permits are issued by the GMO Bureau (*Bureau GGO*).
- Since 1 July 2019 adeno-associated virusses (AAV) have been reclassified in pathogenicity class 1 on Annex 5. This leads to a different pathway of risk assessment. The applicant can make the risk assessment by means of a notification of the classification articles listed in Annex 5. It is not necessary for each application to request an individual decision based on art. 2.8 of the Besluit genetisch gemodificeerde organismen milieubeheer 2013 to arrive at the correct classification.

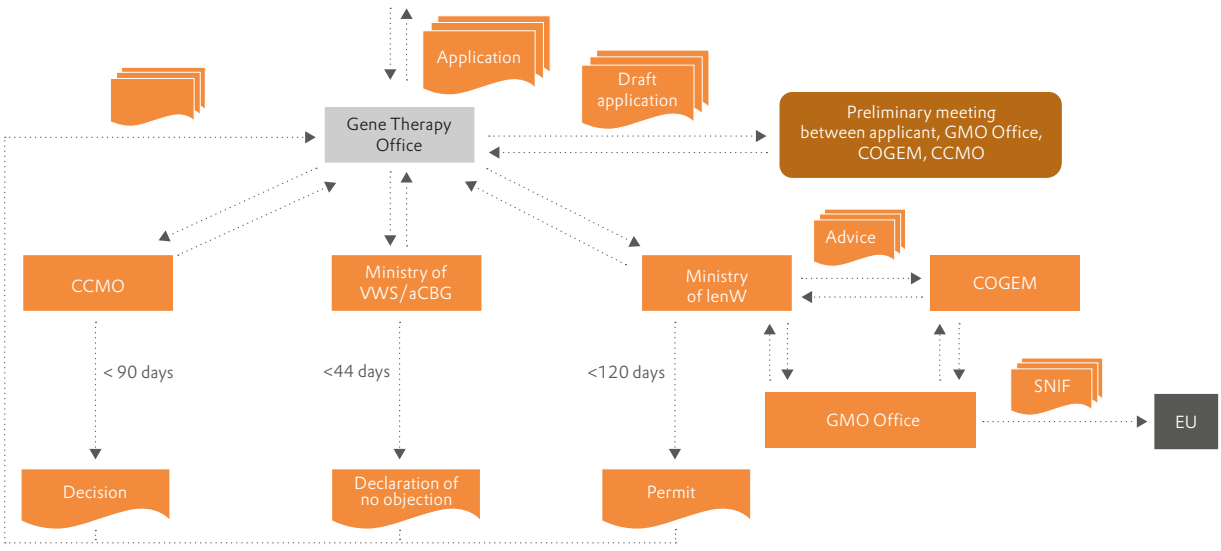
More information about clinical trials with ATMPs can be fond on the websites of 'genetherapynet' (http://www.genetherapynet.com/clinical-trials.html) and that of the loket gentherapie (https://www.loketgentherapie.nl/).

3.3 PROCESS

3.3.1 THREE ASSESSMENTS PROCEDURES IN PARALLEL

In the Netherlands the process is coordinated by gene therapy office (*loket gentherapie*). Three assessment procedures; the Clinical Trial Authorisation (CTA), the Ethical review and the Environmental & biosafety Risk Assessment (ERA) start parallel when all required documents are submitted (see annex 1).

Figure 4: Overview of procedures and timelines of the gene therapy office, showing the three parallel assessments



Following bodies can be involved in the assessment of clinical gene therapy research.

- The Central Committee on Research involving Human Subjects (CCMO).
- The MOH (CBG); responsible for issuing a declaration of no objection regarding the proposed gene therapy research based upon the Medical Research Involving Human Subjects Act (WMO). Suspected unexpected serious adverse reactions (SUSARs) of the investigational medicinal product authorised by EMA that would present unacceptable risks for human subjects will be assessed. MOH has delegated its tasks to the Medicines Evaluation Board (MEB).
- The Ministry of Infrastructure and Water Management (IenW) is responsible for the regulations that protect people and the environment during activities involving genetically modified organisms (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 restricted use and introduction into the environment.
- The Commission on Genetic Modification (COGEM) offers advice to the Ministry of IenW with regard to the 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 gene therapy 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 for the staff involved in treatment, 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 introduction of GMOs into the environment (including gene therapy), in most cases the Minister of IenW will request advice from COGEM in the draft decision phase. The topic report provides more information.

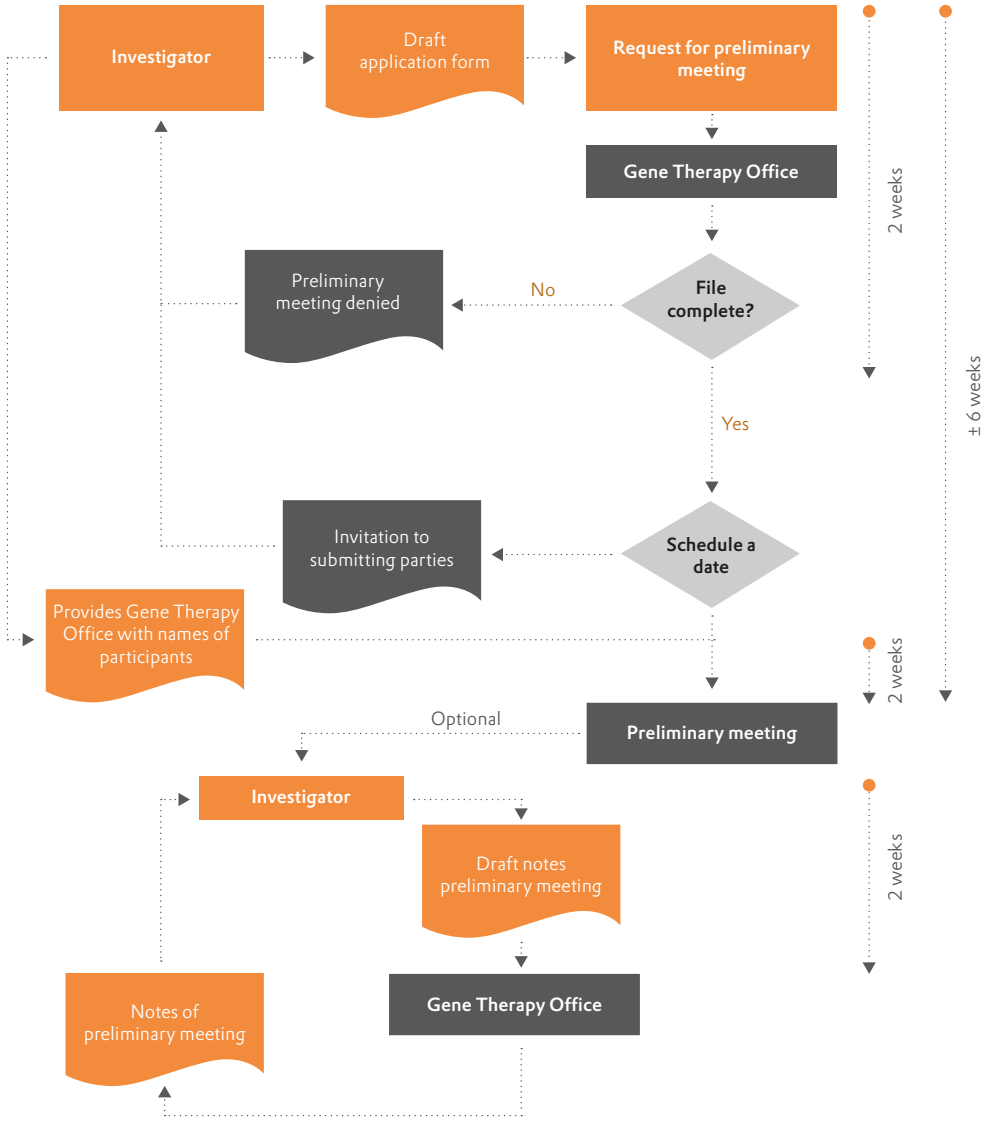
3.3.2 PRELIMINARY MEETING

Preliminary consultation is 8 weeks.

A preliminary meeting/consult is possible. The preliminary meeting is an informal discussion (optional) between the investigator and the bodies that decide or advise on the application. The investigator can either opt for a preliminary meeting that is attended by all bodies relevant to implementation and advice, or conduct preliminary meetings with each assessment body separately.

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.

Figure 5: The Gene Therapy Office procedures concerning the preliminary meeting



3.3.3 A POSITIVE DECISION FROM THE CCMO

Assessment of gene therapy research by the CCMO statutory deadline is 90 days.

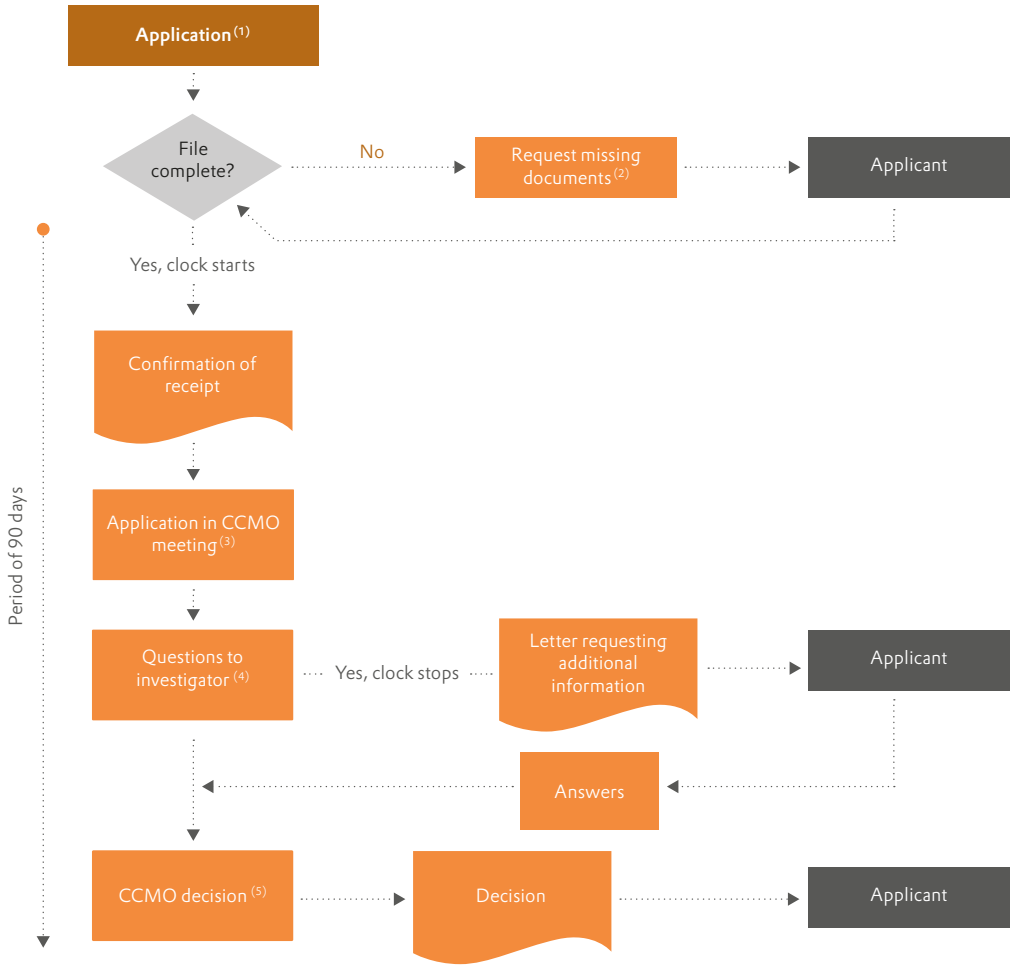
The official assessment of the research file by the CCMO starts as soon as all documents have been received (see step 1 in the CCMO flow chart). A research file that is complete at least 2 weeks prior to the CCMO meeting will be discussed in that meeting. (The Gene Therapy Office has no role to play in this phase because the CCMO will assess the file's completeness and ask questions if necessary).

After discussion of the application during the meeting (step 3 in the flow chart), the applicant will receive a letter that will include questions from the committee, if any (step 4 in the flow chart). The letter will refer to a deadline by which a response from the applicant is expected.

After receiving the response, the CCMO will examine whether the questions have been answered satisfactorily. The research file may then be discussed again in a subsequent CCMO meeting. Assessment of gene therapy research by the CCMO is subject to a statutory deadline of 90 days (step 5 in the flow chart).

After receipt of the research file the competent authority has 14 days to issue grounds for non-acceptance. In case of grounds for non-acceptance, the applicant can appeal this decision by submitting a notice of objection to the competent authority (within 6 weeks).

Figure 6: Overview of the ATMP assessment procedure of the CCMO



Frequent Issues during the CCMO assessment addressed by CCMO

The CCMO regularly encounters the lack of a clear foundation of the proposed use of the therapy, resulting in delay of approval or rejection of a research proposal. Frequently observed issues:

- validation of preclinical assumptions; often safety is mentioned. However, the CCMO requires studies not only to investigate adverse reactions, but also (mechanistic) effects, and a possible relationship between the desired effect and potential adverse reactions;

- if preclinical animal models are not available, the CCMO proposes that studies which primarily intend to investigate a possible therapeutic effect, should be based on clear hypothesis about a presumed mechanism that is as convincing as possible, and that is actually further investigated during the study;
- continuing development of the product. Product changes after phase II, complicate the start of a phase III study. Systematically recording (and conceiving) changes in the cell product is crucial, in order to create as rational a substantiation as possible for the study product (and ultimately the end product). A clear description of the step-by-step development of the product can help the CCMO (and other evaluators) to put the protocol and the study product in perspective of the results obtained with previous products;
- origin of the cells; insufficient argumentation regarding the origin of cells (allogenic vs autologous). The problem of the risks and the short-term survival of the cells in non-immune-compromised patients is not always adequately discussed. In case of equivalence between autologous and allogenic MSC, practical reasons (1e use of batch of allogenic MSC) might result in a preference for allogenic. (however note that CCMO will see these practical argments as secondary and start with therapeutic/safety effects);
- the dosage should be better substantiated if in-vivo proliferation is not necessary or possible, because this actually implies a pharmacological or molecular biological (and therefore dose-dependent) effect of the cell product. The route of administration fits with the presumed effect.

See also (CCMO website) and the Note cellular therapies (in Dutch) and frequently asked questions.

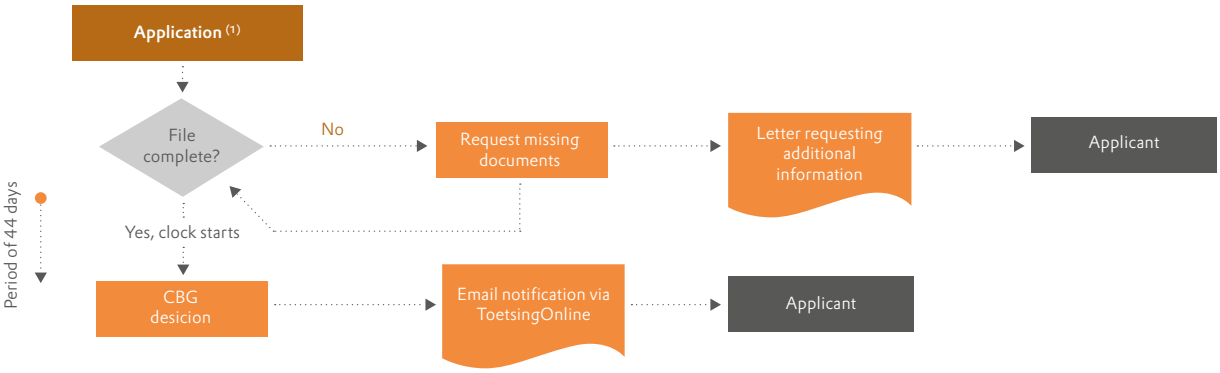
3.3.4 A DECLARATION OF NO OBJECTION FROM THE MINISTER OF VWS (HEALTH, WELFARE AND SPORT)

The deadline by which MOH decision is announced to the applicant is 44 days

A declaration of no objection is issued by the MoH (MOH). The documents to be submitted with the application are the same as the documents that must be submitted to the CCMO. After the research file is received, the applicant may receive a request for any missing data.

If, after receiving the necessary information, the Minister of MOH has not found any suspected unexpected serious adverse reactions (SUSARs) in the EMA EudraVigilance database that would present an unacceptable risk for human subjects, a written declaration of no objection is issued. This is done by means of an email announcement that the ToetsingOnline web portal sends out automatically to the applicant (and CCMO).The CCMO will enter the data into the European EudraCT database.

Figure 7: Diagram of the Minister of MOH's gene therapy assessment procedure



3.3.5 A PERMIT FROM THE MINISTRY OF IENW MINISTRY OF INFRASTRUCTURE AND WATER MANAGEMENT

The permit procedure for gene therapy research submitted to Ministry of Infrastructure and Water Management (IenW, c/o GMO Office) (1) takes a maximum of 120 days (Figure 8).

The procedure period starts as soon as the application has been received and contains clock stops.

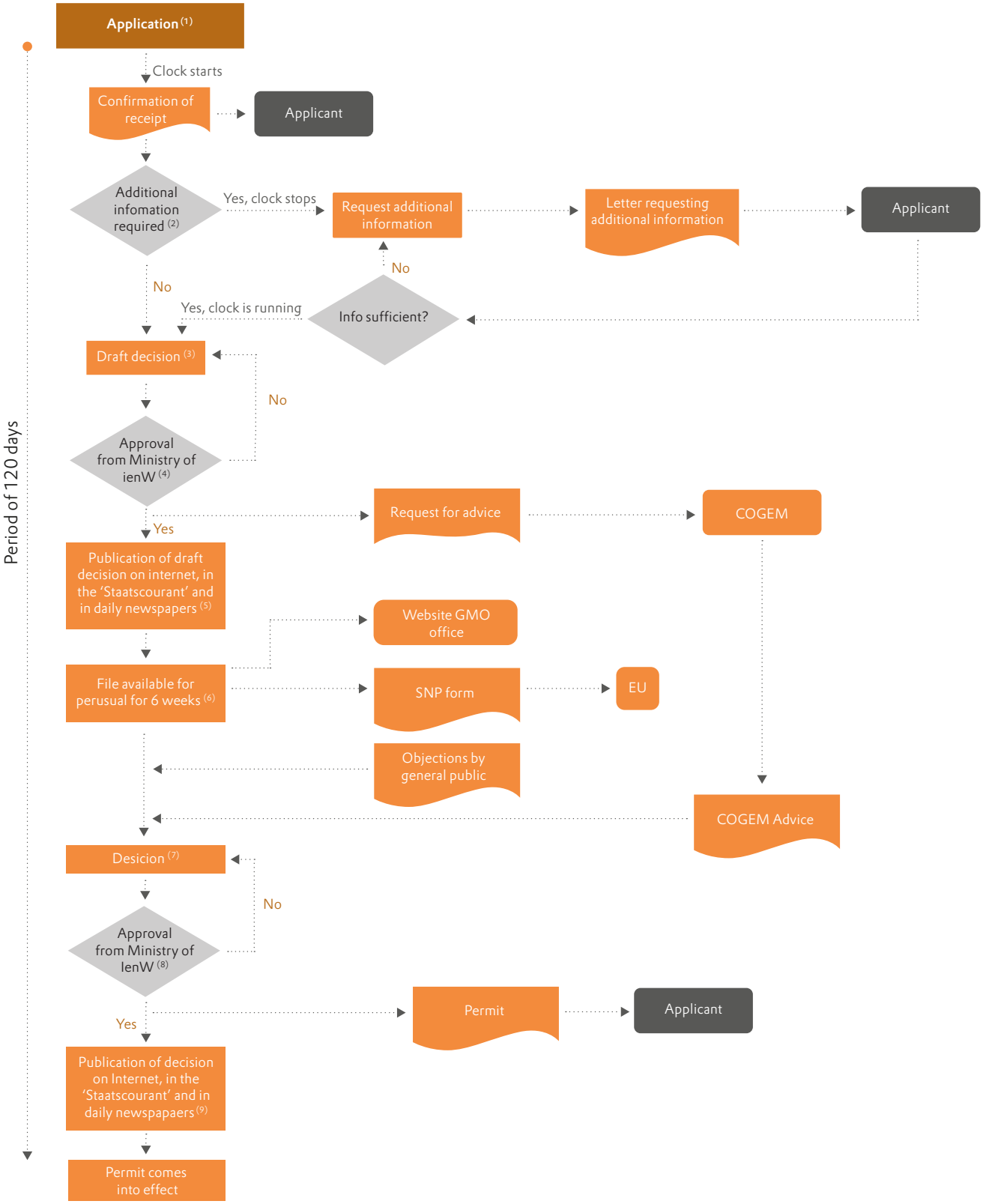
The scope of a permit is in the first instance determined by the 'breadth' of the application. Efforts will be made to draw up the final decision in such a way that, if applicable, multiple clinical protocols can be executed under the permit. Before submitting such a broader permit application, it is advisable to contact the GMO Office for an informal discussion on the possibilities.

A draft decision (3) is initiated by the Ministry of IenW (4) and made available for perusal together with the public part of the file (5) in seven weeks. The notification is published in relevant national and regional daily newspapers. Thereafter, for a period of six weeks, third parties can lodge objections to the proposed permit to be granted (6). COGEM (Netherlands Commission on Genetic Modification) will advise during this period. Objections and OGEM advice received are incorporated into the decision (7).

Apart from requiring a permit from the Ministry of IenW, the proposed work must also be reported to other Member States of the European Union. The GMO Office will send the SNIF (Summary Notification Information Format) form to the European Commission which will publish on Internet.

The decision is signed by the Ministry of IenW (8) no later than week 17. Notification of this decision is sent to the investigator before publication in national and regional daily newspapers (9). This decision takes effect immediately. Until 1 July 2019 a perusal deadline of six weeks needed to be passed, but this is no longer necessary. If any objections to the permit are lodged, the Council of State informs the investigator 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 8: Overview of the permit procedure for gene therapy research, starting with the submission of an application to the Ministry of Infrastructure and Water Management



Issues experienced by companies during GOGEM assessment

- All participating centers need to apply. In cases where an investigator does not come under the authority of the license holder (hospital/ZBC/research institute), an employment contract must be arranged for carrying out work under the license, such as a zero-hours contract with the license holder. Final responsibility remains (by contract) with license holder also for non-clinical procedures carried by other parties outside institution in question. Although CCMO accept draft contracts in the application process, permits can only be provided when signed contract is received. This might cause a delay.
- Company compliance policies often require training of physicians & distributors before contracts can be signed. Make sure training starts early on in process.
- When training will take place in other countries/outside EU check Dutch CGR hospitality obligations.
- Environmental Safety Officer (ESO). This officer must be approved by Ministry of I&W. In order to submit a permit application an ESO must have been appointed by the organisation.
- Technical certificates for apheresis, cell collection, cell modification. 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 JACIE (comply to 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 (in the Netherlands) however this is part of JACIE inspection. NB might cause internal issue in contracting centres when company oblige JACIE inspection.
- 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.
- Risk Management Program (RMP), Product training, Safety training (regarding patient safety), Cell chain training (including identity log) => make sure all parties are trained.
- The procedure is, due to clock stops, misunderstandings or lacking data, longer (6-12 months).

For more insights: applications, discussions and permits can be found on GGO-permits and GOGEM advice.

3.4 GCP REQUIREMENTS FOR ATMPS (COMMISSION DETAILED GUIDELINES)

Like any other medicinal product, clinical trials with ATMPs need to adhere to international ethical and quality standards known as Good Clinical Practice (GCP) guidelines. These guidance documents describe the standard requirements and procedures for the conduct of clinical trials and ensure that the rights, safety, and well-being of trial subjects are protected. Aspects covered include specifications for key documents such as the study protocol and the investigator brochure (IB), the delineation of sponsor and investigator responsibilities, the need to obtain informed consent from subjects prior to participation in any clinical investigation, the procedures for obtaining initial authorization from concerned regulatory bodies and ethics committees, and how to notify these parties of any changes to the study conduct. All these requirements fully apply to ATMPs.

- The rules governing medicinal products in the European Union contains guidance documents applying to clinical trials.
- Good Clinical Practice (E6) of the International Conference on Harmonisation (ICH).
- GCP Directive' (Directive 2001/20/EC).
- Regulations will be replaced once the Clinical Trial Regulation No 536/2014 becomes effective.

The special nature of ATMPs (containing GMO) makes additional standards/measures necessary. For clinical trials with ATMPs the detailed GCP guideline is applicable. It is expected to be replaced by a new guideline (draft for consultation). Aspects where the GCP requirements are more detailed are for example:

- Biodistribution, dose finding.
- The confirmation that the donation, procurement and testing of the cells and tissues used as starting materials are in accordance with Directive 2004/23/EC or Directive 2002/98/EC (see below).
    - For example, if it concerns a CAR-T product where T-cells are harvested from the patient's peripheral blood (apheresis), the donation, procurement, and testing of cells used as starting materials for the ATMP have to comply with the Tissues & Cells Directive (cf. recital 7 of the preamble to Dir. 2004/23). Although this is not clearly regulated in Dutch law, the Dutch rules and regulations regarding tissues, cells, and blood should be applied in accordance with the EU Directives, meaning that the Body Materials (Safety and Quality) Act (Wet veiligheid en kwaliteit lichaamsmateriaal) applies (and not the Blood Provision Act (Wet inzake bloedvoorziening)).
- Route of administration – surgical procedures might that impact the ATMPs safety and efficacy.
- Traceability: the ability to locate and identify each individual unit of tissue/cell during any step from procurement, through processing, testing and storage, to distribution to the recipient or disposal, or vice versa. It also covers the identification of all involved facilities or establishments as well as relevant data on products and materials coming into contact with those tissues/cells during their procurement, processing, testing or storage. The traceability mandated for clinical trials falls under the responsibility of the sponsor, the manufacturer and the investigator/institution where the ATMP is being used and should be described in the study protocol. To ensure full bidirectional traceability (i.e. from source to subject and from subject to source), the system used in the clinical setting explicitly has to be complementary to and compatible with the system in place for the manufacturing of ATMPs.
- Study design – double blind trials often not feasible (either no appropriate comparator, or no blinding possible (e.g. surgical procedure)).
- Specific endpoints (especially for TEPs – how to measure functional and structural aspects of repaired, regenerated or replaced tissue?).
- Combined ATMPs – functionality of device component to be demonstrated.
- Long-term follow-up for safety and efficacy. General reporting requirements for adverse reactions apply to ATMPs. Note: particular emphasis should be place on training investigators on safety issues of particular concern such as adverse events related to product application (e.g. surgical procedure), cases of infection, hypersensitivity and other unexpected reactions, adverse reactions related to concomitant medication such as immunosuppression as well as the reactions related to the medical device component of an ATMP. Long-term follow-up should be implemented depending on the nature of the ATMP and in accordance with the

guidance on risk assessment and follow-up. The follow-up period should consider the protection of subjects (clinical follow-up) as well as the collection of data (e.g. safety and efficacy follow-up).
- All subjects in an ATMP trial need to receive a subject alert card with information about the advanced therapy treatment received.

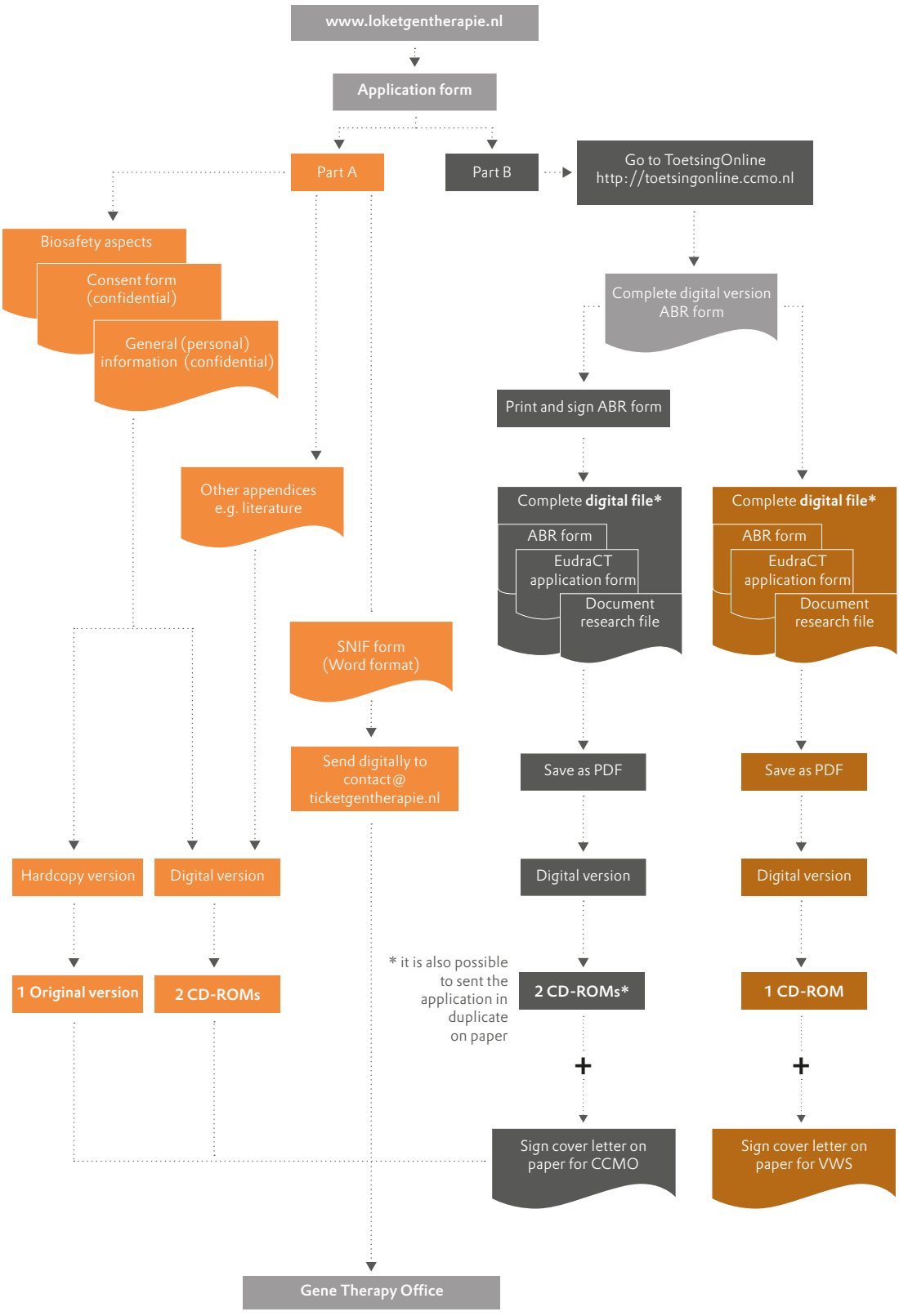
Issues addressed by companies
- Carefully check each individual step in the process which rules apply and which licenses are required (e.g. designation as a TE, requirements re. personnel, quality system, SOPs, traceability). For the purposes of compliance with the rules of Directive 2002/98 (as implemented into Dutch law in the Blood Provision Act or Directive 2004/23 (as implemented in the Body Materials (Safety and Quality) Act). Points of attention:
  - collection of cells at hospital;
  - storage of cells/tissues. Release of cells to the ATMP manufacturer. Note: if the manufacturing facility is not located in the Netherlands, the rules for export may be different depending where it is located; another EU/EEA Member State, Switzerland, Another country (non-EU/EEA, not Switzerland), e.g. USA;
  - Transport of cells from Dutch hospital to manufacturing site. Note: if the manufacturing facility is not located in the Netherlands, the rules for export may be different depending where the facility is located: another EU/EEA Member State, Switzerland, Another country (non-EU/EEA, not Switzerland), e.g. USA.
- The confirmation that there is a traceability system that enables the bidirectional tracking of cells/tissues contained in ATMPs from the point of donation, through manufacturing, up to the administration of the investigational product to the clinical trial subject. Note**:** The roles and responsibilities in implementing the traceability system need to be clearly defined and contractually agreed between all parties involved in the handling of the ATMP.

3.5 PHARMACOVIGILANCE LEGISLATION

A framework of pharmacovigilance legislation is applicable to all medicines, including ATMPs.

European legislation
- Regulation (EU) No 1235/2010 and Regulation (EU) No 1027/2012 amending, regarding pharmacovigilance, Regulation (EC) No 726/2004.
- Directive 2010/84/EU and Directive 2012/26/EU amending, regarding pharmacovigilance, Directive 2001/83/EC.
- Commission Implementing Regulation No 520/2012, which concerns operational aspects of implementing the new legislation.
- In February 2018, EMA released a draft revised guideline on safety and efficacy follow up and risk management of ATMPs: Guideline on safety and efficacy follow-up – risk management of ATMPs. Article 14 (4) of Reuglation (EC) No 1394/2007 and provides advice on certain aspects of pharmacivigilance, risk management planning, safety and efficacy follow-up of authorised ATMPs, as well as some aspects of clinical follow-up of patients treated with such products.

ANNEX 1
GMO APPLICATION REQUIREMENTS



4 MARKETING AUTHORISATION

This process is almost always coordinated by Headquarters and not local. Because local organisations are hardly involved, limited information is provided here.

Key elements

- All normal dossier requirements are applicable DIRECTIVE 2001/83/EC Annex I.
- Additional requirements:
  - assessment is performed by Committee for Advance Therapies (CAT);
  - DIRECTIVE 2001/83/EC Annex I Part IV describes requirements per ATMP type;
  - donation, procurement and testing of the human tissue and cells used as starting materials Directive 2004/23 (human cells and tissues) or Directive 2002/98/EC (human blood cells);
  - Directive 2004/23 (human cells and tissues) and Directive 2002/98/EC (human blood cells) provide additional requirements regarding traceability;
  - The Guideline on the risk-based approach addresses risk factors, risk profiling and the consequences for the dossier.
- For ATMPs it might be necessary to grant marketing authorisations on the basis of less complete data than is normally required. Conditions for a conditional marketing authorisation are laid down in Commission Regulation (EC) No 507/2006.
- If an ATMP is also an orphan medicine, the following framework for orphan medicines is applicable:
  - Regulation (EC) No 141/2000 of December 1999 on orphan medicinal products;
  - Commission Regulation (EC) No 847/2000 of April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicine;
  - Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products.

- Optional: classification procedure (60 days).
- Optional: certification procedure (only for SME) (90 days + submission 70 days before start).
- Submission Marketing Authorisation Application (MAA): Timelines are the same.

Frequent issues;

- discussion on clinical relevant endpoints (long term);
- data is not always supporting the claim. Make sure pharmacodynamic endpoints result in clinical relevant endpoints;
- because of fast scientific development of ATMPs it occurs that production processes change during the filing procedure. Discuss this upfront to make sure all GMP requirements are met;
- how to make sure all GMP requirements are met when every patient is his own batch?

4.1 OPTIONAL CLASSIFICATION PROCEDURE

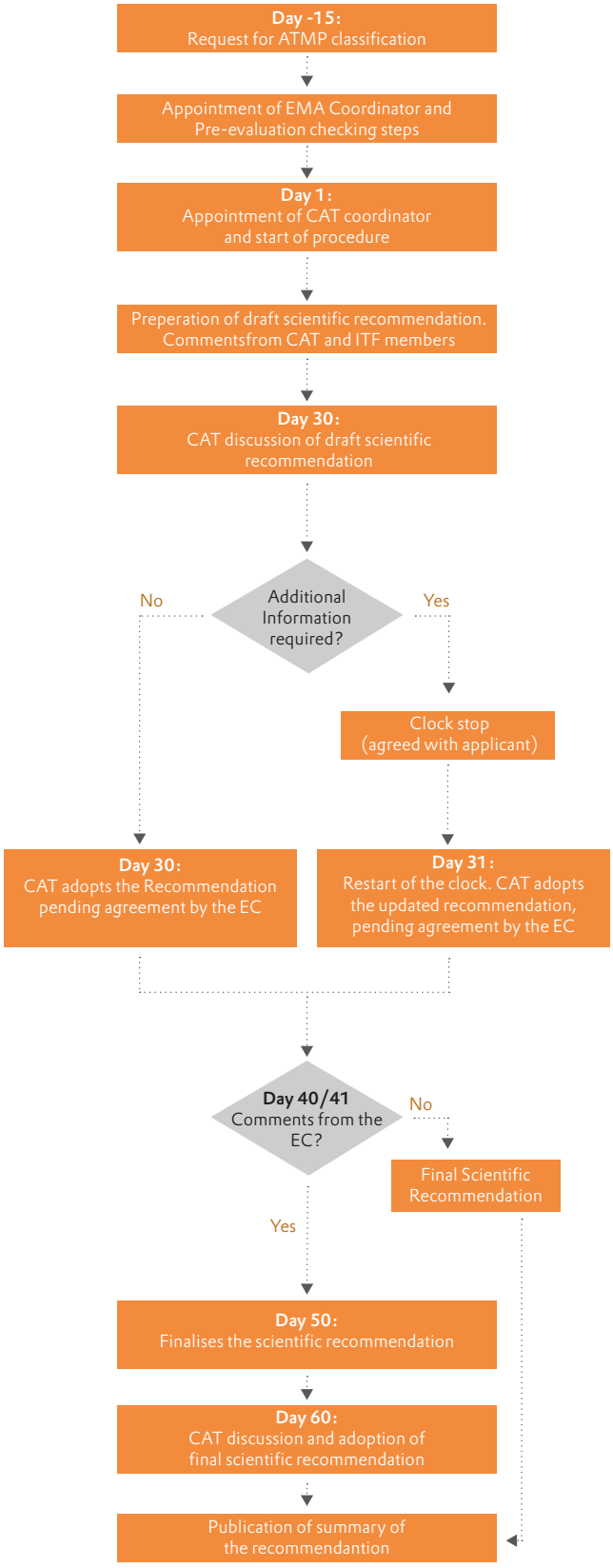
The criteria for ATMPs are set out in Article 17 of Regulation (EC) No 1394/2007. See chapter 2 Classification ATMPs. In case of questions or borderline cases, applicants have access to an optional procedure which is the Committee for Advanced Therapies (CAT) scientific recommendation for the classification 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 (published reports) of the assessment of the classification of ATMPs as summary reports.

Guidelines, information & publication

- 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 take 60 days. At day 30 a clock stop of 1 month is possible when additional information is requested. See timetable figure 9.
- 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 9: Timetable classification procedure of the EMA



4.2 OPTIONAL CERTIFICATION PROCEDURE (APPLICABLE FOR SME'S)

The European Medicines Agency's Committee for Advanced Therapies (CAT) provides a certification procedure for advanced therapy medicinal products (ATMPs) under development by micro-, small- and medium-sized enterprises (SMEs). It's defined in Article 18 of Regulation (EC) No 1394/2007.

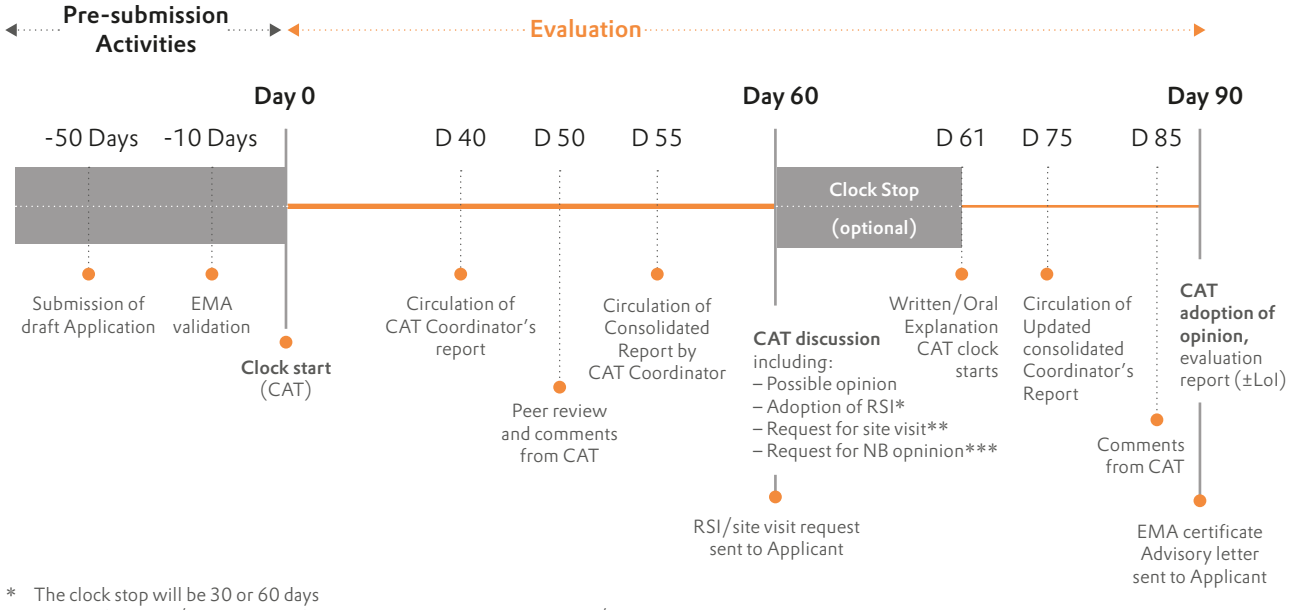
The certification procedure involves the scientific evaluation of quality data and, when available, non-clinical data that SMEs have generated at any stage of the ATMP development process. It aims to identify any potential issues early on, so that these can be addressed prior to the submission of a marketing-authorisation application. 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 marketing-authorisation.

Guidelines, information & publication

- 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 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 10: Activities and timelines for the Certification procedure for SME's



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

ANNEX 2
TIMELINES MARKETING AUTHORISATION APPLICATION PROCEDURE

Day 1	Start of the procedure. In the case of an ATMP containing or consisting of GMOs, the EMA will inform the GMO competent authorities of the start of the procedure and manages the coordination with the GMO competent authorities. In the case of advanced therapy medicinal products which incorporate medical devices or active implantable medical devices, ('combined ATMPs'), the EMA manages the coordination of the consultation with the Notified Body at the relevant time points of the procedure.	EMA
Day 80	Assessment report of CAT rapporteur and Co-Rapporteur to CAT CHMP and EMA. CAT Rapporteur focus RMP on the safety specifications and the need for long-term efficacy follow-up. EMA sends the Day 80 Assessment Reports to the applicant (or information only)	CAT EMA
Day 94	PRAC Rapporteur circulates the RMP assessment report, focusing on the prospective planning aspects: • pharmacovigilance plan; • risk minimisation measures • proposed RMP LoQ.' EMA sends the PRAC Rapporteur AR to the applicant for information.	PRAC
Day 100-106	Comments, adjustment and circulation of updated RMP Assessment Repport, PRAC Procedural advice and PRAC questions (PhV & RMin activities only) for D120 LoQ.	PRAC
Day 114 **(Day 120 LoQ)**	CAT adopts the Day 120 list of questions as well as the overall conclusions and review of the scientific data to be sent to the applicant by the EMA. At the latest by Day 114, the CAT adopts a request for GMP/GLP/GCP inspection, if necessary (Inspection procedure starts). Major objections and key scientific issues (from the LoQ) are presented to the CHMP. The updated LoQ will be circulated to the CAT for information and sent to the applicant.	CAT EMA
Clock stop		Applicant
Day 115	Restart procedure.	

Day 150	Joint Response Assessment Report to CHMP Coordinators, PRAC, CAT, CHMP and EMA. EMA sends this joint Assessment Report to the applicant making clear that it is sent for information only and does not yet represent the position of the CAT.	
Day 160-170	Comments, adjustment and updated Joint AR.	
Day 174 **(Day 180LoOI)**	CAT decision on list of "outstanding issues' (LoOI) and/or an oral explanation by the applicant or CAT draft opinion (overall conclusions and review of the scientific data). EMA sent to the Applicant. Major objections and key scientific issues from the LoOI are presented to the CHMP. If there is no LoOI or oral explanation, the CAT transmit draft opinion to the CHMP.	
Clock stop	'Time allowed to respond to questions and issues raised'.	Applicant
Day 175	Restart.	Applicant
Day 176-204	CAT (Co)-Rapporteurs draft a joint assessment report (including the RMP aspects), circulation, comments, adjustment and final assessment report to CHMP.	CAT
Day 201	Final opinion.	CHMP
Day 215	Provide EMA with product information and Annex A in the 25 languages (EU official languages and Icelandic and Norwegian) and the 'QRD Form 1' by Eudralink'	Applicant
Day 229	Member States will send linguistic comments on the product information to applicant (QRD Form 1).	Member States
Day 235	Applicant provides EMA with final translations of summary of product characteristics, Annex II, labelling and package leaflet in the 25 languages (+ 'QRD Form 2' and 'PDF checklist') by Eudralink.	Applicant
Day 237-277	Finalisation of EPAR in consultation with Rapporteur, Co-Rapporteur, CAT, CHMP and Applicant (the latter for confidentiality aspects). Commission adopts Decision.	EMA

5 ACCESS & REIMBURSEMENT

Key Elements

- ATMP experience is limited among stakeholders (VWS, ZiNL, HCIs). Involve physicians & provide education (disease, treatment, type of ATMP and total treatment procedure).

- ATMPs face challenges in obtaining national & decentral reimbursement.
  - Traditional methodologies and procedures are not (always) appropriate for ATMPs.
  - CE models focus on long term treatment (instead of curation).
  - High uncertainty of long term effects versus high costs in 1st year.
  - Uncertainty of long term effects will raise discussion on ICER and price.
  - Authorities require registry for ATMPs, however stakeholders (EMA, MoH, HCIs, physicians and HQ) are not aligned on purpose of registry, registration items, costs and ownership.
  - Traditional payment models are not (always) appropriate for ATMPs, however experience with other models like pay for performance & annuity limited (assessment criteria are not always clear).
  - For ATMPs with relative small budget impact (BI) and low cost per patient per year a HTA assessment is not required. However HCIs might be reluctant to reimburse without a clear position in (inter)national guidelines or HTA assessment report of ZiNL => delay in reimbursement (and patient access).
  - HCIs and hospitals might challenge price and start negotiation or explore alternatives under HE.

- ATMPs face challenges in patient access even when reimbursement is in place.
  - Unclarity in procedures and permit requirements (lack of knowledge in companies).
  - Lack coordination, case manager between all involved authorities.
  - Dutch situation/requirements differ from other European countries.
  - Start treatment without all required permits is high risk (liability, fines, costs).

- Patient/physician pressure in life threatening situations. Free of charge solution is option, but only when all permits and requirements are fulfilled and parties have agreement on other costs (hospitalisation etc.).
- Alterative payment models are explored, however experience is limited and parties seem reluctant to implement.

5.1 INTRODUCTION

On a global level different challenges are addressed, like; high (upfront) costs of ATMPs, scarcity of budget (ability to fund large sums or small orphan patient population), and the uncertainties as regards effects (efficacy and safety) on longer term.

An additional problem on local/national level is that the current Dutch assessment procedures seem not appropriate for these (curative) treatments. Although MoH, health authorities and insurers acknowledge the special characteristics of ATMPs, up until now procedures are unchanged and stakeholders seem reluctant to design flexible processes. For that reason it's important to start the discussion on reimbursement and funding early to align on the procedures and address pitfalls.

5.2 LEGISLATION

The routes to reimbursement are set out in legislation based on Articles 2, 10 and 11 of the Healthcare Insurance Act, (*ZorgverzekeringsWet* 'Zvw**'**). Pursuant to Article 2 Zvw, the care to which patients are entitled is listed in Article 11 Zvw. Pursuant to Article 11 Zvw, insured patients in the Netherlands have the right to receive the care that they require, as defined in a Decree. The relevant Decree is 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 to which insured patients are entitled – and which HCIs are obliged to offer – are commonly referred to as 'the basic package (het basispakket,reimbursed care).

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

The Dutch Healthcare Authority ('NZa**'**) determines what types of 'care' can be charged to patients by health care providers, and specifically for medicinal products used for inpatient treatment in hospitals, the maximum amounts that can be charged for such health care.

For most treatments, HICs and health care providers negotiate and agree upon arrangements about what each treatment entails, what its quality should be, and what price can be charged for it. As set out below, each of the routes to obtain reimbursement involves one or more rounds of negotiations with the government, payors and/or purchasers, by which they exercise their bargaining power vis-à-vis companies that seek reimbursement of medicinal products.

5.3 NATIONAL REIMBURSEMENT

In order to understand the bargaining power mechanisms built into the reimbursement system in the Netherlands the first distinction to be taken into account is between the reimbursement of medicinal products used for outpatient treatment (outpatient pharmaceutical care or '*farmaceutische zorg*') and medicinal products used for inpatient treatment in hospitals (medical care, or '*geneeskundige zorg*').

- The extramural system is characterised by positive lists of reimbursed medicines ('*Geneesmiddelen Vergoeding Systeem*',or 'GVS'). This is a closed system with an open end funding (no fixed budget). Because ATMPs are often administered in hospital setting, this reimbursement procedure seems less applicable.
- For the intramural system, the scope and contents of care are determined by the 'established medical science and medical practice', '*stand van de wetenschap en praktijk*' (open system). There's no upfront HTA assessment and only products above threshold of € 10 million are applicable for an assessment.
- Next to these two routes a special Lock procedure is official effective from 2018 onwards. This procedure applies for products with an estimate budget impact > 40 million or >10 million and cost per patient per year > 50K. Products placed in the Lock procedure are (temporary) excluded from reimbursement.

5.3.1 HORIZON SCAN

To ensure that all parties (MoH, ZiNL, HCIs, health care professionals and patients) are timely informed of new developments and their possible impact on the macro budget, assessment capacity, healthcare, treatment and hospital budgets, ZiNL produces twice a year a Horizon Scan.

ZiNL gathers information, using public available sources (EMA, MEB, clinical studies, pipeline overviews), expert opinions and information provided by the pharmaceutical industry. 7 expert groups (disease areas) discuss, complete, modify and validate the collected information. An integral, overview of new medicines and new indications/line extensions in the next 2 years and their possible budget impact is published twice a year (Horizon Scan). It includes expected new medicines, related indications, volumes and prices, expected new indications or line extensions registered products. But also expected alternatives (biosimilars / generics) and patent expiration.

Based on the Horizon Scan the MoH determines which product will be placed in the Lock procedure (see below). The Horizon Scan enables ZiNL also to plan their capacity, since the assessment of products placed in the Lock and the outpatient GVS products will be prioritised. Other in hospital products will be assessed based on 'risk-management'. If ZiN does not perform an assessment, HCIs and hospitals will be responsible for appropriate use and cost-effective purchase of the product. For these purposes, HCIs, hospitals and pharmaceutical companies can enter into decentralized financial arrangements (i.e., negotiations). The Horizon Scan enables those parties (HCIs, health care professionals and patients) to estimate the impact of new developments (including biosimilars and patent experiments) on healthcare, treatment and

budgets. Within European discussions on funding new innovations, the Dutch Horizon Scan is seen as an example and will play an important role in the development of an European Horizon Scan.

5.3.2 GVS OUTPATIENT

Whether a drug qualifies for reimbursement is largely determined by the therapeutic value in relation to standard treatment in the Netherlands and the substantiation of its effectiveness. The Minister of Health, Welfare and Sport (VWS), will be advised by Healthcare Institute (Zorginstituut Nederland further ZiNL). ZiNL includes the opinion of a Scientific Advisory Board (WAR) in its recommendation. This advisory board consists of a maximum of 50 external, independent experts. The Commission for medication is part of this advisory board and consists of about 20 members.

The GVS contains lists of reimbursed medicines. Products in the GVS are placed in Appendix 1A or Appendix 1B and sometimes also on Appendix 2.

Appendix 1A
Appendix 1A contains the list of groups of interchangeable medicines. Medicines are regarded as therapeutically substitutable if they:

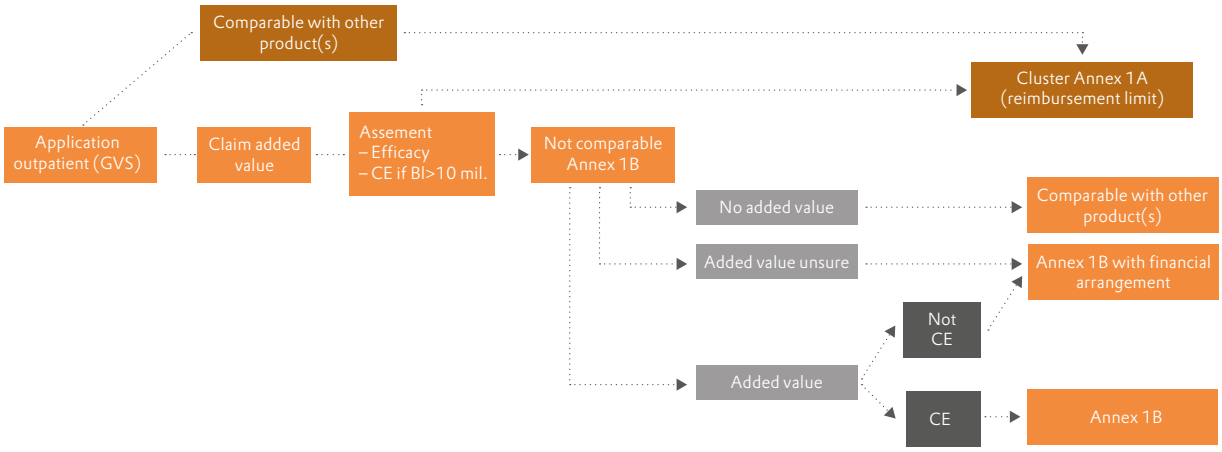
- can be applied to a similar indication area,
- are administered via an equal route of administration, and
- are generally intended for the same age range.

The medicines on this list have a reimbursement limit. If the price of the medicine is above this limit, there will be co-payment (*'eigen bijdrage'*).

Appendix 1B
Appendix 1B contains non-interchangeable medicinal products further to their added therapeutic value (*'therapeutische meerwaarde'*) and their cost-effectiveness (*'doelmatigheid'*). The medicines on this list do not have a reimbursement limit and are 100% reimbursed.

Appendix 2
Products on list 1A and 1B can also be placed on Appendix 2. This means that additional conditions have been set for reimbursement. (e.g. limitations on the patient population (versus label), specific pre-treatments or special conditions.

Figure 11: Procedure for package admission of outpatient medicines



Assessment criteria for GVS outpatient products

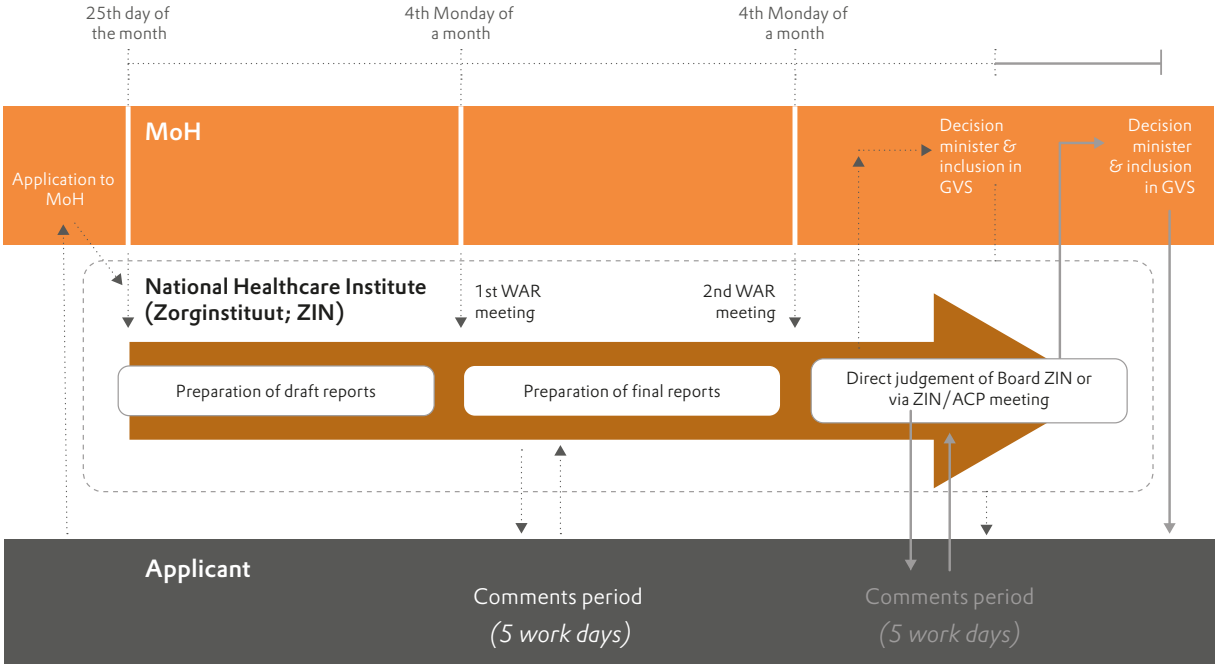
- Efficacy: positive effects of a drug, which are expressed in preferably clinically relevant outcome measures or, in the absence thereof, in surrogate outcome measures.
- Unfavourable/Adverse effects: effects that are not intended but do occur in patients using a medicine.
- Experience: The experience with a medicine is the extent to which (limited, sufficient, spacious) people have learned to know and use the advantages and disadvantages as much as possible in daily practice.
- Applicability: The applicability of a medicine is the extent to which properties limit or allow the use in different (groups of) patients. Examples of this are the applicability in a certain age category, an organ dysfunction, in pregnancy and lactation. Furthermore, limitations due to contraindications and interactions are important.
- Ease of use: The ease of use is the degree of user-friendliness. As the burden on the patient increases when using the medicine, the ease of use decreases.
- Therapeutic value: the sum of the valuation of all treatment-relevant properties of a medicine (beneficial and unfavourable effects, experience, ease of use and applicability) that together determine the place of the drug in the therapy compared to other available and recommended treatment options.
- Products with an estimated budget impact > 10 million (year 3) require a pharmacoeconomic evaluation as well.

Procedure & Timelines

Parties involved are the MoH and the National Healthcare Institute. The MAH submits an application to the MoH. The route starts on the 25th of each month. In time to the 1st Advisory board (WAR) meeting, ZINL drafts concept assessment reports. The WAR assesses the draft reports in its meeting. After the meeting any changes in the draft reports are made and the secretary of the WAR sends these documents to interested parties. They have 5 working days to comment on the draft documents. If more time is required, the MAH can request a cLock stop (of a maximum of 3 months). The comment is processed by ZiNL and discussed in the 2nd WAR meeting. Multiple WAR meetings may be required to arrive at a final opinion on the reports. The completion of the assessment goes through the management of ZiNL program. This program

board has several variants, namely on behalf of the board of directors (Executive Board), or through the Executive Board and with or without ACP advice. After this, the final reports can be sent to the Ministry.
The entire procedure must be finalized in max. 90 days.

Figure 12: Assessment procedure at National Health Institute (ZIN)



5.3.3 IN HOSPITAL PRODUCTS; RISK BASED ASSESSMENT

Products used in hospitals (specialist care) are in principle reimbursed at the time of marketing authorisation (MA).

Pursuant to Article 2.4 Bzv, insured patients have the right to receive 'medical care', which includes care that is commonly provided by medical specialists. Specialist care includes specialist medicines, i.e. medicines used as part of a treatment by or under the responsibility of a medical specialist, administration as part of specialist diagnostics, therapy and/or prevention.[1]

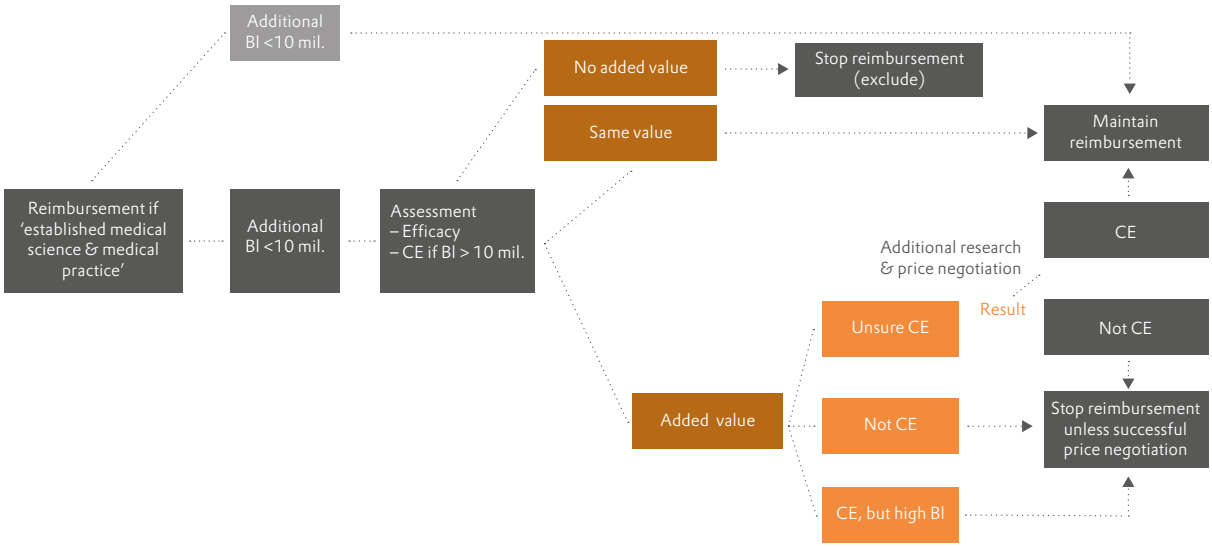
The scope and contents of medical care are determined based on 'established medical science and medical practice' (Art. 2.1(2) Bzv). This means that care is insured if it is sufficiently tried and tested by international medical science (in principle, this is the case if the product has an MA), or

1 ZiN, 'Pakketbeheer specialistische geneesmiddelen'), December 2013: https://www.zorginstituutnederland.nl/binaries/zinl/documenten/rapport/2013/12/03/pakketbeheer-specialistische-geneesmiddelen/Pakketbeheer+specialistische+geneesmiddelen.pdf, page 12: 'a medicine that is part of a treatment that takes place by or under the responsibility of a medical specialist and of which administration takes place within the framework of specialist diagnostics, therapy and/or prevention. (…) The criterion for a specialist medicine is that it must be an authorised medicine of which the authorised indication is part of the specialised medical field. In this respect at least one of the following criteria must be fulfilled: application by a medical specialist, use of specialist equipment, medical supervision by a specialist for monitoring of response or side effect or if the medicine is part of a specialist treatment'.

absent scientific testing, has been accepted in daily practice as correct and responsible. Pursuant to these provisions, insured patients in the Netherlands should, in principle, have direct access to new specialist medicines and hospitals would normally be required to purchase such medicines in order to comply with the standards of good care.

The assessment procedure for those products takes place within the context of 'risk-based management'. Products with a new therapeutic added value (criteria added value) and an estimated budget impact of at least€10 million per year are eligible for an assessment (threshold is also counting expected label extensions in the future)

Figure 13: Procedure for package admission of in hospital medicines



Assessment criteria for GVS outpatient products

- Efficacy: positive effects of a drug, which are expressed in preferably clinically relevant outcome measures or, in the absence thereof, in surrogate outcome measures.
- Unfavourable/Adverse effects: effects that are not intended but do occur in patients using a medicine.
- Experience: The experience with a medicine is the extent to which (limited, sufficient, spacious) people have learned to know and use the advantages and disadvantages as much as possible in daily practice.
- Applicability: The applicability of a medicine is the extent to which properties limit or allow the use in different (groups of) patients. Examples of this are the applicability in a certain age category, an organ dysfunction, in pregnancy and lactation. Furthermore, limitations due to contraindications and interactions are important.
- Ease of use: The ease of use is the degree of user-friendliness. As the burden on the patient increases when using the medicine, the ease of use decreases.
- Therapeutic value: the sum of the valuation of all treatment-relevant properties of a medicine (beneficial and unfavourable effects, experience, ease of use and applicability) that together determine the place of the drug in the therapy compared to other available and recommended treatment options.
- Products with an estimated budget impact > 10 million (year 3) require a pharmacoeconomic evaluation as well.

Procedure & Timelines

ZiNL will draft an assessment report based on these criteria added with the estimated budget impact and requirements for outcomes research. ZiNL receives advice from the Scientific Advisory Board (WAR) and if necessary from the Advisory Committee (ACP). Subsequently, an advice is formulated to the MoH. If there are uncertainties about appropriate use, and/or cost-effectiveness, the advice might be appropriate use requirements or a conditional reimbursement.

Contrary to the GVS procedure, there are no official timelines for this procedure.

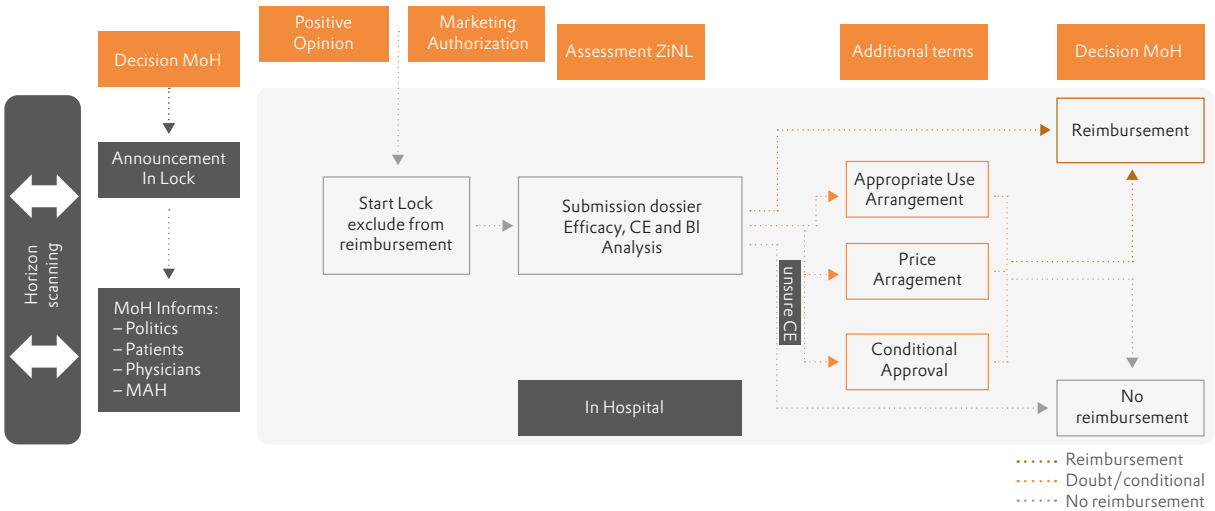
5.3.4 LOCK PROCEDURE

New medicines used in hospital are in principle admitted to the basic package and reimbursed without special (price) agreements. However, the MoH can decide to (temporary) exclude a new product (or new indication) from reimbursement. The product is placed in a so called 'Lock procedure', pursuant to which there is no automatic entry into the open reimbursement system for intramural products. In that case patients are *not* entitled to receive new, expensive medicinal products as part of medical care. In the meantime, ZiNL will perform an HTA assessment and advise the MoH, where after the MoH will negotiate on (confidential) price and conditions with the manufacturer.

The MoH use following thresholds:

- treatment of one new indication (or together with several expected indications) will exceed the macro-cost threshold of € 40 million per year (based on the Horizon Scan). All new indications are placed in the Lock; or
- if the threshold of € 40 million is not met but the costs per patient per year exceed a threshold of € 50,000, ánd the expected macro-costs exceeds the threshold of € 10 million per year (based on the Horizon Scan), this indication is also placed in the Lock.

Figure 14: Procedure for the Lock



Timelines

Although MoH and ZiNL know, based on the Horizon Scan, which product is a candidate for the Lock, the formal procedure and decision-making process can only start after a positive opinion from the CHMP, and at the latest one month after obtaining MA. The MoH will start negotiations based on ZiNL HTA assessment reports. Depending on the outcome of the advice of ZiN and negotiations between the MoH and company, the product can either be placed out of the Lock (successful negotiations) or remain in the Lock.

Although assessments of products in the Lock procedure are prioritized, there are no strict timelines; the MoH does not apply the timelines set by Directive 89/105 (90 days for outpatient reimbursement procedures). The average time for products placed in the Lock, based on the formal Lock decisions as published in the Government Gazette (*'Staatscourant')*, is currently around 12months

5.3.5 CONDITIONAL REIMBURSEMENT

Certain ATMPs may also fullfill the criteria of the new (2019) rules for conditional authorisation. This system is meant for:

- Orphan medicines
- Medicines that have been authorised to the market with certain conditions (so-called conditionals)
- Medicines that have been authorised under special circumstances (so-called exceptionals)

Marketing authorisation holders who want to qualify for conditional authorisation with an orphan medicinal product, conditional or exceptional, and who meet the criteria, can submit an application to ZiNL. They must also submit a file with a proposal for research in collaboration with professional groups, patient organisations and an (independent) research institute.

There are two times when marketing authorisation holders can apply for conditional admission:

- Prior to a drug assessment by ZiNL
- After a negative recommendation or position from ZiNL due to insufficient evidence to be able to answer the package criteria.

The following conditions must be met when submitting a file:

- The medicinal product is registered by the European Medicines Agency (EMA), with the status of orphan medicinal product, conditional or exceptional for the relevant indication on the basis of which conditional authorization is requested;
- There is an unmet medical need (unmet treatment need) according to the current definition of the EMA.
- The main submitter of the file is the market authorisation holder. 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 ZiNL can be completed within the period of conditional admission. This period is a maximum of 7 or 14 years. The registration holder must record the duration of the

process when submitting the file. An interim extension of the conditional admission is not possible.

Applicants must fill in an application form for conditional authorisation of orphan medicinal products, conditionals and exceptionals. The fully completed application form can be sent by e-mail to: VTgeneesmiddelen@zin.nl. When the medicine has been designated by the minister as a potential candidate for conditional reimbursement a model agreement should be used. The complete procedure is described in the document 'Procedure for starting conditional authorisation of orphan medicinal products, conditionals and exceptionals'.

When a medicine has been selected by ZiNL for conditional admission, the Ministry of Health, Welfare and Sport starts negotiations with the marketing authorization holder in order to come to a price agreement for the duration of the conditional admission. The price paid per individual medicine must be made public.

In addition, all parties involved (the registration holder, professional groups and patient organizations) are obliged to draw up a covenant with each other. This contains agreements about the (minimum) outcome measures of the study, about providing information to patients and criteria for starting, stopping and phasing out treatment. In addition, all parties must promise to cooperate if, after the expiry of the period of conditional authorization, the medicine is nevertheless assessed negatively by ZiNL. Then the product cannot be included in the basic health package.

3.5.6 SUBSIDY SCHEME PROMISING CARE

The purpose of the subside scheme Promising Care is to speed up patient access to potentially promising care via inclusion in the basic package. This scheme makes it possible to obtain temporary financing for treatments that appear promising in terms of (cost) effectiveness, but are not yet reimbursed from the basic package because the effectiveness has not yet been proven. A condition for this is that research data of sufficient quality is collected within the subsidy period about the effectiveness and cost-effectiveness of the new treatment compared to standard treatment or usual treatment (s) in the Netherlands. After obtaining the research results, ZiNL assesses within 6 months on the basis of all published research results whether the care in question meets the "state of the art and practice" and whether the relative (additional) costs are acceptable. The scheme is open for non-registered ATMPs (as referred to in Article 2.4 of the Healthcare Insurance Decree) and certain other forms of care.

All applications must meet the following criteria:

- The only reason why care is not yet reimbursed from the basic package is the lack of research results showing that the application is ast least as effective as the standard of care/treatment customary 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 (if applicable; see article 1.6 part a and b of the regulation).

- The risk to the patient must be acceptable in relation to the expected health gain.
- There is a market failure (see article 2.2 part e of the regulation)

A yearly budget of maximum € 69 mln is available annually the subsidy ceiling for the first round in a year is € 40 mln. It this subsidy ceiling is not reached, the remaining amount will be transferred to the second round of the same calendar year. A project subsidy is granted for a maximum of 6 years.

The main applicant must be an administrative representative of a care provider (for example, a hospital or physiotherapy practice, see the OCW, SZW and VWS subsidies framework. In addition, there must be cooperation with relevant patient associations and professional groups, and possibly owners of the intervention.

5.4 ADD ON FUNDING

In practice, add-on funding is essential for obtaining market access for medicinal products costing more than € 1,000 per year per patient. In order to alleviate the budgetary burden that would be incurred by hospitals if they have to pay for expensive specialist medicinal products out of their general budget, a so-called 'add-on' request can be submitted to the NZa.

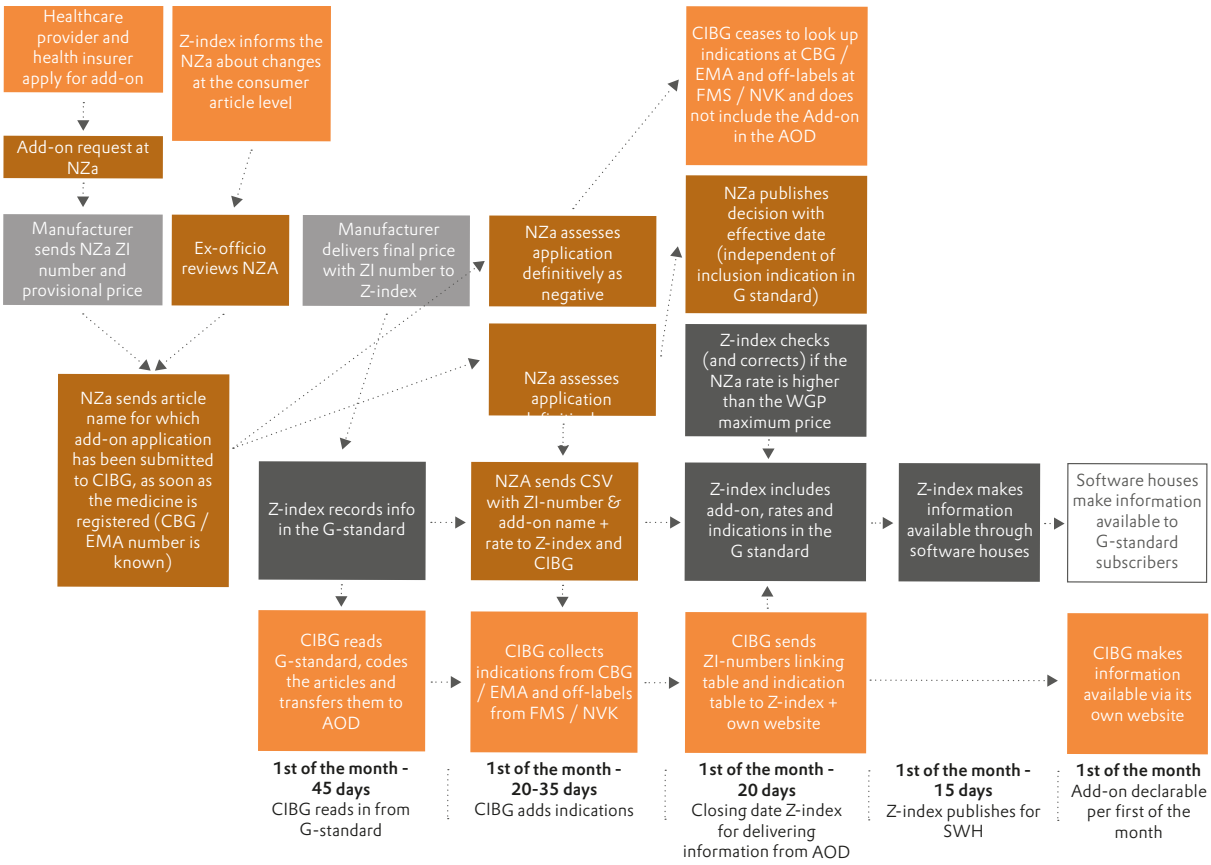
Normally, a hospital can charge HICs for providing 'treatments' (DRG '*diagnose behandel combinaties'* or 'DBC'), and it is up to the hospital to purchase the medicinal products needed to provide state-of-the-art care. However, if an add-on request is granted, hospitals will be permitted to charge insurance companies separately for the price paid for the 'add-on' medicinal to treat their patients with the expensive product. This is why healthcare providers and hospitals will equate the add-on with reimbursement. An add-on is a combination of a performance description and a maximum tariff, meaning that hospitals and HICs can negotiate a price for the add-on medicine below the NZa maximum tariff.

An add-on request cannot be submitted by an MAH. The add-on form must be submitted jointly by:

- 1 or more hospitals and
- 1 or more HCIs, either directly or through their trade associations.

This set-up (i.e. a bilateral application from a hospital and an HIC) stimulates 'decentralised negotiations' between the MA holder, individual hospitals and/or individual HICs about the financial conditions for delivery of the product following add-on designation.

Figure 15: Procedure for requesting add-on funding



5.5 PRICE NEGOTIATIONS

Price negotiations can occur at different levels.

- Central Arrangements (*Bureau Financiële Arrangementen VWS*).
- Decentral Arrangements (HICs or collaboration of HICs and hospitals).
- Local Arrangement (hospitals).

Central negotiation will take place when MoH decides, based on the Horizon Scan, to place a product in de Lock procedure. (see 5.3.3). Decentral Arrangements will take place when HCIs (together with hospitals) postpone funding and reimbursement until appropriate use and price arrangements are in place.

Candidates

- Products just below the national thresholds (BI > € 40 million, BI > € 10 million and cost per patient per year > € 50,000) or when alternative treatments are available (competition).
- Products used in centralized setting (BI for hospital is reasonable).
- Products with relative small macro BI, but with reasonable cost per patient per year and where hospitals consider own production under hospital exemption.

5.5.1 ALTERNATIVE PRICING MODELS

Although payers prefer price-volume arrangements currently, it's necessary to start a discussion on alternative models. Worldwide different models (mostly pay for performance models) are implemented, however the experience is very limited in the Netherlands.

Every ATMP will have their own characteristics and challenges. Starting with payers need, addressing issues like uncertainty, the discrepancy between long term effects and high costs in 1st year, the product characteristics and finally the availability of measurements and data will guide to the best fitting model. Combination of different models is possible.

Because of the Competition Law, only high level description is possible.

Uncertainty about (long term) clinical effects

1. Conditional approval or additional research [2]
- Start with selection of patient population.
- Define start criteria (not always possible).
- Define stop criteria (only applicable in long term treatment products).
- Administer in specialized centres.
- Build registry to collect efficacy data.
- Measured efficacy is basis for re-assessment and reimbursement continuation.

2. Price level related to evidence (national level)
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.

Issues
- Definition of data requirements.
- This implies that in first years of treatment prices are discounted. New innovations, new competitors create new market dynamics over time. Proven safety/efficacy in future won't guarantee undiscounted price still accepted and reimbursed.

3. Cure rate (OS) on population level is measured and based on this percentage an average discount is calculated
- Use cure rate (OS) in clinical trial to calculate average discount
- Measure cure rate in real life and agree on financial consequences in case of deviation

4. Pay for performance on patient level
Pay-for-performance models: in a performance – or outcomes-based payment system, the reimbursement for a treatment would be adjusted based on whether a pre-specified health outcome is achieved. There are many variations of this value-based model. It could be implemented through discounts on future payments, indication-based pricing, rebates or even

2 Subsidy 'Veelbelovende Zorg Sneller bij de Patiënt.

outcomes-based money-back guarantees. This model shares risk between the MAH and the payer.

- In case of relapse/less therapeutic effect an agreed percentage of cost is refunded. In case of relapse, the 2nd/repeated treatment is free of charge.

Issues

- Definition of less therapeutic effect is not always possible.
- How to define long term effect and max. time for relapse free guarantee.

In case of refund/free of charge; who will fund additional treatment/administration costs.

Uncertainty about the right patient pool and/or total Budget Impact

5. Conditional approval or additional research [3].

- Start with selection of patient population.
- Define start criteria (not always possible).
- Define stop criteria (only applicable in long term treatment products).
- Specialized centres.
- Registry to collect data and improve patient selection criteria

6. Step wise reimbursement after additional data is available.

- Start with selection of patient population.
- Define start criteria (not always possible).
- Define stop criteria (only applicable in long term treatment products).
- Specialized centres.
- Register data to improve patient selection criteria.
- Enlarge patient population when treatment effects are proven.

Unacceptable high treatment costs in 1st year

7. 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).

Issues

- Requires a different structure because patients can change their HCI over time. Special ATMP fund at VWS/ZiNL level. This might also be a solution for smaller HCIs.
- Hospitals/lab/transporters etc. will invoice immediately 100%. Who pre-funds?

3 Subsidy Veelbelovende ZorgSneller bij dePatiënt.

8. 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).

Issues
- Requires a different structure because patients can change their HCI over time. Special ATMP fund at VWS/ZiNL level. This might also be a solution for smaller HCIs.
- Hospitals/lab/transporters etc. will invoice immediately 100%. Who pre-funds?

5.6 ADMINISTRATION & PATIENT ACCESS OF COMMERCIAL PRODUCT

5.6.1 PERMITS & OBLIGATIONS

When EMA registration and reimbursement (with HCI) are in place, products can be prescribed. For new and more expensive medication nowadays there's an additional requirement, the product is assessed by the hospital formulary commission and included in the hospital formulary (sometimes accompanied with appropriate use arrangements).

For ATMPs additional requirements are applicable.

MAH and treating hospitals need special permits and contracts. Almost all permits and obligations in the clinical trial phase apply to the commercial phase. However hospitals and companies are less experienced with this process and a clear guidance (like the coordination by Loket Gentherapie) is lacking for products in commercial setting. For each and every step we refer to chapter 3, clinical trials.

This again is a time-consuming processes.

5.7 ISSUES/EXPERIENCES COMPANIES REGARDING REIMBURSEMENT

5.7.1 DISCUSSIONS AT CENTRAL LEVEL

Thresholds/methodologies
- The current thresholds are developed for long term treatments where costs are made yearly. For ATMPs, in case of curative or long term effect, the threshold might be exceeded in the 1st year (year of treatment), however in every following year treatment costs might be nihil. Nevertheless thresholds are still applied to those ATMPs.
- To estimate the budget impact, ZiNL includes the prevalent patient population. In the first years, the budget impact might be higher due to a waiting list. More appropriate is to look at incidence for BI estimations. During negotiations it's good to distinguish these different groups of patients.

- Thresholds focus on costs of the administered drugs & treatment. In case of curative or long term effect there might be reasonable other long term healthcare savings. Since long term data is not available for these treatments, uncertainty in CE analysis will be reasonable. New methodologies are needed.
- ATMPs might require other assessment criteria (one-off treatment with long-lasting effect/ curation instead of life long treatment).
- Start early in process discussion with ZiNL to reassure understanding of treatment, study design, comparator/control arm, reporting (pre-treated patients who didn't receive modified product), study endpoints, study follow up, long lasting effects in relation to current methodologies (CE, GRADE etc.).
- Make use of the possibility for scientific advice. Although these questions will also be raised during the EMA approval process, ZiNL will address these again and may have different criteria or assessments from the EMA. Involvement of physicians in this process is crucial.
- Clinical trials with ATMPs are (mostly) single arm studies. Which doesn't fit the GRADE criteria.

Patient access/free of charge

- During the Lock procedure there's no reimbursement, and thus no patient access. For some ATMPs the unmet medical need is high and urgent. To create patient access MoH requests companies free of charge treatment. Especially for some ATMPs this seems not feasible if:
  - there's a reasonable pool of patients waiting for treatment with disease progression (that can theoretically be treated in a couple of months, during Lock procedure);
  - the administration of the ATMP requires hospitalisation and additional treatment costs. It's questionable whether direct to the ATMP related treatment costs (apheresis, transport, modification, administration) can be funded by the HCIs when the 'drug' is not yet reimbursed;
  - when not all required permits are in place (in case of ATMP with GMO) hospitals and MAH take a risk (liability and fines) treating patients.

Price

- The volumes negotiated in Central Arrangements will/can be based on national volumes (instead of own market share). Negotiated thresholds might form an issue when alternative products enter or have already entered the market.
- It's important to explore (with HQ) different alternative models, although it's noticed that MoH, HICs and hospitals prefer price volume deals currently.

Registries

- Registries are linked to ATMPs by almost all stakeholders, however interests might conflict. For that reason it's crucial to discuss with all relevant stakeholders (EMA, MoH, HCIs, Physicians and HQ) on purpose of the registry, registration items, costs and ownership. When a registry is suggested for re-assessment (conditional approval), make sure there's alignment on registered items, measurement, future changes in treatment paradigm, comparators, accountability for registration/obligation to register and final consequences.

5.7.2 DISCUSSIONS AFTER NATIONAL REIMBURSEMENT

Add on/DRG

- An ATMP will likely not only require an add-on for the medicinal product itself, but also one or more specific DRGs with a treatment description that is tailored to the actual ATMP treatment process, e.g. from obtaining the body materials, processing these materials, and the actual treatment itself. The current procedure is not designed for the complex types of ATMPs and probably need adjustments. A new DRG application can start when the ATMP is reimbursed. During the implementation of a new DRG hospitals can't invoice these costs, unless parties agree to use temporary another DRG. This alignment takes time.
- Some ATMPs may not eligible for an add-on code if they consist of a centralized treatment outside of the Netherlands (because these products will not have a 'Z-index number' which is a requirement for the add-on). For these products a different code need to be designed.

Permits & licences

- For use in commercial setting new permits and contracts are required. (hospital, but also the MAH). For products/treatments in commercial phase, there's no clear process nor coordination. For MAH it seems difficult to contact authorities and get guidance.
- Examples: for permit (tissue-bank '*weefsel-instelling'*) MAH has submitted documents at MoH Farmatec. First assessment (completeness of documentation) is received by MAH several months later. Questions (regarding content) are referred to IGJ (which is referring to general website).
- Pre-meetings or consultations are not foreseen. There's no single point of contact (case manager).
- Lack of clarity regarding requirements, permits and accountability for ATMP with GMO in commercial setting caused at least 4-6 months of delay. Examples:
    - procurement-contract with involved parties (hospital, lab. distributors) are agreed with HQ of MAH. Is the local organisation still obliged to have special permits as well?;
    - IGJ => Local office is accountable for complete process, so permit tissue-bank (*weefsel-instelling)* is required. It seems the Netherlands have an unique position in this. Unclear whether these permits are required for hospital under HE? Starting treatment without the required permits can cause high liability risks and fines;
    - what are the GMP requirements for treating centres when MAH has permit tissue-bank?;
    - what are the GMP requirements for treating centres when they outsource storage/ modification (freeze) and final preparation to cell-lab.?
- Accountabilities for all parties are defined in contracts. However:
    - normally MAH contracts hospital pharmacist regarding accept/storage/release and hospital pharmacists will be trained (RMP, safety etc.). MAH use National BIG-registry to make sure relevant pharmacists are trained.

However ATMPs are mostly not stored in hospital pharmacy, but in cell-lab. There's no national registry of lab. analysts. Is contract with cell-lab. sufficient to make sure all relevant analysts are trained?

- When new indication/dosage is investigated new permits are required.

5.7.3 DISCUSSIONS AT LOCAL LEVEL

Reimbursement by HCIs

- For ATMPs with a relatively small budget impact (BI < 10 million per year) and cost per patient below the threshold, an assessment may not be not required by ZiNL. If ZiN does not perform an assessment, HCIs and hospitals will be responsible for appropriate use and cost-effective purchase of the product. It's up to HCIs to decide whether, and under which conditions, the products is reimbursed. Because of the novelty of ATMPs, HCIs might be reluctant and postpone reimbursement until there's a clear position in guidelines or an assessment report of ZiNL (HCIs may request an assessment as well). However frequency of guideline updates is highly variable and the assessment capacity of ZiNL is limited (assessments in outpatient GVS and Lock procedure are prioritised). This might cause a serious delay in reimbursement (and patient access). Start discussions with Physician Association, HCIs and relevant hospitals early in process.
- Pending the decision of a HCI the ATMP might not be reimbursed to the hospital. In case of a high unmet medical need physicians & patients might ask a free of charge solution. Make sure there's internal (HQ) alignment on how to handle in 'life threatening situations' during this period.

Price

- It's important to explore (with HQ) different alternative models, although it's noticed MoH, HICs and hospitals prefer price volume deals currently.
- The volumes negotiated in Decentral Arrangements will/can be based on national volumes (instead of own market share). Negotiated thresholds might form an issue when alternative products enter or have already entered the market.
- When alternative products are in market, there's a risk that even after successful price negotiations on national level (MoH), HCIs and/or hospitals start price negotiation. Make sure this is discussed with MoH and with HQ.

6 HOSPITAL EXEMPTION

6.1 LAW/REGULATIONS

Introduction

Following the entry into force and application of Regulation 1394/2007 on 30 December 2008, it became mandatory for advanced therapy medicinal products (ATMPs) to obtain a marketing authorisation (MA) through the centralised marketing authorisation application (MAA) procedure pursuant to Regulation 726/2004.

Further to the requirements set forth in Article 6 of Directive 2001/83, Article 40 of the Dutch Medicines Act (*Geneesmiddelenwet*; Gnw) prohibits having in stock, selling, distributing, supplying, importing and exporting medicinal products that do not have an MA for the Netherlands, either a MA for the entire EU (central MA) or a MA obtained from the Dutch Medicines Evaluation Board (national MA). This requirement is intended to fulfil the objectives which Directive 2001/83 and the Gnw seek to attain, namely, first, the protection of public health, and, second, the elimination of hindrances to trade in medicinal products between Member States.

In line with Directive 2001/83, the Gnw provides for some derogations from the general rule of the MA. The so-called 'hospital exemption' (HE) for an ATMP is one of those options. Implementation of the exemption for which it provides is conditional on fulfilment of a set of cumulative conditions.

Under Article 3(7) of Directive 2001/83, there is an exemption from a central MA for:

> 'Any advanced therapy medicinal product, as defined in Regulation (EC) No 1394/2007, which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.
>
> Manufacturing of these products shall be authorised by the competent authority of the Member State. Member States shall ensure that national traceability and pharmacovigilance requirements as well as the specific quality standards referred to in this paragraph are equivalent to those provided for at Community level in respect of advanced therapy medicinal products for which authorisation is required pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (…).'

Member States are required to implement this EU law requirement for the HE. The HE is implemented differently in EU Member States.

In the Netherlands, the HE was implemented by Article 40(3)(d) and Article 40(8) of the Gnw, and currently reads as follows:

> '3. Een verbod als bedoeld in het eerste of tweede lid is niet van toepassing:
>
> (…)
>
> d. op geneesmiddelen voor geavanceerde therapie die met toestemming van de Inspectie gezondheidszorg en jeugd worden bereid volgens een recept voor een op bestelling gemaakt geneesmiddel dat voor een bepaalde patiënt op niet routinematige basis volgens specifieke kwaliteitsnormen en binnen dezelfde lidstaat in een ziekenhuis wordt gebruikt onder de exclusieve professionele verantwoordelijkheid van een arts;
>
> (…)
>
> 8. De Inspectie gezondheidszorg en jeugd ziet erop toe dat bij de bereiding van een geneesmiddel voor geavanceerde therapie als bedoeld in het derde lid, onder d, de eisen ter zake van de traceerbaarheid, de geneesmiddelenbewaking en de kwaliteit van het middel gelijkwaardig zijn aan die welke gelden voor de bereiding van geneesmiddelen voor geavanceerde therapieën waarvoor een vergunning voor het in de handel brengen is vereist op grond van verordening 726/2004.'

In summary, the HE only applies to ATMPs which are prepared on a on a non-routine basis and used in a hospital with a prescription and further to a Doctor's Declaration for an ATMP under HE for a specific patient. The manufacturing/preparation and use of an ATMP under HE requires a prior approval from the Dutch Health and Youth Care Inspectorate (IGJ). Approval will only be granted if the legal entity that is responsible for the manufacture of the ATMP, has submitted a completed application form for an ATMP under HE. Approval for HE can only be obtained for a limited number of patients and a limited period.

Operators who would like to prepare products which they believe may come within the HE are encouraged to seek advice at an early stage from the IGJ.

IGJ has provided some guidance on its website regarding its policy concerning the HE. However, at least some of this information was published in 2010/2011 and therefore may not be up-to-date. The information also does not seem to be fully in line with the IGJ's current practices or the Gnw. Furthermore, the guidance provided by the IGJ should not be taken as a complete or definitive statement of the law, which may only be given by the courts. Also, in so far as the guidance provided by the IGJ should be considered a policy rule, it should be noted that under Dutch administrative law, the IGJ has the inherent power to derogate from its policy rules. It is therefore recommended to contact the IGJ before applying for an HE.

Table 2 Legal terminology and definitions

Legal terminology	Legal definition	Comments
'Advanced therapy medicinal product'	Article 1(1)(b.1) Gnw: a medicinal product within the meaning of Article 2 of Regulation 1394/2007.	In summary: gene therapy medicinal products, somatic cell therapy medicinal products, tissue-engineered products as well as combined ATMPs. Note: according to the IGJ's Q&A about the HE (2010), it is possible to ask the IGJ to review if a certain product or therapy is an ATMP. A manufacturer can also choose to submit this question to the Committee for advanced therapy medicinal products (CAT) of the European Medicines Agency (EMA).

Legal terminology	Legal definition	Comments
'Non-routine'	Not defined in Regulation 1394/2007, Directive 2001/83 or the Gnw. IGJ Q&A about the HE (2010): the IGJ's provisional position is that the following types of ATMP are considered 'non-routine': • ATMP prepared form autologous cells; • ATMP prepared from allogenic cells but specifically for one patient; • ATMP prepared on a small scale.	Note: it seems that the IGJ's provisional position applies regardless of: • the patient population and the number of patients affected by the disease; • the availability of treatments available within the context of a clinical trial, compassionate use program or MA (is there an unmet medical need?); • the scale and regularity/frequency of the preparation of the specific product; • the manufacturing process and the user/owner of the method or any machine that is used to manufacture the ATMP. The use of such a method or machine does not seem to conflict with the 'non-routine' requirement for HE.
'According to specific quality standards'	Not defined in Regulation 1394/2007, Directive 2001/83 or the Gnw.	Because these standards are not defined in the EU or Dutch rules, this leaves room for interpretation.
'Custom-made product'	Not defined in Regulation 1394/2007, Directive 2001/83 or the Gnw. IGJ website: 'custom-made' means that the product is: • prepared on the basis of an order and • on prescription. The order is demonstrated by means of a Doctor's Declaration for an ATMP HE ('Artsenverklaring voor een ATMP hospital exemption').	According to its website, the IGJ defines 'custom-made' in quantitative terms. The IGJ considers a preparation made for max. 5 patients as 'custom-made' for a specific patient. However, according to other statements on the IGJ website, approval can be granted for a preparation made for max. 10 treatments, for max. 1 year. The LUMC report states that that an HE can be obtained either for the treatment of max. 10 patients or for max. 1 year *(procedure 1)* or for the treatment of 50 patients for max. 1 year *(procedure 2)*

Legal terminology	Legal definition	Comments
'For an individual patient'	Not defined in Regulation 1394/2007, Directive 2001/83 or the Gnw.	Note: in light of the similar wording of the exemption for pharmacy preparations (*formula magistralis*) in Directive 2001/83 and by analogy with the judgment of the Court of Justice of the European Union (ECJ) in the Abcur case (Cases C-544/13 and C-545/13), it could be argued that this means that the prescription must be for a particular named patient who must be identified before the ATMP is prepared and it must be prepared specifically for that patient. Note: the Gnw does not rule out the possibility that the product is used in the hospital for a patient who only uses the hospital's services for the treatment with the ATMP, e.g. as 'relocated care' ('*ziekenhuisverplaatste zorg*'), and receives his/her main treatment in another hospital. In that case the patient will have a treatment contract with both the hospital where he/she receives his/her main treatment, as well as a treatment contract with the hospital where he/she treatment with the ATMP.
'Prepared (…) and used within the same Member State'	Not defined in Regulation 1394/2007, Directive 2001/83 or the Gnw. According to the information on the IGJ website, 'prepared (…) and used within the same Member State' means that the manufacturing/preparation step that makes the end product an ATMP (i.e. the substantial manipulation) has to take place in the Netherlands. An ATMP that is manufactured/ prepared in another EU Member State and which is not authorised, cannot benefit from the Dutch HE regime.	Note: relevant for import/export (see below). Note: the wording of the Gnw does not prevent providing treatment with an ATMP HE in the Netherlands to a patient who resides in another country/EU Member State but is treated in the Netherlands (cross-border healthcare). The Gnw also does not prevent a patient residing in the Netherlands receiving treatment in another country. Whether or not the care provided in the other country will be reimbursed, will have to be assessed under the Dutch reimbursement rules.
	Further to the Application Form for an ATMP Hospital Exemption, the actual manufacturing/preparation should be done by: • a manufacturer who is authorised to produce medicinal products in a place/ room falling within the scope of the manufacturing authorisation, or • in a hospital pharmacy.	Note: the authorisation/GMP-certificate of the manufacturer should also include the manufacturing operations for the proposed specific product type (e.g. gene therapy medicinal products, tissue engineered products).

Legal terminology	Legal definition	Comments
'In a hospital'	Not defined in Regulation 1394/2007, Directive 2001/83 or the Gnw.	Note: neither the Gnw nor other Dutch healthcare regulations provide a definition of 'hospital'. The category of 'institution for medical specialist care' within the meaning of the Dutch Care Institutions (Accreditation) Act (*Wet toelating zorginstellingen*; WTZi). It should be noted that this could also include healthcare institutions such as independent clinics (*zelfstandige klinieken*), that focus on a particular type of care.
'Under the exclusive professional responsibility of a medical practitioner'	Not defined in Regulation 1394/2007, Directive 2001/83 or the Gnw.	The IGJ requires a completed Doctor's Declaration for an ATMP Hospital Exemption (Annex 1 to the application form). Further to this template, the physician has to declare that: • his/her patient (pseudonymised) with the disease [X] would like to have the ATMP; • that the physician is aware of the fact that the product does not have a MA for the Netherlands, and therefore its efficacy, harmful effects and validity have not been reviewed, and that he has explicitly advised his/her patient(s) or his patient's legal representatives about this; • the physician bears full responsibility and accepts any risks related to the treatment of his/her patient with this product; • the physician will notify the IGJ of any adverse reactions (pseudonymised). Note: contrary to the Regular Doctor's Declaration for named patient use of an unauthorised medicinal product, the Doctor's Declaration for an ATMP Hospital Exemption does not refer to an 'unmet medical need'and does not include a statement about the lack of alternative treatments including under clinical trial schemes or MA.

Legal terminology	Legal definition	Comments
'Prescription'	'Medicinal Prescription' is defined in Article 1 point 19 of Directive 2001/83 as 'any medicinal prescription issued by a professional person qualified to do so'. Commission Implementing Directive 2012/52 laying down measures to facilitate the recognition of medical prescriptions issued in another Member State provides a non-exhaustive list of elements to be included in medical prescriptions. Article 1(1)(pp) Gnw provides a definition of prescription that includes the elements listed in the Annex to Directive 2012/52.	

6.2 PROCEDURE

The Hospital Exemption is granted by the IGJ.

Further to the Application Form for an ATMP Hospital Exemption the HE can only be applied for by the legal entity that is responsible for the actual preparation of the ATMP. This can either be the manufacturer (if the product is prepared by the manufacturer) or the hospital (if the product is prepared in a hospital).

Neither the Gnw nor other Dutch healthcare regulations provide a definition of 'hospital'. The category of 'institution for medical specialist care' within the meaning of the Dutch Care Institutions (*Accreditation*) Act (*Wet toelating zorginstellingen*; WTZi). It should be noted that this could also include healthcare institutions such as independent clinics (*zelfstandige klinieken*), that focus on a particular type of care.

The ATMP should be manufactured/prepared at a manufacturing site falling under a manufacturing authorisation or in the hospital pharmacy. The application should list the site(s)/location(s) where the products are prepared (manufacturer or hospital pharmacy) and where the patients will be treated, i.e.:

- the manufacturing site does not necessarily have to be the same as the site for patient treatment and
- there can be more than one site for patient treatment.

Pre-submission consultations with IGJ

The IGJ advises to conduct preliminary consultations with the IGJ before filing the application. Topics that will be discussed are:

- is an HE possible for this specific product?
- what information is required to apply for the HE for that product?

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.

Information required to apply for a HE

Applicants should complete an Application Form for an ATMP Hospital Exemption. For this, additional documentation with regard to the following, non-exhaustive points should be added:

- the Qualified Person (QP)/pharmacist;
- information regarding the patient(s), e.g. number of patients, age, immune status, concomitant medication. Application can be made for a group of patients. The IGJ does not require any information about the patient population in general or the number of patients affected by the disease.
- application should include a completed Doctor's Declaration for an ATMP Hospital Exemption (Annex 1 to the application form). Unmet medical need' (defined as no approved product available for the same indication and patient group in the Netherlands) is not a criterion. In contrast to a Regular Doctor's Declaration for named patient use of an unauthorised medicinal product, the Doctor's Declaration for an ATMP Hospital Exemption does not have to include a statement from the prescribing physician that there is no there is no authorised equivalent available on the Dutch market;
- documentation regarding the quality, manufacturing/preparation and safety;
- intended starting date of the preparation of the ATMPs;
- intended starting date of treatment;
- information regarding the site(s) (location/locations) where the products are prepared (manufacturer or hospital pharmacy) and where the patients will be treated;
- if applicable, copy of the scientific advice from EMA;
- if applicable, information regarding the marketing authorisation application ('MAA') (assessment report, and/or EMA opinion);
- if applicable, documentation regarding the certification of quality and non-clinical information by EMA;
- if applicable, CAT opinion;
- if applicable, scientific recommendation by CAT on the classification of ATMP;
- classification of the ATMP;
- a substantiation that the product is prepared on a non-routine basis;
- is the product prepared in accordance with a medical prescription for an individual patient: yes/no?
- if the product has been used in a clinical trial (CT), copies of the IB and IMPD, as well as details regarding the CT (EudraCT No, phase, number of patients, results);
- if it concerns gene therapy products, information regarding the viral vector gene therapy, plasmide, species of bacteria, etc.;
- if it concerns a somatic cell therapy medicinal product or a tissue engineered product, details regarding the type of therapy (autologous, allogenic), the cells;
- if it concerns a combination product, additional information regarding the combination;

- a detailed product dossier, including details regarding the manufacturing authorisation (if any), good manufacturing practice ('GMP'), the availability of monographs of the European Pharmacopoeia, cell bank systems, the manufacturing/preparation processes, starting materials, TSE/BSE (if starting materials of animal origin);
- detailed information regarding pharmacovigilance and the risk management plan (RMP);
- detailed information regarding the traceability system (data should be kept for a minimum of 30 years after the expiry date of the product).

The IGJ does not require an opinion from an ethics committee. Further to the application form, the IGJ does not require information about licensing and permit granting procedures for clinical gene therapy / genetically modified organisms ('GMOs'). However, if the ATMP itself or any materials used (e.g. a viral vector) can be considered a GMO, the GMO rules apply.

- According to the IGJ website, the IGJ reviews HE applications only once per month. All HE applications have to be filed with the IGJ at least 2 weeks before the review date. IGJ will inform the applicant about the outcome of the assessment within 2 weeks of the review date. Further to the Gnw, approval can be granted for ATMPs prepared for use by a specific patient. The Gnw does not provide any guidance or limits as regards scale, regularity/frequency of the preparation of a specific product. According to the IGJ website, approval can be granted for a preparation made for max. 10 treatments, for max. 1 year. However, the LUMC report (p. 22)[4] states that that an HE can be obtained for:
- the treatment of max. 10 patients or for max. 1 year (procedure 1) or
- the treatment of 50 patients for max. 1 year (procedure 2).

Renewal of the HE is possible for 1 year. The conditions are specified in the Application Form for an ATMP Hospital Exemption.

The application must refer to the previous HE and should include inter alia:
- a substantiation why renewal is necessary;
- a report on any previous HE authorisations, including information regarding the number of patients treated with the specific ATMP based on the HE, treatment results, pharmacovigilance/safety data.

The IGJ requires a report:
- after the approval period has expired, or the maximum number of treatments for which approval was obtained;
- when applying for a renewal of the HE;
- if the treatments have been stopped prematurely.

The report should include the following information:
- the number of patients treated with the ATMP based on the HE;
- any adverse reactions and unexpected results;
- any particulars that have occurred during the manufacturing/preparation of the ATMP.

4 P. Meij et al., *Advanced Therapy Medicinal Products (ATMPs) naar de reguliere klinische zorg. Knelpunten en Mogelijkheden*, 2016.

Note: it seems that the IGJ will not review:

- The patient population and the number of patients affected by the disease;
- The availability of treatments available within the context of a clinical trial, compassionate use program or MA (is there an unmet medical need?).

In contrast to a Regular Doctor's Declaration for named patient use of an unauthorised medicinal product, the Doctor's Declaration for an ATMP Hospital Exemption does not have to include a statement from the prescribing physician that there is no there is no authorised equivalent available on the Dutch market.

6.3 OTHER LICENSES

In addition, other licenses might be necessary for an HE.

Wet veiligheid en kwaliteit lichaamsmateriaal

The donation, procurement and testing of the cells and tissues used as starting materials have to be in accordance with the applicable rules concerning blood, tissues and cells (Directive 2002/98, as implemented in the Blood Provision Act (Wet inzake bloedvoorziening) or Directive 2004/23, as implemented in the Body Materials (Safety and Quality) Act (Wet veiligheid en kwaliteit lichaamsmateriaal)).

Although this is not clearly regulated in Dutch law, the Dutch rules and regulations regarding tissues, cells and blood should be applied in accordance with the EU Directives. For example, if it concerns a CAR-T product where T-cells are harvested from the patient's peripheral blood (apheresis), the donation, procurement and testing of cells used as starting materials for the ATMP have to comply with the Tissues & Cells Directive (cf. recital 7 of the preamble to Dir. 2004/23) and thus the Body Materials (Safety and Quality) Act. Note that under to the Body Materials (Safety and Quality) Act, the entity that receives the cells should operate on a non-profit basis.

For the purposes of compliance with these rules at each step of the process, it is advisable to carefully check for each individual step in the process which rules apply and which licenses are required (e.g. designation as a tissue establishment (TE), requirements re. personnel, quality system, SOPs, traceability), e.g.

- Collection of cells at hospital.
- Storage of cells/tissues.
- Release of cells to the ATMP manufacturer.
- Transport of cells from hospital to manufacturing site.

The designation as a tissue establishment can be obtained from the Dutch Ministry of Health. Designated tissue establishments are subject to:

- data retention requirements and traceability;
- specific requirements regarding data protection and confidentiality (in addition to the general data protection and confidentiality requirements under the Medical Treatment Contracts Act (+ informed consent) and the GDPR (+ explicit consent).

Special Medical Procedures Act
Next to Article 1(2) of the Designation of Special Medical Procedures Act Regulations (Regeling aanwijziging bijzondere medische verrichtingen) no license is required for cell transplants if (a) an MA applies for the cells that are used, or (b) it concerns an ATMP under HE, or (c) it concerns an approved compassionate use program. Further to the application form for an ATMP under HE, the IGJ does not require information about licensing and permit granting procedures for clinical gene therapy (GMO) or spatial planning.

GMO regulations
If the ATMP fulfils the GMO definition, the GMO regulations apply, regardless if it is an ATMP under MA or under HA, or an ATMP supplied under another exception regime.

6.4 LABELLING, PACKAGING

There are no specific labelling or packaging requirements. IGJ inspection reports suggest that the labelling requirements for investigational medicinal products (''IMPs') (GMP Annex 13. Articles 26-30) may apply by analogy.

6.5 MANUFACTURING AND DISTRIBUTION

Further to Article 40(8) Gnw and Article 3(7) of Directive 2001/83, the manufacturing of an ATMP under HE should be in accordance with the specific quality standards equivalent to those provided for at EU level in respect of ATMPs for which an MA is required pursuant to Regulation 726/2004.

Manufacturing by hospital
If the actual manufacturing process takes place outside of the premises of the hospital pharmacy, for example in the operating room or a hospital laboratory, the manufacture is subject to the holding of a manufacturing licence from the Minister for Medical Care. This means that the hospital will require a manufacturing licence/GMP certificate. Since it does not concern the manufacturing of an IMP, the hospital can probably not use its manufacturing licence for IMPs (if it has such a licence).

However, if the actual preparation takes place in the hospital pharmacy by or under the responsibility of the hospital pharmacist, and provided that these processes are carried out on a small scale, a manufacturing licence may not be required if the pharmacist exemption for pharmacy preparations applies (Article 18(5) Gnw).

Manufacturing by company
The manufacturing of the products is subject to the holding of a manufacturing licence from the Minister for Medical Care. The company will require a manufacturing licence/GMP certificate. Note that the manufacturing of the specific product should fall under the scope of the manufacturing licence; the application and the licence should list the specifications, manufacturing formulae and processing and packaging instructions, procedures and records covering the various

manufacturing operations performed for the types of products which an licence has been granted, e.g. gene therapy products. The licence applies only to the medicinal products and pharmaceutical forms specified in that same application (cf. Article 18(2) Gnw jo. Article 41 and 42 of Directive 2001/83).

Furthermore, the different production operations have to be carried out in accordance with pre-established instructions and procedures and in accordance with GMP. This also applies to 'specials' and 'compassionate use products' that are produced under a manufacturing authorisation, as well as for medicinal products prepared by a pharmacist for the patients of another pharmacy.

Specific quality standards that apply to ATMPs under HE have not been specified. The applicant for an ATMP under HE has to submit a completed Application Form for an ATMP Hospital Exemption, including additional documentation to enable a review by the IGJ of the quality, manufacturing and safety. For example, the applicant should indicate if the manufacturing falls within the scope of an existing manufacturing licence/GMP certificate, has to provide a detailed description of the manufacturing processes and should also specify any relevant monographs of the European Pharmacopoeia.

Starting materials

Further to Article 40(8) Gnw and Article 3(7) of Directive 2001/83, the manufacturing of an ATMP under HE should be in accordance with the specific quality standards equivalent to those provided for at EU level in respect of ATMPs for which an MA is required pursuant to Regulation 726/2004. Part IV, of Annex I to Directive 2001/83 specifically refers to Directive 2002/98 and the Tissues & Cells Directive as regards the donation, procurement and testing of the cells used as starting materials for the ATMP.

Blood components

If the starting materials are derived from blood components or plasma, the Directive 2002/98 standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components apply (as implemented in the Blood Provision Act (Wet inzake bloedvoorziening).

Tissues and cells

The donation, procurement and testing of tissues and cells including haematopoietic peripheral blood, umbilical-cord (blood) and bone-marrow stem cells, reproductive cells (eggs, sperm), foetal tissues and cells and adult and embryonic stem cells used as starting materials for the ATMP, fall within the scope of the Tissues & Cells Directive (cf. recital 7 of the preamble to Directive 2004/23). Although this is not clearly regulated in Dutch law, the Dutch rules and regulations regarding tissues, cells and blood should be applied in accordance with the EU Directives, meaning that the Body Materials (Safety and Quality) Act (Wet veiligheid en kwaliteit lichaamsmateriaal) applies.

Vector

If a vector is used and can be considered as an active substance used as starting material, an API registration is required, which can be obtained from the Ministry of Health's Farmatec division. If

the vector is considered to be a GMO, by the holder of a GMO permit and an environmental permit for GMO.

ATMPs under the HE can either be manufactured/prepared in one single centre (no transport) or produced in a network model where one manufacturing site supplies multiple hospitals. The Dutch rules and the IGJ policies seem flexible. Further to the Application Form for an ATMP Hospital Exemption the ATMP should be manufactured/prepared at a manufacturing site falling under a manufacturing authorisation *or* in the hospital pharmacy. The application should list the site(s) (location/locations) where the products are prepared (manufacturer or hospital pharmacy) and where the patients will be treated, i.e. the HE rules seem to allow that the manufacturing site is not the same as the site for patient treatment.

Distribution rules

The general rules regarding the distribution apply. The Gnw and the IGJ policies do not include any specific distribution, transport or sale requirements/restrictions for such products, in addition to the general GMP/GDP rules. Further to Article 18(1) Gnw, distribution of exempt ATMPs may only be carried out by the holder of a manufacturer's license who manufactured the products. Since an ATMP under HE is an unauthorised medicinal product, such products may not be distributed by the holder of a wholesale license. Certain requirements/restrictions may exist under the Dutch rules concerning GMOs.

Import and export of an ATMP under HE

In principle, an ATMP under HE may not be imported from or exported to another country. An ATMP under an HE has to be manufactured and used in the Netherlands and so can be neither imported from another country nor exported to another country. However, export is arguably possible if the ATMP is manufactured by a Netherlands-based company holding a manufacturing license from the Minister for Medical Care and the country of destination allows such imports. In that case, the company may be able to benefit from the exemptions provided by Articles 18(1) and 40(3)(h) Gnw, which allows the export of unauthorised medicinal products (including ATMPs) by a (licensed) manufacturer. Furthermore, based on the IGJ website, this means that the manufacturing/preparation step that makes the end product an ATMP (i.e. the substantial manipulation) has to take place in the Netherlands.

6.6 TREATMENT

Although an ATMP under HE cannot be exported from the Netherlands, it might be possible that patients travel to the Netherlands from other (European) countries to obtain a treatment with these ATMPs. The wording of the Gnw does not rule out cross-border healthcare, i.e. providing treatment with an ATMP under HE in the Netherlands to a patient who resides in another country/EU Member State but is treated in the Netherlands. We also note that EU citizens have the right to access healthcare in any EU country and to be reimbursed for care abroad by their home country. Directive 2011/24 on patients' rights in cross-border healthcare sets out the conditions under which a patient may travel to another EU country to receive medical care and reimbursement. It covers healthcare costs, as well as the prescription and delivery of medications and medical devices.

6.7 PHARMACOVIGILANCE, TRACEABILITY

The pharmacovigilance requirements for ATMP under HE are not the same as for ATMP under MA, but have to be equivalent to those requirements. In particular,

- Appointment of a QPPV.
- RMP: submission and implementation of a RMP, with details of the system in place to allow follow-up of the efficacy and to identify, characterize and minimize any risks related to the product. The plan should also include details on 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).
- PSUR: IGJ requires periodic reports including information regarding any (serious) adverse reactions and unexpected adverse reactions (including frequency), safety data analysis and information on the body that has reviewed this analysis.

Further to the Dutch rules and IGJ's policies, any suspected serious adverse events and reactions that may be attributed to cells have to be reported to the IGJ.

In addition, Dutch hospitals and tissue establishments use the notification system 'Transfusion and Transplantation Reactions in Patients' ('TRIP'). TRIP's mission is to receive and analyse 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.

Based on the information on the IGJ website, it seems that the vigilance rules apply in addition to the pharmacovigilance requirements.

The pharmacovigilance requirements for medicinal products supplied under the pharmacy preparation (*formula magistralis/officinalis*) and specials exception regimes are not the same as those for ATMP under HE. They are less stringent because there is no obligation to submit and implement a RMP or to file periodic reports (PSURs) to the IGJ. However, the pharmacovigilance requirements for preparation and supply of medicinal products prepared by a pharmacist for the patients of another pharmacy and compassionate use are as stringent (or even stricter) as those for ATMP under HE.

The traceability requirements for ATMP under HE are not the same as for ATMP under MA. They have to be equivalent to those requirements and have to be compatible with the traceability requirements under the Tissues & Cells Directive and the Blood Directive. In particular,

- Appointment of a person who is responsible for traceability.
- Traceability: a system for patient and product traceability with sufficient detail to enable traceability between each recipient of an ATMP, the ATMP (final product), the active substance and starting materials used in the manufacture for each individual ATMP (data should be kept for a minimum of 30 years after the expiry date of the product). The system has to be compatible with the traceability system required further to the Tissues and Cells Directive (Directive 2004/23).

The data retention requirements for ATMPs containing GMOs can be higher

6.8 TRANSPARENCY, DATA REPORTING

There is no obligation to systematically collate clinical efficacy and safety data under HE (e.g. in patient registries). The clinical data requirements are limited to the reporting obligations as described above. The IGJ requires a report:

- after the approval period has expired, or the maximum number of treatments for which approval was obtained;
- when applying for a renewal of the HE;
- if the treatments have been stopped prematurely.

The report should include the following information:

- the number of patients treated with the ATMP based on the HE;
- any adverse reactions and unexpected results;
- any particulars that have occurred during the manufacturing/preparation of the ATMP

Currently there is no public (national) database of HE. According to the RIVM report on ATMPs (2017), between 2010 – 2017, 11 applications for an ATMP under HE have been submitted to the IGJ. A renewal was requested for 6 ATMPs under HE. In total there have been 11 applications for a renewal (for some products more than once). The ATMPs under HE belonged to the following categories: 'autologe tumorcellen, lymfocyten, mesenchymale stamcellen, huidcellen, mononucleaire cellen, specifieke T-cellen en tumor-infiltrerende lymfocyten'.

Note: it may be possible to obtain certain information further to a request for access under the Dutch Government Information (Public Access) Act (Wob). It is still unclear whether IGJ will proactively disclose such information.

6.9 ADVERTISING

Since an ATMP under HE is an unauthorised medicinal product, it is not permitted to advertise any specific ATMPs made and used under the exemption. It may be permissible to advertise the service that is provided. Check with the IGJ or the Foundation for the Code for Pharmaceutical Advertising (CGR).

6.10 SANCTIONS AND PENALTIES

There is no specific sanctions regime for ATMPs under HE. The general regime of the Gnm applies.

6.11 REIMBURSEMENT

A distinction must be made between pricing, reimbursement and funding/tariffs.

Pricing
The Medicine Prices Act (Wet geneesmiddelenprijzen) only applies to authorised medicinal products, which means that there is no maximum pharmacy purchase price for an ATMP under HE.

Reimbursement, funding
There are no specific rules regarding the reimbursement of ATMPS under HE. Under the Dutch Healthcare Insurance Act (reimbursement) and the Health Care (Market Regulation) Act (financing of reimbursed care), ATMPs, including HE products, will likely be considered as 'medical specialist care' or hospital care.

The current system for the financing of intramural medicinal products (including ATMPs), in particular the add-on maximum tariffs (i.e. the hospital's legal basis for charging the product to the healthcare insurer), do not seem to be tailored for personalized medicine. ATMPs that are provided on the basis of the HE do not have a MA and thus they cannot qualify for an add-on maximum tariff from the Dutch Healthcare Authority (NZa).

Furthermore, the HTA procedures of the National Healthcare Institute (Zorginstituut Nederland) do not seem to be tailored for HTA of ATMPs. As per 2019, ATMPs under HE may be able to qualify for a subsidy under the new 'Subsidieregeling veelbelovende zorg'.

6.12 THE RELATIONSHIP BETWEEN HE AND OTHER EXEMPTION REGIMES

Next to the HE regime there are other exception regimes for medicines available, like 'compassionate use' or 'named patient sales' (Art. 5 Directive 2001/83), or pharmacy preparations (Art. 3(1) and (2) Directive 2001/83).

Article 5 Directive 2001/83 is implemented into Dutch law in Article 40(3)(c) Gnw. This scheme is also called the 'special needs' or 'named patient' regime (hereinafter: 'specials' regime). The term 'compassionate use' is generally reserved for compassionate use programmes within the meaning of Article 83 of Regulation 726/2004.

The Gnw does not explicitly exclude the application of the 'specials' regime to ATMPs. However, in practice, the IGJ department that handles applications under the named patient regime will forward the application for the preparation and supply of an ATMP to the IGJ department that handles HEs. Thus, in practice it should not be possible to use the named patient regime to circumvent, or instead of, the HE regime.

In the past, the IGJ has allowed the preparation and supply of an ATMP under the named patient regime, but this concerned a very exceptional case in which (i) the product was not available in

the Netherlands but could be prepared under the ATMP HE regime in another country and (ii) there was only one specific patient in the Netherlands. In that specific case, the product was prepared under the ATMP HE regime in the other country and was imported and supplied for that patient in the Netherlands under the Dutch named patient regime.

It is unclear if an ATMP under HE may benefit from an exception regime in addition to the HE. Generally, exceptions must be interpreted strictly, and the wording of Article 3(7) of Directive 2001/83 does not seem to allow such an interpretation. Moreover, Article 3(7) of the Directive was introduced by the ATMP Regulation which is a lex specialis in relation to Directive 2001/83. The only exception that may apply in addition to (but not instead of) the HE regime, is the exception of Article 3(1) or (2) Directive 2001/83, i.e. pharmacy preparations (formula magistralis/officinalis). However, this means that the products must be prepared 'in a pharmacy', 'in accordance with a medical prescription for an individual patient' (formula magistralis) or in accordance with the prescriptions of a pharmacopoeia (formula officinalis). Further to the implementing text of Article 18(5) and Article 40(3)(a) Gnw this also means that the products may only be prepared on 'a small scale', for the preparing pharmacist's own patient(s), and the products have to be directly supplied by or on behalf of the preparing pharmacist to his/her own patient(s).

Unmet medical need' (defined as no approved product available for the same indication and patient group in the Netherlands) is not a criterion. In contrast to a Regular Doctor's Declaration for named patient use of an unauthorised medicinal product, the Doctor's Declaration for an ATMP Hospital Exemption does not have to include a statement from the prescribing physician that there is no there is no authorised equivalent available on the Dutch market.

6.13 OTHER ISSUES

HE and clinical trials

Whether or not a study qualifies as 'research' or a 'clinical trial' within the meaning of the Wet medisch-wetenschappelijk onderzoek met mensen (WMO), does not depend on quantitative criteria (in principle, n=1 studies are also possible under the WMO), but will depend on whether (1) it concerns medical/scientific research, and (2) participants are subject to procedures or are required to follow rules of behavior, and/or as a clinical trial: within the meaning of the WMO (cf. the Directive 2001/20 definition).

HE in parallel to CT: The HE falls within the scope of the Gnw. A HE exemption cannot be used for the purposes of a CT. CTs with ATMPs, including the investigational products, have to be reviewed under the rules of the Medical Research (Human Subjects) Act (Wet medisch-wetenschappelijk onderzoek met mensen; WMO) and fall outside the scope of the Gnw. This means that the HE option cannot be used for the preparation of ATMPs that are used in a CT.

HE to replace CT: Further to IGJ's policy, in exceptional circumstances it is possible to have a CT and a HE in parallel for the same medicinal product if there is a need to treat certain patients with an ATMP outside of the scope of a CT. In principle, the HE cannot be used as an alternative to a CT.

HE and market authorisation

It is possible to get an HE if an ATMP has been or becomes authorised (MA) for the same or a different therapeutic indication. Based on the Gnw and the policies of the IGJ, the unavailability of an authorised therapeutic equivalent or therapeutic alternative is not a criterion for the granting of an HE. There is no legal obligation for the IGJ or the legal entity that has obtained the HE to inform the MA holder of the authorised product. Also, there is limited transparency on the use of exemption products; industry cannot obtain information on the number, type and indication of HE products in publicly accessible registries or other electronic databases.

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