REPORT OF THE RSNN EXPERT MEETING

HOW TO BRING ADVANCED THERAPY MEDICINAL PRODUCTS FROM BENCH TO BEDSIDE: THE LOCAL HOSPITAL EXEMPTION PROCEDURE VERSUS EMAS' CENTRALISED AUTHORISATION

On 10 March 2021, an RSNN expert meeting was held to discuss 'The route for Advanced Therapy Medicinal Products from bench to bedside: the local hospital exemption procedure versus the EMA centralised authorisation'. Advanced Therapy Medicinal Products (ATMPs) form a new group of drugs for somatic cell therapy, gene therapy and tissue engineering. Although ATMPs have only found their way into the clinic in recent years, this innovative group of drugs is considered to hold great promise for the development of future treatments. As a rule, a European marketing authorisation granted by the EMA is required before an ATMP treatment can be applied outside a research environment. An exception may be made in certain situations, such as the for the 'hospital exemption' procedure. What are the characteristics of these two procedures? Are both routes easy to follow for all involved product developers (e.g., universities and the industry)? Should both routes exist side by side or can a synergistic pathway be developed to reinforce the effect of both procedures? Twenty-seven experts with various affiliations were invited to discuss these and other questions pertaining to the current regulatory procedures for ATMPs. The invited participants brought together a wide spectrum of knowledge and experience and discussed freely in their personal capacity under the Chatham House Rule. The current report provides a summary of that discussion.

1. EUROPEAN MARKETING AUTHORISATION THROUGH THE CENTRALISED PROCEDURE

As a rule, ATMPs are authorised through the centralised procedure, whereby a market authorisation is valid in all member states that are party to the EMA system. During the assessment of the central market application for ATMPs, specific requirements for proven clinical effectiveness, safety and quality are applied (European Medicines Agency, 2021). The manufacturing and treatment standards require compliance with *Good Manufacturing Practice* (European Commission, 2021) and *Good Clinical Practice* guidelines (European Medicines Agency, 2016). In addition, an appropriate pharmacovigilance and risk-reduction strategy must be in place. These standards are the same as those for drugs not covered by the ATMP classification. Compliance with these standards is required to provide guarantees at the European level that the positive effects of an ATMP treatment outweigh the negative effects, taking into account any uncertainties.

ATMPs largely go through the regular assessment procedure, in line with other medical products (see Figure 1). The assessment is carried out by two different rapporteurs from different Member States who carry out the assessment independently of each other. The assessment of ATMPs differs from the regular assessment procedure in that the rapporteurs are members of the Committee for Advanced Therapies (CAT), and not the Committee for Medicinal Products for Human Use (CHMP). The CAT is a multidisciplinary team with specific expertise in ATMPs and other new scientific

developments in the field. The CAT rapporteurs are responsible for assessing the quality, safety, and efficacy of the ATMP and submit their findings to the CHMP for a final decision. Several assessment rounds of 60-80 days are conducted as part of the assessment process. Two to three rounds are sufficient for most products, but this can increase to five to six rounds in some cases. After each assessment round of up to 80 days, the two separate assessment reports from the first assessment round are shared with other agencies in Europe to provide the opportunity to comment within 40 days. These comments are incorporated into a single summary assessment report with a list of questions for the manufacturer (this may amount to 100-200 questions). When the manufacturer receives the assessment report, the regulatory clock stops for a period of two to three (and maximum six) months so they can answer the questions raised in the form of a preliminary response. The second assessment round starts from day 121 after this preliminary response has been delivered to the rapporteurs. From day 150 at the latest, the various Member States' comments on the responses are aggregated and a 'list of outstanding issues' is compiled within 30 days. After the second assessment procedure is completed on day 180, the clock is stopped again, and the manufacturer is given the opportunity to respond to the list of outstanding issues within one to two months. The procedure continues on day 181 after the second response from the manufacturer has been received. Once the list of outstanding issues has been satisfactorily answered, and if additional assessment rounds are not required, a final file is formed. The CAT adopts the preliminary report based on the final file, on which the CHMP will base its final conclusion. This procedure has been established to make the most of the CAT's expertise while ensuring that the same standard is applied to ATMPs as to regular medicinal products. If the risk-benefit balance is not assessed positively, the manufacturer has the right to provide a verbal explanation to refute this. The EMA submits an advice (opinion) to the European Commission on whether or not to grant the requested marketing authorisation. The European Commission ultimately decides whether the marketing authorisation will be granted.

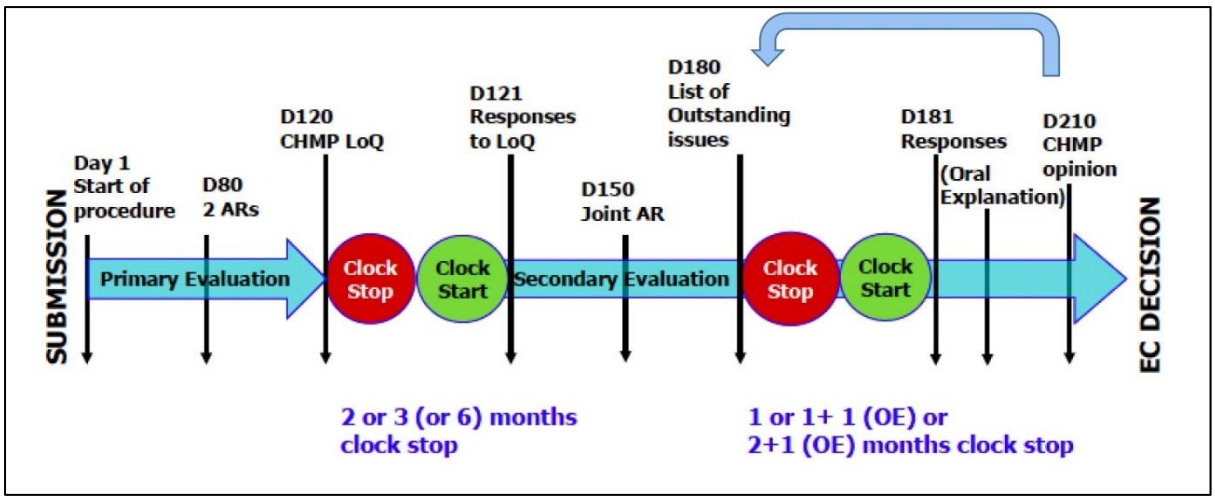

Figure 1: *Summary overview of the assessment procedure for a European marketing authorisation through the centralised EMA procedure.*

When an applicant submits a marketing authorisation application via the centralised EMA procedure, they do not have to consider products that have not yet been authorised (i.e., not covered by a European marketing authorisation). The CAT does consider whether alternative products were available when the main clinical trials started and may request a brief comparison with alternatives

that have recently come on the market. Applicants are advised to seek scientific advice from the CAT before and during the assessment procedure to increase the chance of success.

During the expert meeting, it was suggested that not all stakeholders have the same opportunities to follow such scientific advice (e.g., industry versus academia). From an academic perspective, for example, there may be a perception that the industry has access to more financial resources to carry out global, multi-centre studies in comparison with the academic world. However, from the perspective of the CAT, all parties have equal opportunities, and it is not relevant who submits an application, but only that the involved products are of sufficient quality to be granted a European marketing authorisation. During the expert meeting, various challenges were mentioned relating to the assessment of applications for marketing authorisations for ATMPs from the perspective of the CAT:

- The majority of the trials reviewed were conducted with a limited number of patients and were designed as single arm trials (no control group), which complicates the validation of the observed effect of an ATMP treatment.
- ATMP treatments hold out the promise of a long-term effect, but the exact duration of the effect is often unknown. This raises the question how long the period of follow-up should be to ensure effectiveness and safety.
- It is difficult to ascertain how changes in the production process translate into the effectiveness and safety of the final product. The products are produced in limited batch sizes, which provides a limited opportunity for testing.

In conclusion, the EMA's centralised procedure provides the opportunity to obtain a marketing authorisation for ATMPs in Europe. Although the procedure for obtaining this European marketing authorisation does offer commercial opportunities, it also requires that the effectiveness, safety, and quality of the ATMP is demonstrated to meet strict and documentable standards.

2. THE HOSPITAL EXEMPTION IN THE NETHERLANDS AND EUROPE

An exception to the requirement for a marketing authorisation for an ATMP may be made in certain situations (The European Parliament and the Council of the European Union, 2007). One of these is the 'hospital exemption' (HE), which assumes the application of an ATMP in non-routine use. The European regulations give the Member States some leeway to organise the regulation and use of the HE at a national level. This has led to strong differences in how national authorities grant applications for a HE licenses. In the Netherlands, the Healthcare and Youth Inspectorate (IGJ) assesses the preparation and use of products under the HE. Specific rules apply for the production, marketing authorisation, and pharmacovigilance of ATMPs which are supervised by the IGJ. The rationale behind the HE is to facilitate access to potentially beneficial treatments for patients with an unmet medical need. In the Netherlands, an ATMP may qualify for authorisation under the HE if it meets the following requirements:

- The product is used for an indication for which no alternative medicinal product with the same or similar efficacy is available (both registered products and clinical trials).
- The product is made for an individual patient.
- The product does not cause any harm to the patient. The manufacturer/preparer of the ATMP must have a system of pharmacovigilance and traceability in place. Side effects and adverse

events must be reported immediately (within 48 hours) to the IGJ. The applicant must also submit an annual report of side effects and adverse events to the IGJ, and again after termination of the treatment.

- The product is used on a non-routine basis for treatment.
- The product meets specific quality standards. The product must be prepared in accordance with the principles of Good Manufacturing Practice, as described in the GMP for ATMPs (Eurdralex, vol. 4, part IV), in a hospital pharmacy or by a pharmaceutical company.
- The product is both produced and administered in a hospital within the Netherlands.
- The product is used under the exclusive professional responsibility of a physician. A doctor's certificate for an ATMP HE must be provided to the manufacturer or the Board of Directors of the hospital that has obtained authorisation to produce, provide and use an ATMP HE.

It is important to note that the assessment of an application for an authorisation to prepare and use an ATMP under the HE does not include an assessment of clinical effectiveness. However, clinical experience is considered and information on the product specification must be provided. When an ATMP is authorised under a HE, this license is usually valid for one year and a maximum of ten patients. It is possible to apply for an extension of the treatment period or an increase in the number of patients. There is currently no guideline for the maximum number of extensions or expansions.

During the expert meeting, it was reported that eighteen applications for a HE licence were submitted by nine different applicants in the Netherlands between 2010 and 2019. Only one of these applications was submitted by a commercial party. Of the eighteen applications, the IGJ assessed fifteen positively and rejected two. One application was withdrawn by the applicant. In addition, eighteen applications were submitted to extend the treatment period of existing ATMPs for six different products. Of these, seventeen products received a positive response, and a few were granted several extensions. It is challenging for the IGJ to conduct a proper safety assessment, because these treatments are performed as a last resort for a small group of patients who suffer from conditions with high morbidity and a poor prognosis. The data reveal that the HE procedure plays an important role in the Netherlands in that it can offer patients with unmet medical needs a potentially beneficial treatment.

When comparing the intended use of the HE at the European level, we can conclude that the use of the HE in the Netherlands is in line with the original objective of this instrument (The European Parliament and the Council of the European Union, 2007). In the Netherlands, the HE is aimed at providing access for patients in exceptional situations based on the evidence of a preliminary risk-benefit analysis, in which safety is paramount and an unmet medical need plays a key role. Germany and Spain deviate from this and use the HE in a broader context, also deploying it to collect data as a first step towards obtaining a European marketing authorisation through centralised registration. These differences in HE interpretation between European countries go hand in hand with a strong variation in the scale of production. ATMPs are produced on a small scale In the Netherlands, in contrast with Germany for example, where ATMPs are produced under a HE license on a relatively large scale by private parties. Some countries choose to make the HE accessible only to public parties or hospitals (e.g., Spain and Italy). This is a way to reduce the risk of unfair competition between private parties from different EU countries.

ATMP REGULATORY ROADMAP

Centralised authorisation in Europe

Regulatory authority:
- Committee for Advanced Therapies (CAT) of the EMA

Main applicant:
- Pharmaceutical companies

Regulatory rational:
- Centralised marketing authorisation is required to ensure the quality, safety, and efficacy of ATMPs placed on the market in the EU. The evaluation of ATMPs often requires very specific expertise, which goes beyond the traditional pharmaceutical field. For this reason, the CAT is responsible for preparing a draft opinion on the quality, safety and efficacy of each ATMP for final approval by the CMPH.

Review procedure:
- Duration of 277 days (accelerated assessment of 217 days)
- Scientific advice provided by CAT recommended

Review requirements:
- ATMP classification according Article 17 of Regulation (EC) No 1394/2007
- Clinical efficacy
- Clinical safety
- Production quality
- Compliance with Good Clinical Practice, Good Laboratory Practice, and Good Manufacturing practice
- Pharmacovigilance and risk minimization plan
- ATMP has a favourable clinical effect over authorized treatments or clinical trials.

Regulatory outcome:
- ATMP production and administration is authorised in all European member states without limitations in the number of treated patients or duration of treatment.

Opportunities
- Authorised ATMPs can be administrated to a large, international patient population
- Commercially attractive
- Transparency of authorised ATMPs

Limitations
- Duration of review process
- High review requirements

Hospital exemption in the Netherlands

Regulatory authority:
- Health and Youth Care Inspectorate (IGJ)

Main applicant:
- Academic organisations

Regulatory rational:
- In exceptional situations, the HE-clause permits European member states to use specific ATMPs in their territories without the need for centralised marketing authorisation in order to facilitate treatment with a potentially beneficial product for a limited group of patients in unmet medical need.

Review procedure:
- Duration of 6 weeks
- Scientific advice provided by IGJ recommended

Review requirements:
- ATMP classification according Article 17 of Regulation (EC) No 1394/2007
- Clinical safety
- Production quality
- No authorized treatment or clinical trial is available.
- The administration of the ATMP takes place in a hospital setting on a non-routine basis for an individual patient.
- The administration as well as the stages of production which determine the classification as an ATMP all take place in the Netherlands
- *Not reviewed for clinical efficacy*

Regulatory outcome:
- Production and administration in a hospital setting is authorised, within the Netherlands, for a limited number of 10 patients with a maximum period for 1 year. Extension of the treatment duration and expansion of the number of treated patients can be requested.

Opportunities
- Innovative ATMPs without proven clinical efficacy can be used to provide a potentially beneficial treatment
- Relatively low review requirements

Limitations
- Licensed ATMPs can be administrated to a limited patient population for one year
- Commercially unattractive
- Lack of transparency of licensed ATMPs

Figure 2: *Summary overview of the centralised procedure and the hospital exemption that can be followed to provide patients with ATMP treatments.*

3. CAN THE HOSPITAL EXEMPTION BE DEPLOYED AS A GROWTH PATHWAY TO CENTRALISED REGISTRATION?

When the two regulatory procedures are placed side-by-side (see Figure 2), it is notable that, in the Netherlands, the use of an ATMP treatment under the HE does not stand in the way of a European marketing authorisation (or vice versa). On the contrary, the HE procedure can be instrumental in an early phase to enable drug development and provide patients with earlier access to treatments, outside the context of a clinical trial. The HE procedure in the Netherlands allows for treatment with innovative, academic ATMPs and offers a perspective to an exceptional group of patients where no alternative treatment methods are available. In order to obtain a European marketing authorisation via the centralised procedure, higher requirements are set for effectiveness and safety in consideration of a broader European population. An 'ATMP decision tree' has been drawn up to help ATMP developers choose when to apply for a European marketing authorisation or a HE (see Figure 3). In other European Member States, such as Germany and Spain, the HE procedure is also used as a growth path to bring academic ATMPs a step closer to an application for a centralised marketing authorisation. Is it desirable and feasible to deploy the HE procedure in the Netherlands in a similar way?

The experts present all agreed that the primary purpose of the HE in the Netherlands is to offer a potential treatment to patients with unmet medical needs. At the same time, it is recognised that the development potential of ATMPs is not fully exploited under the current regulatory framework, and so an international patient population is being denied access to promising ATMPs.

Research questions:

- Can the HE, currently intended as an exceptional treatment for patients with unmet medical needs, also be deployed in the Netherlands as a growth path for the development of promising ATMPs for the purposes of acquiring a European marketing authorisation?
- If the HE is also deployed as a growth path, how can the legislation and regulations in the Netherlands be changed to make academic ATMP treatments under a HE complementary to an application for a European marketing authorisation via the centralised authorisation procedure?
- In this context, what are the requirements for scientific evidence in order to obtain a marketing authorisation (and ultimately get the ATMP covered by health insurance)?

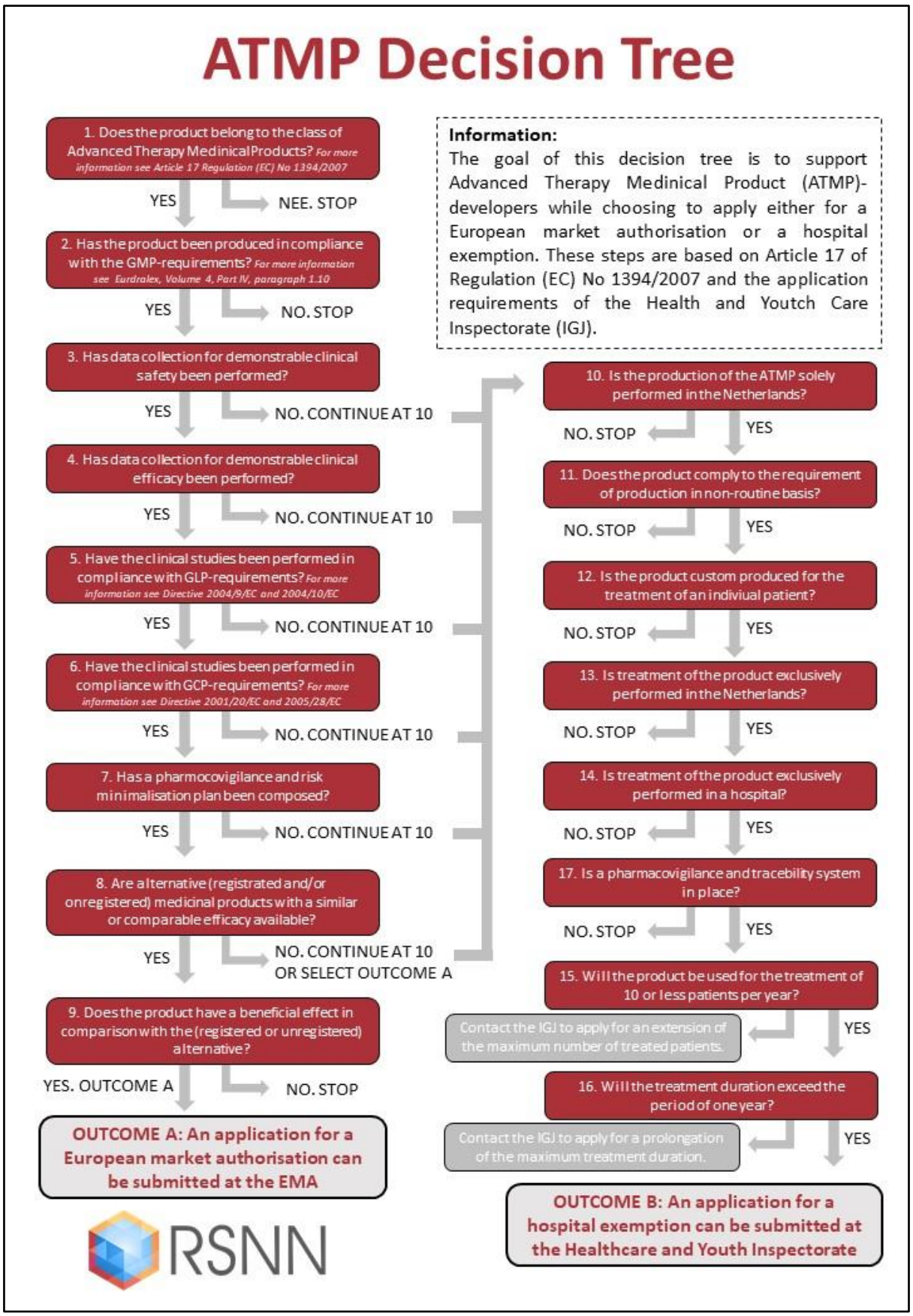

Figure 3: ATMP decision tree

4. IMPROVED TRANSPARENCY ENCOURAGES INTRADISCIPLINARY COOPERATION

In Europe, there are only limited possibilities for evaluating ATMP treatments performed under the HE and the corresponding motives. This lack of transparency limits our understanding of the development of ATMPs under the HE and makes it harder to identify bottlenecks to translate promising ATMPs into a marketing authorisation. Is this discontinuity caused by a lack of knowledge, or commercial incentive, or are the requirements imposed by legislation and regulations on the safety, efficacy, and effectiveness of ATMPs with a marketing authorisation? Is there a case of a knowledge hiatus? How will changing the regulatory requirements affect the reimbursement of ATMPs? The essential knowledge, expertise and patient groups for ATMP treatments under the HE are currently mainly found in the academic centres, the IGJ, and the Medicines Evaluation Board (MEB). The attendees of the expert meeting consider it of the utmost importance that this expertise will be widely shared in order to provide opportunities for other stakeholders to advance the development of products. Transparency of this information is crucial, among others to encourage public-private partnerships that can translate successful ATMPs into commercial applications. For example, industrial parties and regulators can provide support to academic ATMP developers with their commercialisation strategy and the clinical requirements necessary to successfully guide ATMPs used as exceptions through the centralised EMA procedure and obtain a European marketing authorisation.

The proposed strategy of early, interdisciplinary cooperation prior to a marketing authorisation process is not unique to this particular group of therapies. Regulators have implemented various regulatory procedures to provide new therapies to patients with high medical needs faster. Before obtaining a European marketing authorisation, patients are treated with various types of non-registered or off-label drugs, through rolling review procedures or via adaptive pathways. All these examples are intended to ensure that academia, pharmaceutical companies, and the regulator work together from an early stage.

Research questions:

- How do the regulatory requirements for ATMPs with a European marketing authorisation differ from the regulatory requirements for ATMPs with a HE?
- What information is available in the Netherlands about ATMPs under a HE? Are authorisations for ATMPs under a HE published? If not, why?
- How can the available information on ATMP treatments under a HE be made (inter)nationally available at an early stage to encourage interdisciplinary collaboration?
- How can market access be achieved once a marketing authorisation has been granted? Are the regulatory requirements for obtaining a European marketing authorisation in line with the requirements of funding bodies (such as governments and health insurers) in relation to health insurance reimbursements?
- How can this information be used to encourage public-private partnerships and complementary integration of the HE and centralised registration?

5. REGULATORY GAP BETWEEN THE HOSPITAL EXEMPTION AND CENTRALISED MARKETING AUTHORISATION

A limiting factor in the development pathway of ATMPs is the significant differences in assessment requirements between the HE and the centralised authorisation procedure. In contrast to the centralised registration procedure, an application for a HE is not assessed for demonstrable clinical effectiveness. It is the responsibility of the IGJ to ensure patient safety and production quality. For European marketing authorisations, a strong emphasis is placed on assessing the clinical effectiveness of the ATMP (in addition to ensuring safety and manufacturing quality). This raises the question of whether the HE procedure might also be suitable for collecting early data on the clinical effectiveness of ATMP treatments. Is it possible to implement requirements during this 'early stage' data collection so that the clinical effectiveness data could be used during a subsequent assessment for a centralised authorisation?

The requirements for obtaining a HE for the aspects assessed in both procedures, namely safety and production quality, are significantly lower than the standards for a European marketing authorisation. For academic ATMP developers, these high standards under the centralised market authorisation are sometimes difficult to meet. If the safety and manufacturing quality standards applied by the IGJ in the assessment of HE applications were raised to a similar level as the standards applied by the CAT (EMA), the gap between exemption treatments and centralised authorisation could be narrowed. Despite the small numbers of patients and limited batch sizes, the opportunities under the HE could be used to take academic ATMP treatments to the next level. Currently, the various academic centres in the Netherlands are each developing their own products with unique properties. Despite the fact that this group of ATMP drugs comprises a wide spectrum of therapies, there is significant overlap in specific elements of the design of certain subcategories of ATMPs. Nationally accepted and available designs of ATMPs (or parts of ATMPs) could be achieved by joining forces with the various academic centres in the Netherlands in cooperation with the IGJ and the MEB. For example, the development of a recombinant adeno-associated vector that has been assessed by the MEB as safe and of high quality has brought the academic development of gene therapies in the Netherlands a step further. The ATMP drugs group will need to be further specified in subcategories to be able to implement a nationally harmonised academic production process for ATMPs (or parts of ATMPs) with IGJ and MEB oversight.

Research questions:

- Can the quality requirements for safety, production, and effectiveness of ATMP treatments be raised to a higher level under the HE to narrow the gap with the standards applicable to assessments for centralised registration? If yes, can this be done without negatively affecting patient access?
- Can regulators (e.g., IGJ or MEB) be empowered to approve production designs of specific ATMPs (or parts of ATMPs) under a HE licence to enable more efficient assessments of future new ATMP treatments for new indications?

FOLLOW-UP ATMP EXPERT MEETING

This expert meeting has provided a clear overview of the existing regulatory pathways and associated requirements for providing patients with ATMP treatments. Given the relatively recent development

of ATMPs as a group of drugs, the regulatory framework for assessing their effective and safe use in the clinical setting is still under development. To ensure that current regulatory procedures can allow for the efficient regulation of future ATMP treatments, an adaptive regulatory system should now be developed. How can we support developers who want to further develop ATMP treatments for an exceptional group of patients into an application for a European marketing authorisation? The research questions identified during this first exploratory ATMP expert meeting will be further discussed in a follow-up ATMP expert meeting.