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Translation of academic medicinal products towards clinical practice

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Translation of Academic Medicinal Products towards Clinical Practice

Sofieke Pauline de Wilde

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Translation of Academic Medicinal Products towards Clinical Practice

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in 1988

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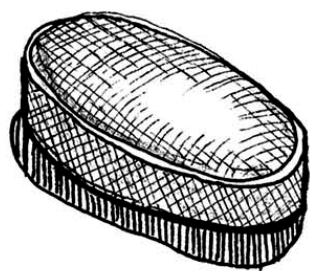
Voor pap & mam

Als ik zou willen dat je het begreep, had ik het wel beter uitgelegd

Johan Cruijff (1947 – 2016)

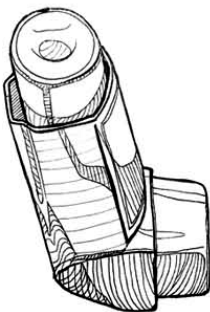
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CHAPTER 1

General introduction



Introduction

On a daily basis, a whole range of totally diverse patients present themselves to health care professionals. Health care practitioners endeavour to treat them all as adequately as possible. Although the majority of the patients can be treated by regular care, often including conventional, licensed medicinal products, regrettably not all patients can be sufficiently treated with the licensed medicinal products currently available[1]. Medicinal products developed and manufactured in academic institutions, including tailor-made pharmaceutical products, can help fill the needs of special (small) patient cohorts that, at present, have no available licensed treatments. Reaching these specific patients with academic medicinal products does most frequently not occur via the commercial licensing route. In this thesis, two groups of academic medicinal products and their implementation in regular clinical care are discussed: advanced therapy medicinal products (ATMPs, Part I) and unlicensed pharmaceutical preparations (Part II).

Part I - Advanced therapy medicinal products

ATMPs* are a relatively new group of medicinal products, where the preclinical and early clinical development most frequently originate in academic institutions[2]. ATMPs are considered as innovative and complex medicinal products that differ from conventional products in their characteristics and manufacturing. Since the special Regulation (EC) No. 1394/2007 came into force in 2009, a centralized regulatory framework for obtaining marketing authorization for these innovative products was established[3,4]. The Committee for Medicinal Products for Human Use (CHMP) is responsible for the evaluation of quality, safety and efficacy of all medicinal products within the centralized procedures[5]. However, due to its complexity, a new group of experts, the Committee for Advanced Therapies (CAT), has been installed by the European Medicines Agency (EMA) to support the CHMP[4]. After the scientific assessment evaluation of an ATMP by the CAT, the CHMP provides a recommendation for marketing authorization, followed by a final decision of the European Commission (EC)[3]. Increasing numbers of clinical trials with ATMPs have been performed globally and more and with increasing involvement of commercial companies in clinical development has been established[6], leading to nine ATMPs receiving marketing approval in Europe in 2017 (table 1)[2].

* ATMP is a European definition. Globally, various terms are used for these therapies. In different chapters of this thesis the both ATMPs and gene and cell based therapy products (GCTs) will be used.

Three subtypes of ATMPs are distinguished in Regulation (EC) No.1394/2007[4,7,8], see figure 1:

1. Gene Therapy Medicinal Products (GTMP)
2. Cell Therapy Medicinal Products (CTMP)
3. Tissue Engineered Products (TEP).

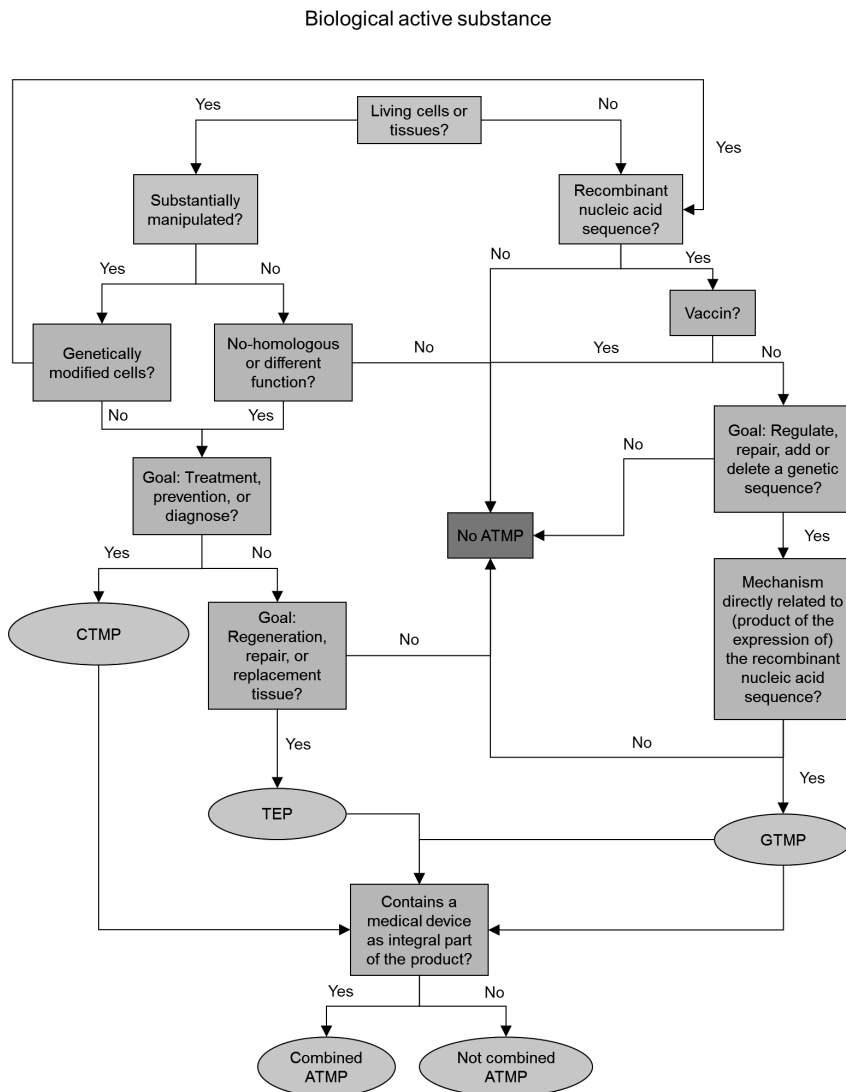


Figure 1. Schematic flowchart of ATMP classification. Adapted from the European Medicines Agency[8]. ATMP = advanced therapy medicinal product; CTMP = cell therapy medicinal product; GTMP = gene therapy medicinal product; TEP = tissue engineered product.

GTMPs are products that include genes for diagnostic, prophylactic or therapeutic purposes. Classification of a GTMP is based on two requirements: (1) the active ingredient should exist of a biological originated recombinant nucleic acid and (2) the nucleic acid should directly be responsible for the main mode of action, hence incorporating in a genetic sequence for the regulation, replacement, reparation, deletion or addition purposes. These nucleic acids are administered, after packaging in vectors or replicating micro-organisms, to the patient suffering from a disease, e.g. monogenic inherited diseases or oncology[8–10]. In case of direct administration of these vectors into the human body, it is classified as GTMP - *in vivo*[8], such as Imlygic®. Another possibility is that such cells, derived from either the patient (autologous) or from a donor (allogeneic), are transduced with the vector to alter their gene expression pattern, after which the cells are (re)administered to the body. This product will be classified as GTMP – *ex vivo*[8]. An example of a GTMP – *ex vivo*, which is elaborated in this thesis, is the Chimeric Antigen Receptor T-cell (CAR T-cell). In this type of product, a receptor for antigen recognition is introduced in T-cells, by which T-cells specifically can recognise and attack unwanted target cells. Both the GTMPs - *in vivo* and *ex vivo* are illustrated in figure 2.

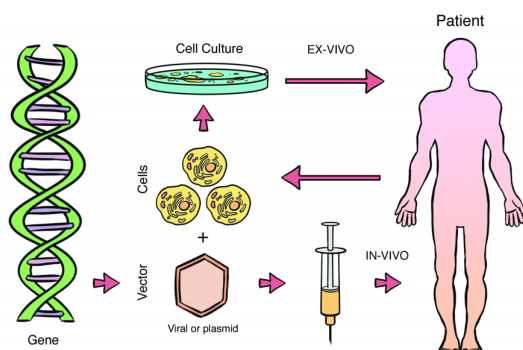


Figure 2. Illustration of gene therapy medicinal product (GTMP).

The second subtype is the CTMPs, consisting of substantially manipulated cells that are administered to the patient for diagnosis, prevention, or as a treatment, for example, Zalmoxis®. Substantial manipulation, such as cell culturing or differentiation with growth factors, is defined by the EMA as “during the manufacturing process the cells or tissue(s) have been manipulated so that their biological characteristics, physiological functions or structural properties have been modified to achieve their intended function”[8], see table 2 for a list of non-substantial manipulations[8]. Cell therapy products are also classified as CTMP when the cells receive a different function in the recipient compared to the original function (non-homologous use)[8,9].

For the manufacturing of CTMPs, both allogeneic or autologous cells are used. A basic summary of a CTMP production is shown in figure 3.

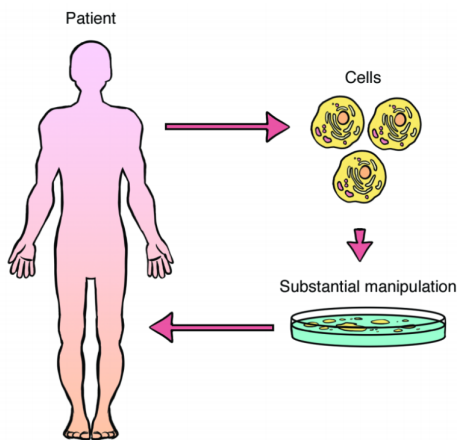


Figure 3. Illustration of cell therapy medicinal product (CTMP). Cells can be extracted from either the patient (autologous) or from a donor (allogeneic).

The third group is classified as TEPs. These cells are either substantially manipulated or received a non-homologous function, with the main purpose to regenerate, repair, or replace tissue, such as skin, for example Holoclar®[8,9]. A simple illustration of a TEP is shown in figure 4.

Finally, apart from these three subtypes of ATMPs, we can distinguish a group of so-called “combined ATMPs”, in which case ATMPs contain at least one medical device integrated into the product[8].

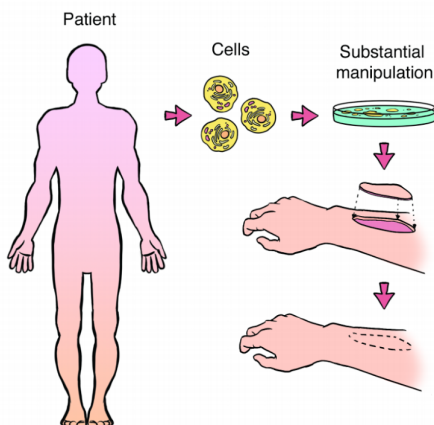


Figure 4. Illustration of tissue engineered product (TEP). Cells can be extracted from either the patient (autologous) or from a donor (allogeneic).

Table 1. ATMPs approved in Europe

Product Name	Classification	Characteristic	Therapeutic Indication	OD	Year MA	Authorization	Status MA
Chondrocelect®	TEP	Characterised viable autologous cartilage cells expanded <i>ex vivo</i> expressing specific markers	Repair of single symptomatic cartilage defects of the femoral condyle of the knee in adults	No	2009	SMA	Withdrawn by MAH for commercial reasons per 30th November 2016
Glybera®	GTMP – <i>in vivo</i>	Alipogene tiparovec	Treatment of adult patients with familial lipoprotein lipase deficiency with detectable levels of LPL protein and suffering from (multiple) severe pancreatitis attacks despite dietary fat restrictions	Yes	2012	MA UEC	No pursue for renewal of MA by the MAH in October 25, 2017
Provenge®	CTMP	Autologous peripheral blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage-colony-stimulating factor	Treatment of asymptomatic/minimally symptomatic metastatic (non-visceral) castrate resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated	No	2013	SMA	Withdrawn by MAH for commercial reasons in 2015
MACI®	TEP	Matrix-applied characterised autologous cultured chondrocytes	Repair of symptomatic cartilage defects of the knee in skeletally mature patients	No	2013	SMA	Suspended as the EU manufacturing site closed in 2014
Holoclar®	TEP	<i>Ex vivo</i> expanded autologous human corneal epithelial cells containing stem cells	Treatment of adult patients with moderate to severe limbal stem cell deficiency due to ocular burns	Yes	2015	CMA	-
Imlygic®	GTMP – <i>in vivo</i>	Talimogene laherparepvec	Treatment of adults with unresectable melanoma that is regionally or distantly metastatic	No	2015	SMA	-
Zalmoxis®	CTMP	Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human LINGFR and the HSV-TK Mut2	Adjunctive treatment in haploidentical HSCT of adult patients with high-risk haematological malignancies	Yes	2016	CMA	-
Strimvelis®	GTMP – <i>ex vivo</i>	Autologous CD34+ enriched cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	Treatment of ADA severe combined immunodeficiency in patients that do not have an HLA-matched related stem cells	Yes	2016	SMA	-
Spherox®	TEP	spheroids of human autologous matrix-associated chondrocytes	Repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (ICRS grade III or IV) with defect sizes up to 10 cm2 in adults.	No	2017	SMA	-

ADA = Adenosine deaminase; ATMP = Advanced Therapy Medicinal Product; CMA = Conditional Marketing Authorization; CTMP = Cell Therapy Medicinal Product; GTMP = Gene Therapy Medicinal Product; HLA = Human leukocyte antigen; HSCT = Hematopoietic Stem Cell transplant; HSV-TK = herpes simplex virus thymidine kinase; ICBS = International Cartilage Repair Society; LINGFR = low-affinity nerve growth factor receptor; LPL = lipoprotein lipase; MA = Marketing Authorization; MAH = marketing authorization holder; OD = orphan drug designation; SMA = Standard Marketing Authorization; TEP = Tissue Engineered Product; UEC = Under Exceptional Circumstances.

It can be challenging to gather comprehensive data on quality, safety and efficacy, considering that we are dealing with a novel and complex type of medicinal products. In clinical studies, this should be balanced with the fact that these products include personalized aspects and that they can be used for treatment of serious medical conditions, left untreated until now [11]. Authorities also recognise that performing a proper benefit/risk assessment can be challenging for these products[3]. The production of ATMPs differs from conventional products and faces less precise controls. Non-clinical animal models are not always required due to the differences between species and humans[11]. Furthermore, pharmacokinetic studies are not feasible, driven by the different mechanisms in the body compared to conventional products, such as the possibility that the product can be taken up by the body instead of being metabolised[11]. Finally, due to the special nature of product characteristics of these products, it is not always possible to follow the standard and required set of rules for clinical development. For example, due to use of autologous cells, it is not possible to use healthy volunteers in the exploratory phase I clinical trial[6]. But also the pivotal trial design, for retrieving comprehensive data for marketing approval, can be a small uncontrolled open label study for ATMPs instead of a preferred randomised controlled trial[6]. All such characteristics and challenges play an important role in the development of ATMPs towards marketing approval.

Table 2. List of non-substantial manipulation activities, as a tool for classification of ATMPs[8]

No substantial manipulation
Cell separation
Centrifugation
Concentration or purification
Cryopreservation
Cutting
Filtering
Freezing
Grinding
Irradiation
Lyophilisation
Shaping
Soaking in antibiotic or antimicrobial solutions
Sterilization
Vitrification

Literature shows that much clinical development with ATMPs takes place globally, of which only a few products have obtained marketing approval in the EU until now[2,12]. It is important to determine whether this is caused by the products being relatively new and thus in need of time, or whether the current system is not suitable for these ATMPs, leading to hurdles in the development procedure.

Knowledge on this will support understanding the yet limited number of licensed ATMPs and could help in the future to increase the number of approved products and thus to be able to treat more patients.

Part II - Unlicensed pharmaceutical preparations

Unlicensed pharmaceutical preparations, the second group of medicinal products discussed in this thesis, produced in (hospital) pharmacies are already used in regular patient care, in contrast to the innovative ATMPs[13]. As mentioned before, not all existing diseases can be treated by means of licensed medicinal products. For these patients, often suffering from orphan diseases (<5 patients per 10.000 people)[12], pharmaceutical preparations can be the solution. However, since these pharmaceutical preparations are unlicensed no formal independent product approval is in place. It is therefore important to discuss how patient safety can be guaranteed. Although academic institutions are often involved in development, they are not involved in obtaining marketing approval for these products. Whenever marketing approval is granted, commercial parties are involved and drug prices are very high. These high costs conflict with the relatively low prices of pharmaceutical preparations and may therefore lead to continued non-treatment of patients. Understanding pharmaceutical preparations including the safety requirements and proper documentation can facilitate these pharmaceutical preparations to the special patient cohorts in need.

An example of a pharmaceutical preparation used in regular clinical care is 3,4-diaminopyridine (3,4-DAP) for the treatment of the orphan autoimmune disease Lambert-Eaton Myasthenic Syndrome (LEMS). As there is no current curative treatment for LEMS, other therapy goals are pursued. 3,4-DAP is globally the most frequently used symptomatic treatment. It is an inhibitor of the voltage-gated potassium channels, which extends the presynaptic action potential, resulting in more open calcium channels. Finally, this leads to an increased calcium influx and subsequently in higher concentrations of acetylcholine release[14]. The drug has been developed in an academic setting and has been available as a pharmaceutical preparation for a long time. However, this product was taken up by industry which has led to a tremendous price increase after marketing approval, risking the non-treatment of patients since health care insurances are not willing to pay these higher costs.

General Aim

The ultimate goal of academic medicinal products is to provide treatment for all patients, also those whose medical needs have, thus far, not been met. These types of patients would strongly benefit from academic medicinal products whether these are licensed or not. The general aim of this thesis is to investigate how these academic medicinal products could eventually reach regular patient care. This will be explored by investigating the ATMP development field from hurdles experienced in early clinical development towards the decision-making by regulatory authorities of these products (Part I) and by describing how unlicensed pharmaceutical preparations should remain available in regular clinical care with guaranteed safety at an affordable price (Part II).

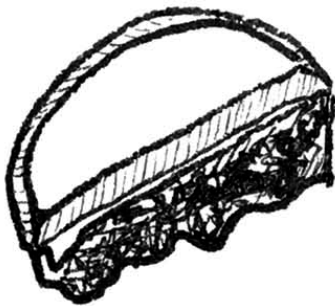
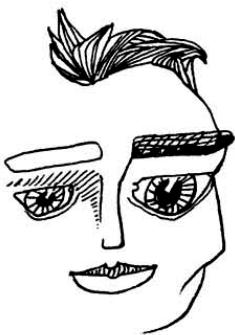
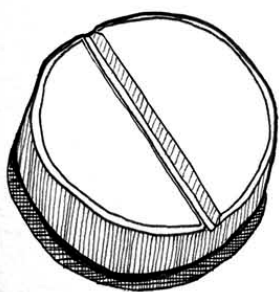
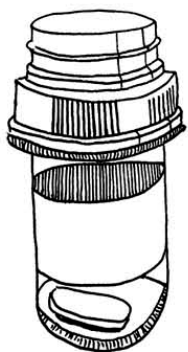
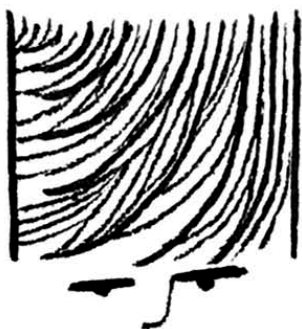
In the first part of this thesis, the focus is on the new innovative group of ATMPs. In **Chapter 2** a summary of the strengths of academic institutions during the development trajectory of ATMPs is discussed, with recommendations to improve this field. **Chapter 3** describes the hurdles which are experienced during the (early) clinical development of ATMPs in The Netherlands. An overview of clinical trials performed with ATMPs in Europe is presented in **Chapter 4**. In **Chapter 5** the focus lies on clinical development of the CAR T-cells. It was investigated whether the product and clinical trial characteristics differ for clinical trials progress to a subsequent phase or not, as a proxy for success in clinical development. Finally, in **Chapter 6** the decision-making of (non-)approved ATMPs in the EU is investigated. Variables and the interpretation of these variables by the regulatory authorities which led to (non-)approval of an ATMP are compared among the different approval decisions.

The second part of this thesis begins with an overview of the different types of pharmaceutical preparations in **Chapter 7**. It is discussed how safe use of these products should be ensured, based on pharmaceutical quality assurance and benefit/risk-assessment. In **Chapter 8** a case-study of an unlicensed pharmaceutical preparation, 3,4-DAP, is described. Here, available data of the unlicensed 3,4-DAP is compared with data available for marketing authorization approval of the licensed formulation, Firdapse®, to investigate whether the increased costs of the licensed formulation can be justified.

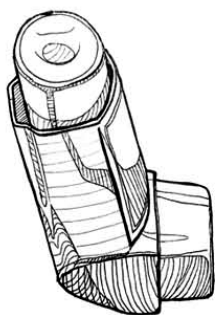
Finally, a general discussion of this thesis, including concluding remarks, is presented in **Chapter 9**, followed by an English and Dutch summary in **Chapter 10 & 11**, respectively.

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PART I - ADVANCED THERAPY MEDICINAL PRODUCTS



CHAPTER 2

Development of cell therapy medicinal products by academic institutes

Sofieke de Wilde, Henk-Jan Guchelaar, Carla Herberts, Mark Lowdell, Martin Hildebrandt, Maarten L. Zandvliet and Pauline Meij

Drug Discovery Today. 2016;21(8):1206-2012



Abstract

In the rapidly evolving fields of cellular immunotherapy, gene therapy and regenerative medicine, a wide range of promising cell therapy medicinal products are in clinical development. Most products originate from academic research and are explored in early exploratory clinical trials. However, the success rate toward approval for regular patient care is disappointingly low. In this paper, we define strengths and hurdles applying to the development of cell therapy medicinal products in academic institutes, and analyse why only a few promising cell therapies have reached late stage clinical development. Subsequently, we provide recommendations to stakeholders involved in development of cell therapies to exploit their potential clinical benefit.

Introduction

Increasing pathophysiological knowledge and technological advances should permit development of a variety of safe and effective innovative drugs. In particular, the field of cell and tissue therapies has been boosted by improved insights into immunology and disease biology, especially for regenerative and cancer medicines[1]. These therapies, particularly autologous ones, are technically challenging when compared with the manufacture of conventional pharmaceutical products but are akin to cell and organ transplant products making their development fit better with academic institutes than conventional manufacturers[2,3]. This explains why most cell therapy strategies originate from academic research groups across the EU and the USA. The development of these promising novel therapies results in high-impact scientific publication of preclinical and clinical data, but only very few cell therapies have obtained a marketing authorization (MA) (for regulatory background see Box 1)[4].

Box 1. Regulatory framework for cell therapies in the USA and Europe

In Europe cell therapies belong to the advanced therapy medicinal products (ATMPs), which are defined in EU regulation 1394/2007/EC, implemented on the 30th of December 2008. This implies that compliance with the full medicinal product regulatory framework is required. The ATMP regulation stipulates that an application for marketing authorization (MA) should be submitted by the centralized procedure at the European Medicines Agency (EMA). The Committee for Advanced Therapies (CAT) at the EMA is responsible for assessing the quality, safety and efficacy of ATMPs. The CAT is also responsible for ATMP classifications and involved in scientific advice procedures on development of ATMPs[5,31].

In the USA the MA of cell therapies, defined as cellular therapy products, is coordinated by the FDA's centre for Biologics Evaluation and Research (CBER) via Title 21 Part 1271, Human Cells, Tissues and Cellular And Tissue-Based Products (HCT/P), in the Code of Federal Regulations[32].

The EMA and the FDA have defined distinctive features that distinguish the cell therapies from other cellular products, falling under the Tissue and Cells Directive (2004/23/EC) in the EU and the HCT/Ps in the USA. Cells which have been subjected to substantial^a manipulation and/or cells which are used in a non-homologous fashion^a are defined as cell therapy (<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm427692.htm>).

^a The precise definitions 'non-homologous use' and 'substantial manipulation' are different for the USA and the EU.

Many cell therapies are in development for (ultra-)orphan indications[5,6]; possibly because of the disease-specific mode of action, and because most cell therapies are 'tailored' for each patient. Cell therapies have been thought to be of limited commercial value owing to the challenging logistics that are associated with personalized manufacturing. In addition, commercial developers are more cautious in committing to high risk products in early development[7]. Only in recent years, a series of breakthrough results have persuaded companies to invest in academic cell therapies toward commercial development (Box 2).

Box 2. Commercial agreements between academic institutes and commercial companies**Table 1.** Examples of successful cell therapy commercial agreements

Product	Characteristic ^a	Indication	Academic origin	Commercial agreement	Year of agreement
Holoclair	Human corneal epithelium	Severe cornea damage	University of Modena and Reggio Emilia	Holostem and Chiesi Farmaceutici	2008
CTL019	CAR-T	CLL	University of Pennsylvania	Novartis	2012
Multiple TCRs	TCR platform	Various tumours	Netherlands Cancer Institute	Kite Pharma	2015
GSK2696273	Lentiviral vector gene modified CD34+ cells	ADA-SCID	Ospedale San Raffaele, Fondazione Telethon	GSK	2015

^a All from autologous origin

Abbreviations: CTL= Cytotoxic T-Lymphocyte; CAR-T = Chimeric Antigen Receptor T-Cell; CLL = Chronic Lymphoblastic Leukemia; ADA-SCID = Adenosine Deaminase Deficiency – Severe Combined Immunodeficiency; GSK = GlaxoSmithKline.

<http://ir.kitepharma.com/releasedetail.cfm?releaseid=901985>; <http://www.pharmaworldmagazine.com/italy-leader-in-the-regenerative-medicine-field-with-holoclair/>; http://www.uphs.upenn.edu/news/News_Releases/2014/12/ctl019/; <https://www.gsk.com/en-gb/media/press-releases/2015/gsk-fondazione-telethon-and-ospedale-san-raffaele-announce-eu-regulatory-submission-for-gene-therapy-to-treat-rare-disease-ada-scid/>)

Example of a commercial agreement: CTL019 (http://www.uphs.upenn.edu/news/News_Releases/2014/12/ctl019/)

- 2011: breakthrough results published by the University of Pennsylvania
- 2012: global research and licensing agreement between the University of Pennsylvania and Novartis
- 2014: CTL019 receives FDA Breakthrough Therapy Designation

Agreement:

- Novartis receives a global license to the technologies for the specific patient group and CAR-based therapies
- Investment in future research of the technology by Novartis
- Additional payments to the University of Pennsylvania by Novartis
- Building and investment of ‘Center for Advanced Cellular Therapies’ (CACT) on the University of Pennsylvania campus, for T cell immunotherapies:
 - Discovery
 - Development
 - Manufacturing

Many of the academic cell therapies have been tested in multiple early-phase exploratory clinical trials, resulting in peer-reviewed publications[8]. However, in Europe 98% of clinical cell therapy trials have not contributed to development of licensed products yet[5]. Even successful early clinical trials were rarely followed up by well-designed (controlled) Phase II/ III trials[5]. Thus, although academic product development receives medical ethical clinical trial approval, the collected data are not sufficient to build a dossier for MA. A possible explanation could be that academic drug developers are driven by novelty which does not fit with the requirement for registration and generally requires confirmatory trials. Therefore, it seems that promising innovative cell therapies remain in early clinical development. Here, we discuss the strengths and hurdles of academic institutes in the development of innovative cell therapies and try to understand why only a few of the large number of cell therapies reach late-phase

development and even fewer have become standard patient care. Subsequently, we aim to provide recommendations to public stakeholders involved in development of cell therapies, to exploit their potential clinical benefit fully. The focus in this paper is on cell therapies in general, as defined by the EMA and FDA (Box 1). When more-specific subtypes are mentioned, this is to illustrate an example.

Cell therapies originate from academic research

The academic strengths can be identified by analysing why cell therapies mainly originate from academic research.

Academic strength: disease-specific expertise

As tertiary referral centres, academic institutes have an inherent focus on complex and orphan diseases. Specialized clinicians and scientists integrate best patient care with pathophysiological, fundamental and therapeutic research in multidisciplinary teams. Continuous collaboration, with active cross-disciplinary interactions, leads to understanding of the disease biology and direct translation of this knowledge toward new interventions[9–14]. This curiosity-driven research combined with access to patient cohorts and their clinical samples is a fruitful setting for creative design of innovative cell therapies[10,12].

Academic strength: access to human samples for research

Unlike commercial research teams, academic researchers have direct access to (orphan) patient-derived cell and tissue samples[4]. Biobanking of patient samples has become well organized and for many indications these collections are shared among academic centres at national and international levels. High-quality collections of patient samples are essential to start proper pathophysiological research, and generate in vitro and, if possible and when needed, in vivo disease models[14]. Furthermore, patient and donor samples can be used for the establishment of cell banks [e.g. induced pluripotent stem cells (iPS)] for diagnostic or therapeutic purposes.

Academic strength: access to human starting material

Even larger amounts of human cells or tissues are required to start translation toward clinical development. In most academic institutes, core facilities are operational for procurement, processing and storage of human cells and tissues to facilitate transplantation of hematopoietic stem cells and tissues[15]. These facilities are often suitable to supply the local cell therapy manufacturing facilities directly and to support the transport of human material to other academic institutes. Driven by promising preclinical data, many academic institutes have constructed cell therapy manufacturing facilities that are compliant with GMP guidelines over the past 15 years[3].

For autologous and allogeneic cell therapies, patient or (un)matched donor material procurement up to

product release and treatment can therefore be rapidly and efficiently organized within a single institute. By contrast, pharmaceutical companies frequently rely on centralized manufacturing facilities, often limited to only a few sites or even one site globally, which means shipment of the starting materials and released cell therapies. Cryopreservation or rapid logistics are required to preserve cellular viability and quality of the products. These challenging logistics have appeared to be a serious hurdle for companies[16].

Academic strength: clinical trial enrolment and follow-up

Because patients already receive medical treatment at academic institutes, efficient clinical trial recruitment, enrolment and compliance are well supported by dedicated research teams at clinical departments. For (ultra)-orphan diseases, relatively large patient cohorts are concentrated in specific academic institutes, which can efficiently be connected to other cohorts through existing regional or international collaborations, consortia and patient registries[17]. For clinical trials investigating safety, it is crucial to have an intensive and long-term patient follow-up. As (modified) living cells are administered, clinical and mechanistic monitoring of direct and long-term effects is needed and provides highly informative data regarding effects of in vivo differentiation, expansion and possible indirect effects through endogenous cellular systems. In academic institutes, these intensive follow-up regimens can be easily integrated with standard patient care visits and sampling performed by committed expert clinicians[10].

Cell therapies do not reach late-phase clinical development

To improve understanding about why only a few cell therapies reach standard patient care, hurdles restraining late-phase clinical development were analysed.

Academic hurdle: science-driven instead of product-driven

The system of academic research is mainly driven by scientific output in peer-reviewed publications[9,13,18,19], which is an effective driver of innovative design of new cell therapies. Although governmental and charity grant programs have pushed the translation of cell therapy strategies, these grants are mainly aimed at exploratory translational and clinical research[20], and have not supported late-phase clinical trials nor further product development such as optimization, standardization and quality improvements. Thus, so far academic institutes receive little stimulation to progress cell therapies further from exploratory studies toward standard patient care.

In contrast to the pharmaceutical industry, academic scientists are not used to designing their products for long-term goals, or to improving the product continuously. Target product profiles (TPP) are not

being drafted or even discussed by the academic research teams. The technology transfer offices (TTOs) mainly manage intellectual property, and not-for-profit business development[21], but do not have experience in the complex business model of medicinal product development.

Academic hurdle: lack of regulatory expertise

The current regulatory framework for cell therapies has only been established in the past decade, and increasing experience with cell therapies has improved the interpretation thereof by regulatory authorities such as the FDA and EMA[22]. Investment in GMP-compliant facilities has resulted in adequate quality management systems and cell therapy development expertise in academic institutes. However, academic product quality assurance aims for GMP and Investigational Medicinal Product Dossier (IMPD) compliance, and does not take into account the more detailed set of regulatory requirements that is expected for an MA application. As a consequence, successful academic-driven product development only has been achieved when partnering with (larger) pharmaceutical companies (Box 2)[6]. In the absence of academic staff with appropriate regulatory expertise, academic cell therapies cannot efficiently be transferred to (commercial) late-stage development[5,14,22].

Academic hurdle: limited funding

Early clinical trial development of cell therapies in academic institutes is supported by a variety of financial sources. Governmental programs enable establishment and utilization of high level infrastructure for academic research and development[23–25]. In addition, governmental funding, usually allocated by national grant funding agencies, is available to support specific projects. These governmental grants synergize with charities and philanthropy to drive innovative preclinical cell therapy research and translation effectively toward exploratory clinical research. However, because these grants are given for a limited timeframe, the continuity of financial support is hindered, but this is needed for persistent drug development.

That transfer to commercial development with for-profit investment can result in highly safe and effective cell therapies to be marketed (Box 2). However, only the commercially most attractive cell therapies will be transferred to commercial development (figure 1), and the majority of potential useful cell therapies for (ultra) orphan diseases might not become available at all, or only against pricing that is perceived as being excessive by society[26]. Unfortunately, funding of not-for-profit product development toward low-cost transfer to commercial entities or toward academic supply for standard patient care is rarely available.

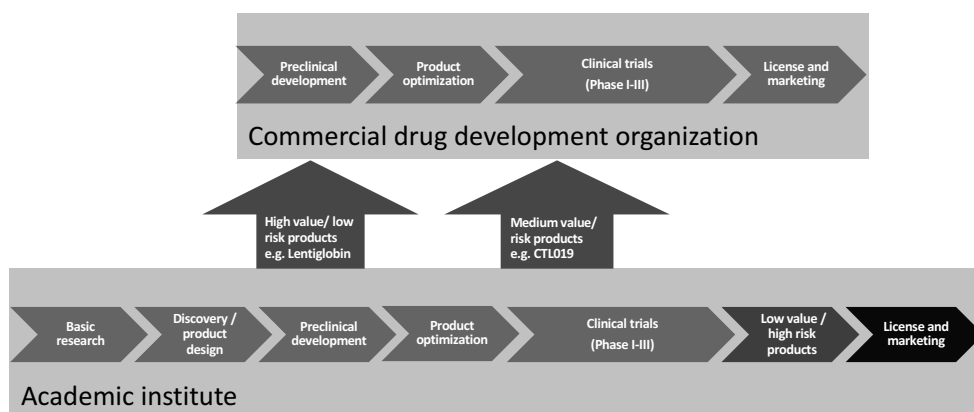


Figure 1. Cell therapy development originating from academic institutes. Cell therapies originating in academic institutes can be picked up by commercial companies or can stay in the academic setting. Cell therapies that have a potentially high commercial value, or include low-risk for a company, can be transferred during preclinical development. Cell therapies with a medium risk and with medium commercial value can be transferred after clinical proof-of-concept; whereas cell therapies with a low commercial value or with a high company risk will not be transferred and will remain in the academic institute, and be halted in further development.

Stakeholder recommendations to exploit the academic cell therapy potential

Figure 2 illustrates the discussed strengths and hurdles in the drug development trajectory for academic institutes. To improve the level of academic cell therapy development, we propose a set of recommendations for the specific stakeholders (summarized in figure 3).

Academic research groups: aim for the target product profile

A very straightforward and feasible recommendation for academic principal investigators leading cell therapy research would be to draft a TPP. Many academic researchers will see the TPP as something relevant only to commercial drug developers. However, putting patients at risk in a Phase I/II trial is only ethical if, in the event the trial was successful, this would be developed further so that the therapy is made available to standard patient care. The design of a TPP could be drafted most realistically and effectively with a broad multidisciplinary cell therapy development team within the institute. It should include sufficient details and provide a path for further product development[27], and be drafted with realistic timelines (<http://agora-gmp.org> provides a TPP outline). The TPP can be used to align priorities and financial planning over time, and facilitate communication with other stakeholders including regulatory authorities and potentially interested partners in development [<https://www.marsdd.com/wp-content/uploads/2011/02/Defining-Your-Target-Product-Profile-Therapeutics-WorkbookGuide.pdf>]. To integrate product development in the academic research setting

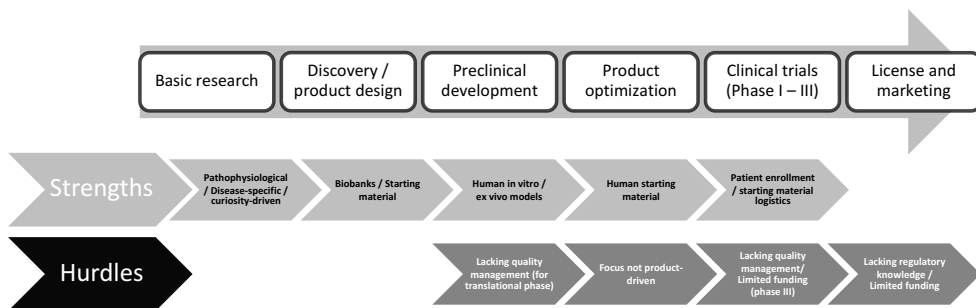


Figure 2. Available strengths and limitations in academic drug development. Academic institutes have strengths and hurdles in the development trajectory of cell therapies. Whereas the strengths are more available in the beginning of this development trajectory, the hurdles are increasing further in the development trajectory.

Academic institutes: establish central coordination of product development

In the complex organizational structure of academic institutes it might be helpful to support medicinal product development efficiently by a central coordinating body[10,12]. A strategic and product-independent advisory board could be key to shape the organization to become more suitable for product development, including investments in facilities, equipment and expertise, and to initiate collaborations with the proper partners[12]. Furthermore, this advisory board could stimulate the project teams to meet targeted milestones in scientific output and in building the product development dossier[10–12,27,28]. Besides scientific and pharmaceutical expertise, the regulatory, legal and business expertise should be sufficient to support the project teams during the development[12].

Importantly, besides the scientific output, additional success parameters should be defined and rewarded, including improvements in quality systems, product development milestones and funding or collaboration with appropriate partners.

Although academic institutes could hesitate to invest in product development instead of merely in scientific research, the cell therapies in early clinical trials could become much more attractive for transfer to commercial partners. Apart from the ethical reasons to develop better therapies, successful transfer of cell therapies toward commercial development might result in significant financial rewards (<http://ir.kitepharma.com/releasedetail.cfm?releaseid=901985>)[18], which can be directly invested for self-sustaining not-for-profit product development and manufacturing[3]. A successful example is the Canadian Centre for Commercialization of regenerative Medicine (CCRM).

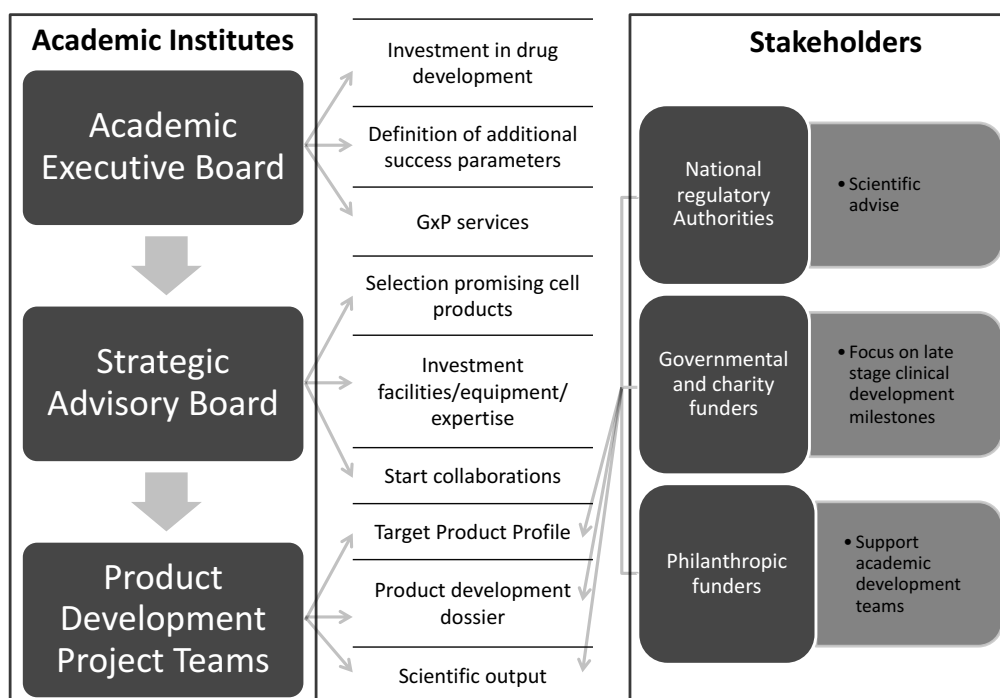


Figure 3. Organizational model for academic development of cell therapies. The actions in the central panel are proposed to improve the yield of cell therapies that reach standard patient care.

Academic institutes: provide regional GxP cell therapy services

To progress academic cell therapies further toward later stage development, it might be efficient to establish synergistic collaborations for GMP manufacturing and good distribution practice (GDP) supply among multiple academic institutes, and share facilities, equipment and expertise[29]. Collaborative investment could more efficiently increase the manufacturing and quality control and assurance capacities and might reduce the associated costs. An example of a huge collaborative effort on cell therapy development and GMP/GDP-compliant operations is the Cell Therapy Catapult in the UK. This initiative provides the possibility of academic research teams to connect with excellent GMP-compliant and GDP-compliant, but also regulatory-compliant, development and manufacturing teams, and is expected to boost the cell therapy field in the UK.

We think these recommendations provided are important to improve academic cell therapy development. Nevertheless, academic institutes should remain aware that their academic strengths are being maintained. Furthermore, it is important to realize that investments are needed to implement such recommendations. However, these investments are expected to return into more financial support (e.g. by more collaborations with commercial companies or more grants).

National regulatory authorities: provide scientific advice

The regulatory framework for cell therapy requires central application for MA in the USA and the EU and evaluation through the USA FDA Cellular, Tissue and Gene Therapies Advisory Committee, and the EU EMA Committee for Advanced Therapies. In the EU it is also possible to request scientific advice at a national level and several national regulatory agencies have opened this scientific advice possibility specifically for not-for-profit organizations. Early interaction with the regulatory authorities provides an excellent and accessible opportunity for academic cell therapy development teams to discuss their product dossier, and use the regulatory advice to direct further steps. Simultaneously, these scientific discussions increase the knowledge of the national regulatory agency experts on cell therapies, and will also contribute to discussions in central procedures. Funders: reward product development milestones and support specific academic programs

Currently, several governmental funders and charities, such as the EU H2020 program and the USA Cancer Research Institute, are exploring possibilities to aim for real patient benefit in standard care, by stimulating research teams to develop their research results toward successive stages of clinical development and synergize with commercial partners where appropriate [http://www.eusscience technology.eu/sites/default/files/SME%20opportunities%20in%20H2020_Feb2014_0.pdf]. Hopefully, these organizations will succeed to adapt their funding strategy and strengthen the not-for-profit development, manufacturing and supply of cell therapies.

In addition, philanthropic funders will be interested in contributing to not-for-profit development of specific innovative cell therapies. The open academic setting is suitable to enable close interactions between product development teams and philanthropic funders. Many principal investigators and cell therapy manufacturing teams, including ours, are open for visits. Furthermore, large numbers of citizens interested to support specific not-for-profit product development might be attracted by social media and online in crowdfunding campaigns[13,30]. Initial attempts resulted in relevant funding, and academic development of exciting new cell therapy modalities might be even more attractive[30]. It is important that all these different types of financial support are handled in well designed and fully transparent public entities under proper governance, because public funding is not for profit.

Concluding remarks

It is now well recognized that cell therapies have enormous potential in the fields of cancer immunotherapy, gene modified stem cell therapy and regenerative medicine. These cell therapies originate naturally in the academic setting because of their direct access to patients and donors. Unfortunately, the system of academic research has rarely driven development of promising cell therapy medicinal products to expensive late stage development and marketing application. However, we believe that academic institutes will be able to integrate their excellent translational research programs with a more pronounced focus on cell therapy development. With support of dedicated public funding and regulatory authorities, the yield of innovative cell therapies that eventually reach standard patient care is expected to increase over time.

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CHAPTER 3

Hurdles in clinical implementation of academic advanced therapy medicinal products: A national evaluation

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Abstract

Background. Since the implementation of the European Union (EU) regulation for advanced therapy medicinal products (ATMPs) in 2009, only six ATMPs achieved marketing authorization approval in the EU. Recognizing the major developments in the ATMP field, starting mostly in academic institutions, we investigated which hurdles were experienced in the whole pathway of ATMP development towards clinical care. **Methods.** Quality interviews were executed with different stakeholders in The Netherlands involved in the ATMP development field, e.g. academic research groups, national authorities and patient organizations. Based on the hurdles mentioned in the interviews, questionnaires were subsequently sent to the academic principal investigators (PIs) and ATMP good manufacturing practice (GMP) facility managers to quantify these hurdles. **Results.** Besides the familiar regulatory routes of marketing authorization (MA) and hospital exemption (HE), a part of the academic PIs perceived that ATMPs should become available by the Tissues and Cells Directive or did not anticipate on the next development steps towards implementation of their ATMP towards regular clinical care. The main hurdles identified were: inadequate financial support, rapidly evolving field, study-related problems, lacking regulatory knowledge, lack of collaborations and responsibility issues. **Discussion.** Creating an academic environment stimulating and planning ATMP development and licensing as well as investing in expanding the relevant regulatory knowledge in academic institutions seems a prerequisite to develop ATMPs from bench to patient.

Introduction

The field of cell therapy, gene therapy and tissue engineered medicinal products (CTMPs, GTMPs and TEPs) is innovative and evolving rapidly[1]. However, only 14 products have applied for marketing authorization (MA) in Europe, from which six have received MA approval[2]. Since 2009, the European Union regulation (EC) No. 1394/2007, specific for these so-called advanced therapy medicinal products (ATMPs) has in effect[3]. A Committee for Advanced Therapies was established by the European Medicines Agency (EMA) for ATMP classification, scientific advice procedures and evaluation of the MA applications[4–11]. Since then, 165 ATMP classification procedures have been performed, 172 Scientific Advices have been issued[2], and considerably more ATMP (pre)clinical trials have been performed[6]. On the basis of the numbers provided by the EMA, it seems that ATMP development toward MA application has a low success rate. Besides the standard EMA MA route, the ATMP regulation defines a second route to reach clinical care with ATMPs: the hospital exemption (HE) clause. Under the HE, ATMPs can be used for non-routine therapy, manufactured for an individual patient, within the same member state[12]. Although laid out in the EU regulation, the implementation of the HE clause by national authorities differs among individual member states [13].

In the Netherlands, ATMPs manufactured in compliance with Good Manufacturing Practice (GMP) may be eligible for HE therapy after evaluation of quality, safety and efficacy by the Dutch health care inspectorate[13]. HEs can be approved for 1 year and for either 10 or 50 batches[14,15]. Subsequently, it is possible to apply for an extension of the HE[15]. As many as 92 clinical trials and even more preclinical research projects with ATMPs have been performed in the Netherlands so far, and only one MA has been granted for alipogene tiparvovec (Glybera®)[16,17]. As of December 2015, applications for HE approval for 11 ATMPs had been submitted[15]. Again, these numbers imply that, also in the Netherlands, the success rate of ATMP development is low.

The aim of this national study was to identify hurdles to ATMP development for clinical care in the Netherlands. For this purpose, experiences by different stakeholders in the field were systematically analysed. We also investigated what stakeholders perceived brought their ATMP closer to use in regular clinical care after successful clinical trials have shown safety and efficacy.

Methods

Interviews

From grants provided between 2005 and 2013 by the Netherlands Organization of Health Research and Development (ZonMw) and the Dutch Cancer Society (DCS), ATMP projects were selected for interviews. Projects were independently classified as ATMPs according to ATMP regulation 1394/2007 by two authors (LVD and PM, researchers with >5-year experience in ATMP development and manufacturing). Projects aiming for at least a phase I clinical trial with an ATMP were selected. In the second and third quarters of 2014, qualitative interviews were conducted with the corresponding 29 academic principal investigators and project leaders (PIs), from 10 institutions. During the interviews, 45 ATMPs were discussed.

In addition to the PIs, other stakeholders were selected on the basis of their role in the path of ATMP development toward regular clinical care: authorities covering regulatory affairs, health technology assessment (HTA), health insurance or patient representation, ATMP GMP facility managers and small or medium sized enterprises. Qualitative interviews with these stakeholders were conducted in the first half of 2015.

To create an open interview setting, the interviews were not recorded. Objectivity was ensured by conducting the interviews with two or three of the authors in attendance (LVD, PM, and SdW). The documented interview summaries were conducted by LVD and reviewed by the other two authors (PM, SdW, or both). All answers were considered to be personal opinions from the individual persons interviewed, unrelated to the formal position of their employers or to the opinion of the authors who conducted the interviews.

The two key questions for all interviews, asked as open questions, were, for both the PIs and the other stakeholders: “How should an/your ATMP be implemented in regular clinical care after successful clinical phase I/II trials?” and “What are the main hurdles experienced during development and implementation of an ATMP?”

Questionnaires

The hurdles mentioned in the interviews were objectively documented and classified into sub-hurdles see Table 1. Subsequently, these hurdles were adopted in digital questionnaires to be able to further quantify the relevance of these hurdles for the academic PIs and the ATMP GMP facility managers, both directly involved in the development of ATMPs (see Supplementary Table S1). Each Dutch ATMP GMP facility was represented by one ATMP GMP facility manager.

The hurdles were graded with a scale from 0 to 5 with 0 meaning “we do not see a hurdle” and 5

meaning “it is a substantial hurdle.” The mean score per sub-classification of the hurdles was calculated and a cutoff score of 2.5 was used for identification of relevant hurdles.

The questionnaire was sent to 29 PIs: 26 PIs (90%) began the questionnaire, and 19 (66%) completed it. Only completed questionnaires were included for analysis. The questionnaire was also sent to eight ATMP GMP facility managers, of which seven were completed. GMP facilities were a subdivision of hospital pharmacy (n = 5), the hematology department (n = 1) and an independent unit (n = 1).

Table 1. Hurdles in ATMP development with sub-classification.

Hurdles	Subclassification
Financial support	Phase IV trials
	Phase III trials
	Marketing Authorization
	Phase I/II trials
	Reimbursement
	Employees training
Regulatory knowledge	Hospital Exemption (HE)
	Preclinical trials
	EMA Documentation
	Marketing Authorization
	Clinical trials and HE Documentation
Rapid evolving field	Drug development
	Intellectual Property (IP)
	Modify product
Study-related problems	New innovative treatments
	Starting materials
	Patient Recruitment
	Publication rate
Collaboration and responsibility	Control group
	Employees
	Other companies
	IP Responsibility
	Other departments

Results

ATMPs sub-classification and study phases

The different subtypes of ATMPs that were discussed during the interviews are shown in Figure 1A. The main group consisted of CTMPs/TEPs (71%). Within this group, personalized CTMPs/TEPs, generated from autologous or specific allogeneic cells, were the biggest group (66%). Twenty-nine percent of the discussed products were GTMPs, representing both in vivo as ex vivo gene therapy products. Figure 1B shows the study phase of the ATMPs at the time of conducting the interviews. Most ATMPs were either in the preclinical phase or in phase I and/or II (38% and 53%, respectively), 7% were in (preparation for) phase III, and one product obtained MA approval (2%).

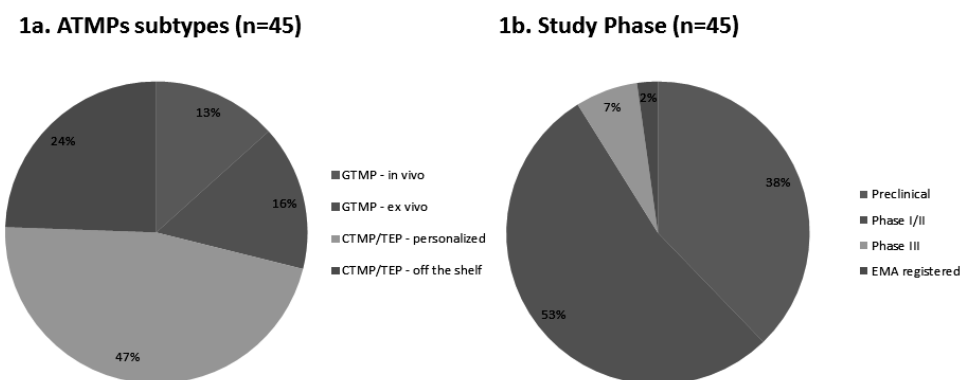


Figure 1. Overview of ATMPs discussed in interviews. (A) ATMP sub-classification: CTMP, cell therapy medicinal product; GTMP, gene therapy medicinal product; GTMP—ex vivo, genetic modification in target cells of the patients, manipulated outside of the body; GTMP—in vivo, introduction of therapeutic DNA directly into the body; TEP, tissue-engineered product. (B) Study phases of discussed ATMPs.

ATMPs toward clinical care

Of the interviewed PIs, 29% planned to reach clinical care via MA approval, 18% via HE and 8% via HE followed by MA approval. Furthermore, 26% of the PIs thought it would be possible to reach clinical care via the Tissues and Cells Directive and 19% did not yet have a future plan for implementation. PIs involved in the development of GTMPs saw more opportunities to obtain MA for their product (50%) compared with PIs involved in the development of CTMPs/TEPs (33%).

On the basis of the questionnaires, which were sent a year after the interviews, an increasing percentage of PIs intended to reach clinical care after successful safety and efficacy trials, via either MA (47%) or HE (20%) or first HE followed by MA (11%), as shown in Figure 2. The other 22% intended to reach clinical care via other routes: 4% thought that their product should reach the

patient via the Tissues and Cells Directive, 16% did not have a development plan for implementation yet and 2% did not consider implementation as a task for not-for-profit institutes.

The ATMP GMP facility managers and the other stakeholders mentioned both MA and HE as the only possible way to reach clinical care with ATMPs. According to the questionnaires, for all the ATMP GMP facility managers, HE was seen as the preferable way to reach clinical care, and for most of them (71%), HE could be followed by MA.

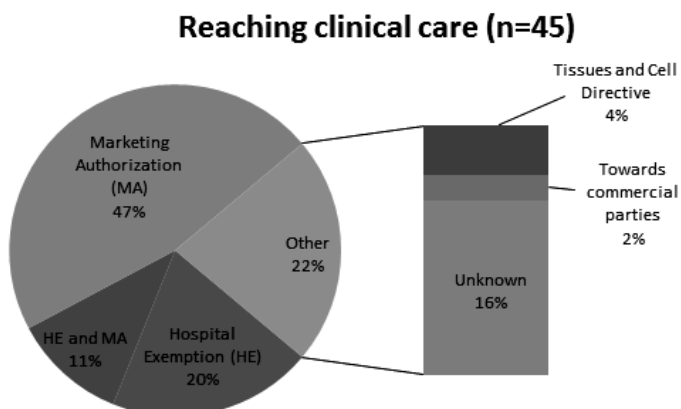


Figure 2. Route to clinical care according to the questionnaire results. Route according to respondent PIs on how they think that ATMPs should reach clinical care after safety and efficacy have been shown.

Hurdles in ATMP development

The following five categories were identified, based on the interviews, as main hurdles in ATMP development (percentage of all the interviewed PIs and other stakeholders): inadequate financial support (76%), rapidly evolving field (48%), study-related problems (48%), lacking regulatory knowledge (45%) and lack of collaborations and responsibility issues (28%). On the basis of data from the interviews, more specific hurdles were subdivided into these main categories of hurdles. For the PIs and the ATMP GMP facility managers, the scores for all subclassified hurdles are presented in Figures 3 and 4, respectively.

Inadequate financial support

The main hurdle identified in the PI group was inadequate financial support, which was also indicated as a major hurdle by the other stakeholders in the interviews. All interviewees obtained grants for their product development because the selection of the products for this study was based on grants provided by DCS and ZonMw. Other funding sources were companies (18%) and insurance

(4%). Difficulties in acquiring financial support for phase III and IV trials and for MA and reimbursement after HE approval are major hurdles for all groups (PIs: mean 4.6; ATMP GMP facility managers: mean 4.5). For the PIs, lack of financial support already formed a problem in the preclinical phase and ATMP GMP facility managers experienced this as a hurdle from the start of phase I/II trials. For both groups, acquiring financial support seems to be an increasing hurdle during later stages of development. During the interviews, all stakeholders mentioned that financial support is not an issue in obtaining HE approval. Most ATMP GMP facility managers also indicated on the questionnaires that financial support for HE approval is not a major hurdle (mean: 2.2), whereas the PIs did classify this as a hurdle (mean: 3.3). Inadequate financial support for HE mainly concerns the production costs and treatment reimbursement.

Other hurdles mentioned were the high manufacturing costs, expensive employee training and little flexibility by funding agencies to extend timelines, as experienced by PIs.

Regulatory knowledge

Both the PIs and the ATMP GMP facility managers indicated that regulatory knowledge to build the full product dossier toward obtaining an MA was lacking (mean: 3.4 vs 3.5, respectively). The knowledge and documentation needed to acquire a clinical trial authorization (CTA) was not experienced as a substantial hurdle by the ATMP GMP facility managers, whereas for the PIs, this was perceived as a more substantial hurdle (mean: 1.7 vs 3.2, respectively). Intellectual property (IP) management was not perceived as a major hurdle by either group. Furthermore, as mentioned by the authorities in the interviews, lacking knowledge concerning MA application could lead to PIs' underestimating how complicated the MA route may be.

A major portion of the questionnaire responders (72%) and the majority of the interviewed PIs thought it would be helpful if there were a knowledge platform to support the development route of ATMPs to share knowledge or obtain help from an expert during the various stages of the development process.

Rapidly evolving field

All groups (PIs, ATMP GMP facility managers and other stakeholders) mentioned that the ATMP field is innovative and dynamic, with new developments rapidly succeeding others. Therefore, PIs expressed difficulty in deciding to continue with one specific ATMP for an MA, perceiving that it was not possible to further modify the product in later stages of product development based on the most recent knowledge (mean score: 3.1). Authorities mentioned in the interviews that modifications on a product are possible during preclinical research and clinical trials, but researchers

Hurdles - Principal Investigators

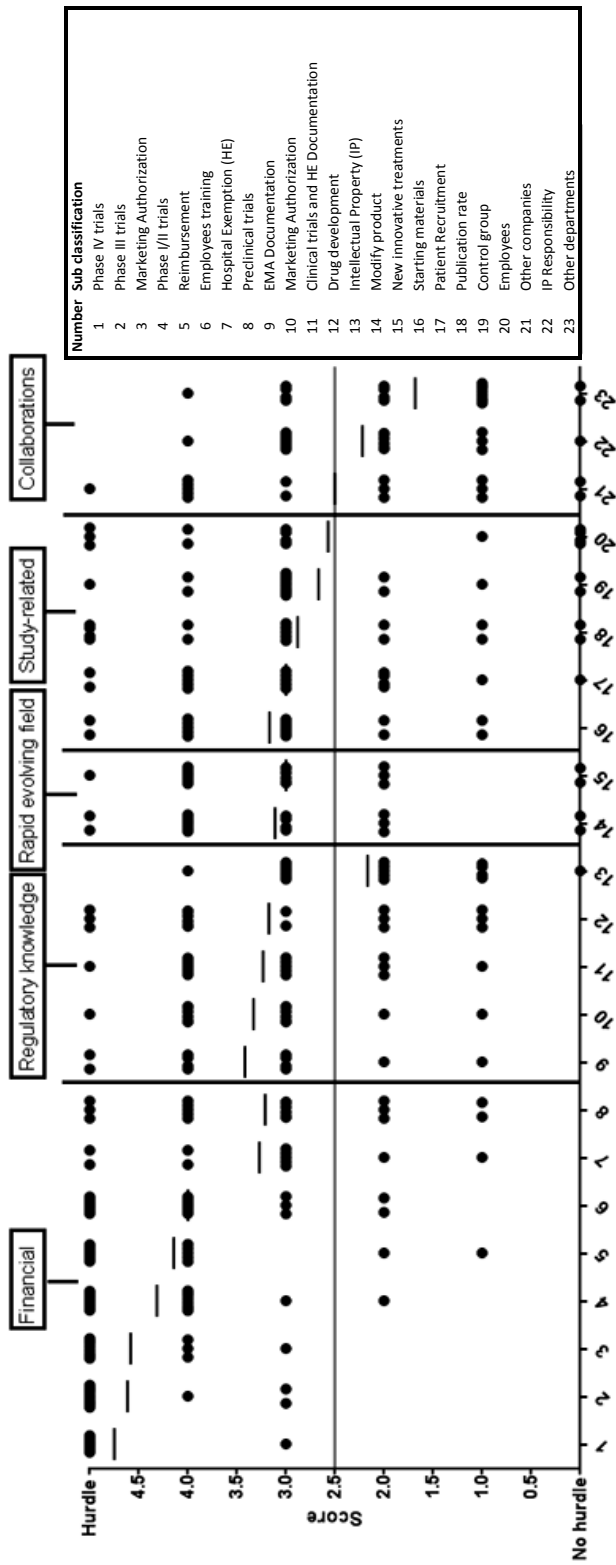


Figure 3. Hurdles in ATMP development scored by PIs and/or project leaders. The black points are the data points indicating whether the specific issue is experienced not as a hurdle (0) or as a substantial hurdle (5) by individual PIs and project leaders. The mean scores are shown by black dashes. The line at score 2.5 represents the cutoff value for identification of a relevant hurdle (above the line).

Hurdles - A TMP Good Manufacturing Practice facility managers

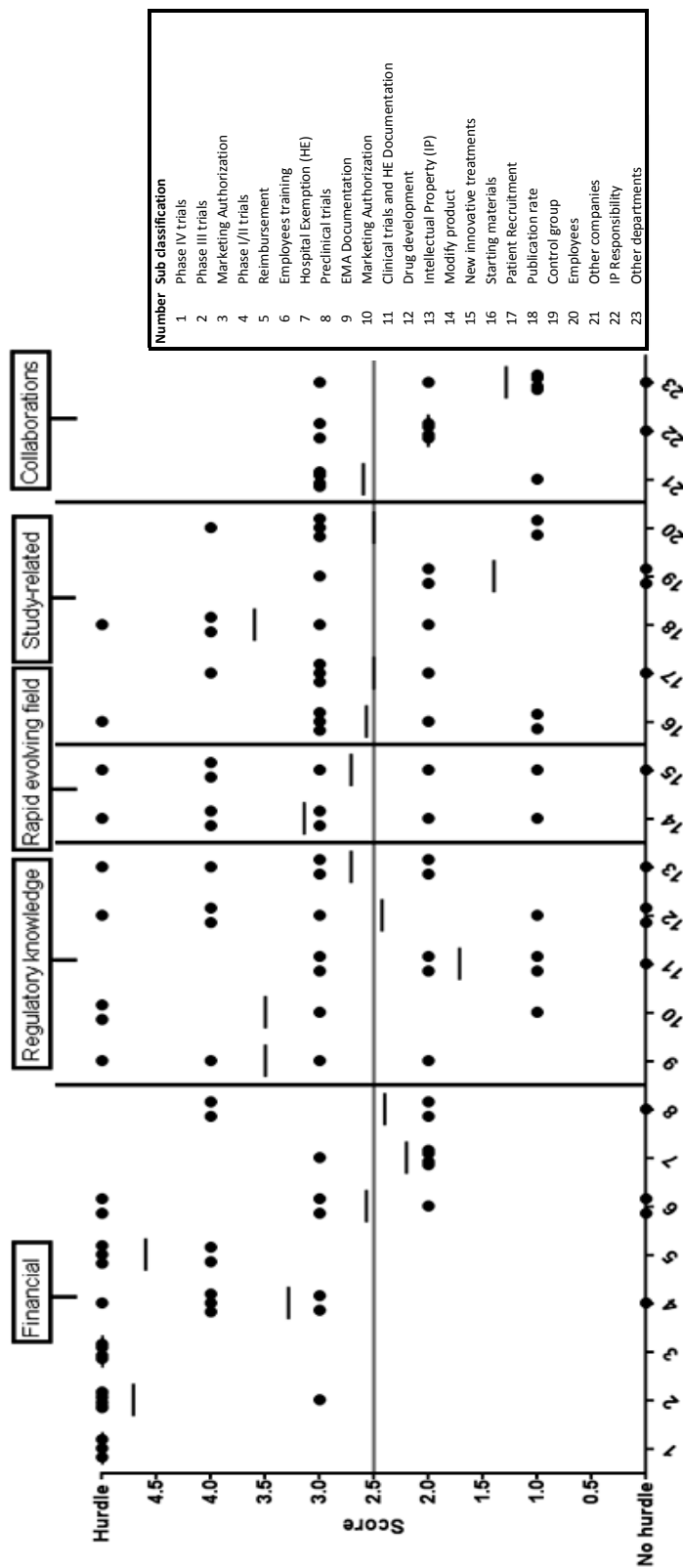


Figure 4. Hurdles in ATMP development scored by ATMP GMP facility managers. The black points are the data points indicating whether the specific issue is experienced not as a hurdle (0) or as a substantial hurdle (5) by individual ATMP GMP facility managers. The mean scores are shown by black dashes. The line at score 2.5 represents the cutoff value for identification of a relevant hurdle (above the line).

must be aware that a modification might change critical product quality attributes. Another consequence of the field's dynamics is the risk of a selected promising ATMP to be overtaken by other innovative medicinal products before reaching MA (mean: 2.9).

Study-related problems

The study-related problems were scored as substantial hurdles by both groups. Material-related problems, such as limited availability of human starting material (e.g. tissue, blood) and raw materials (reagents used for manufacturing), were considered by PIs as the main problem for this specific hurdle. The PIs also experienced problems with patient enrollment, and recruitment of qualified employees. Furthermore, the longer lasting late stage clinical trials (phase III) may conflict with the need for a high publication rate, which is an incentive for success in academic institutions and careers. This is mentioned as a relevant hurdle by both PIs and the ATMP GMP facility managers (mean: 3.6 and 2.8, respectively) because it may conflict with long term development goals. This latter issue was also mentioned as a hurdle in the interviews with various authorities and patient organizations. Other stakeholders also indicated that shortcomings in the design of academic clinical trials were a substantial hurdle in the development of ATMPs for regular clinical care.

Collaborations and responsibility

In collaborative ATMP development, uncertainty about who is responsible for development of the end product was classified as a minor hurdle by both groups (mean: 2.1). For instance, this was a concern when several partners were involved in an IP.

Discussion

Despite active ATMP development in the Netherlands, this study identified many hurdles that may explain the low success rate of implementation of ATMPs in regular clinical care. Lacking financial support is being perceived as the major hurdle for clinical trials and the MA trajectory, which is also seen in the United States[18]. Reimbursement for ATMPs is lacking, especially after HE approval. Furthermore, knowledge about regulation and documentation with regard to ATMP development and MA applications is limited in academic institutions. The field's dynamics produce anxiety to create increasingly innovative products, and PIs perceive that it is impossible to modify a product after the decision has been made to proceed toward further development. The design of pivotal clinical trials is often difficult, as is patient enrollment and obtaining suitable starting and/or raw materials.

Of the interviewed PIs, 26% thought that ATMPs should become available according to the Tissues and Cells Directive, 2004/23/EC[19]. We conclude that PIs are not fully aware of the regulations toward implementation into regular clinical care. The fact that the Tissues and Cells Directive is mentioned might be because some of these responders are familiar with stem cell transplantation and experience fewer hurdles in that particular regulatory framework. We experienced that conducting these interviews, in itself, led to an increase in awareness concerning the ATMP regulation. Comparing the results of the interviews held in 2014 and the questionnaires completed a year later, when only 4% of the PIs preferred to use the Tissues and Cells Directive, it seems that more PIs realized that implementation of ATMPs in regular clinical care is only possible by HE or MA. We indeed confirmed that many PIs changed from this perspective of the Tissues and Cells Directive toward HE and/or MA as the means to reach regular clinical care. However, response bias cannot fully be excluded for the questionnaire-completed PIs because not all PIs who mentioned the Tissues and Cells Directive did complete this questionnaire. The research groups were better informed about ways to reach patients in clinical care with their ATMP due to the interviews as well as increasing awareness (e.g., achieved by attending congresses). To improve knowledge of the development routes, we propose that research groups (and PIs) who are involved in the development of medicinal products should be encouraged to extend their knowledge on product development and issues such as MA and IP regulations. Furthermore, a (national) ATMP development knowledge platform could be established. Remarkably, 16% of the PIs did not have a future plan for their product to be implemented into regular clinical care. It may be valuable to stimulate product and implementation-oriented thinking, including realistic future development plans, for academic institutions. Writing a product dossier (e.g. based on a target product profile (TPP)) would help research groups make future plans for their ATMPs early in development. This TPP can also be directive in making important product decisions such as when to (dis)continue investments in one specific ATMP at a certain stage, creating awareness and a proper risk assessment on the chance that the product would be surpassed by other new therapies before it could be introduced into practice. A TPP would also be helpful to start fruitful collaborations with partners to move the ATMP further in the development trajectory. Furthermore, when several partners are involved, this TPP could be used to address the partners' responsibilities in the development process or to clarify specific parts of the product. Academic institutions may consider expanding the scientific reward system of publication rates with milestones in the development route [20]. Finally, proper clinical trial design is essential for reaching the end goals as defined in the TPP. These end goals should help start discussions on reimbursement with the appropriate

authorities in early development. It is important to realize that the assessments may differ from stakeholder to stakeholder, and, in addition, it is important to realize that positive assessment not necessarily means that the product or clinical trial will be serving the end goal as defined in the TPP. In the Netherlands, the HE clause is increasingly being used. Currently, academic institutions often pay for treatment with HE-approved ATMPs, which limits the number of patients who can potentially benefit from the treatment. The opportunity to receive reimbursement from the health insurers is limited because the Dutch HTA board evaluates safety and comparative effectiveness based on well-designed controlled trials. Academic institutions experience great difficulty performing such controlled trials with ATMPs because of limited patient numbers and starting materials. It is important to keep in mind that it may be unethical to expose patients to an ATMP in clinical trials to prove safety and efficacy when the feasibility to implement it in regular clinical care remains limited. Considering these conflicts, there might be a place in the HTA board discussion or in negotiations between academic institutions and health insurance organizations for reimbursement of ATMPs with an obtained HE. However, the lack of uniformity within the EU may hinder the ability to establish an unambiguous policy, which in turn means that insufficient financial support will remain one of the major hurdles.

We should add that the ATMPs selected for this study do not fully cover all Dutch ATMPs currently in development. There is an indication bias in ATMP projects because selection is based on grants, which focus mainly on cancer therapy. Nevertheless, we do expect to see the same hurdles in other ATMP projects because the identified hurdles are non-disease specific but rather ATMP specific or specific for development in academic institutions. The main hurdles identified in this study, inadequate financial support and lacking regulatory knowledge, are more specific to academic development than to ATMPs[21].

In conclusion, for both academic PIs and other stakeholders, this article offers advice on several ways to improve ATMP development to facilitate reaching regular clinical care for (Dutch) ATMPs. (1) Academic research groups should be encouraged to write a TPP for promising ATMPs and subsequently (2) design proper clinical trials for further development. Improvement of (regulatory) knowledge in drug development may be organized by governmental and/or academic institutions by providing education and training (3). All these measures should result in more awareness and knowledge on how to efficiently reach patients with innovative ATMPs, including proper reimbursement. This project was specific for Dutch ATMP development, but it would be interesting to see whether the hurdles identified in this article are equally relevant in other countries.

Acknowledgement

We thank all the individuals who were interviewed and those who responded to the questionnaires. We also thank the members of the advisory board for this study for their valuable input, including the following: J.B. van den Wijngaard MSc, Ir. F.J.M. van Linden, Dr. H.F. Storms, Prof. Dr. A.G.Vulto, Dr. I. Slaper-Cortenbach and Dr. A. Rietveld. We thank M. Blonk for her valuable input on English language for the manuscript.

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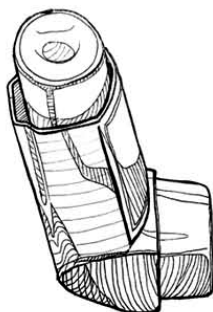
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Supplementary

Table S1. Topics in the questionnaire

Hurdles
Financial
Executing preclinical trials
Executing phase I/II trials
Executing phase III trials
Executing phase IV trials
Registration
Hospital Exemption
Reimbursement
Employees
Rapidly evolving field
Not possible to further modify product
New treatments become available
Study-related
Problems with material for manufacturing
Control group
Publication rate as measure for success contradicts involvement of the product
Recruitment
Qualified employees
Regulatory
Missing drug development knowledge
Documentation clinical trials/HE application
Documentation EMA applications
Missing registration knowledge
Missing knowledge intellectual property
Collaboration
Intellectual property—responsibility
With other clinical departments
With other companies
Other hurdles?
If yes, ...

Each hurdle could be scored from 0 (*no hurdle*) to 5 (*a substantial hurdle*).

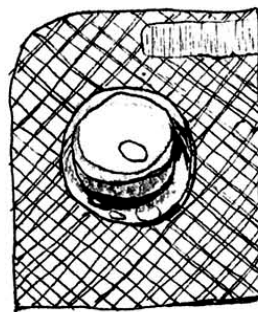


CHAPTER 4

Clinical development of gene and cell-based therapies: overview of the European landscape

Sofieke de Wilde, Henk-Jan Guchelaar, Maarten L. Zandvliet and Pauline Meij

Molecular Therapy — Methods & Clinical Development. 2016;3;16073



Abstract

In the last decade, many clinical trials with gene and cell-based therapies were performed and increasing interest in the development was established by (national) authorities, academic developers, and commercial companies. However, until now only eight products have received marketing authorization (MA) approval. In this study, a comprehensive overview of the clinical development of gene and cell-based therapies in Europe is presented, with a strong focus on product-technical aspects. Public data regarding clinical trials with gene and cell-based therapies, obtained from the European Union (EU) clinical trial database (EudraCT) between 2004 and 2014 were analysed, including product-technical variables as potential determinants affecting development. 198 unique gene and cell therapy products were identified, which were studied in 278 clinical trials, mostly in phase 1/2 trials and with cell therapies as major group. Furthermore, most products were manufactured from autologous starting material mostly manufactured from stem cells. The majority of the trials were sponsored by academia, whereas phase 3 trials mostly by large companies. Academia dominated early-stage development by mainly using bone marrow derived products and stem cells. Conversely, commercial sponsors were more actively pursuing in vivo gene therapy medicinal product development, and cell therapies derived from differentiated tissue in later-stage development.

Introduction

Gene and cell-based therapies hold great promise to provide novel treatment modalities for a wide range of severe diseases. Due to better insight into disease biology, cellular mechanisms, and rapidly evolving technology, development of regenerative and immunotherapeutic drugs is being pursued[1]. In the European Union (EU), gene and cell-based therapies are defined as advanced therapy medicinal products[2]. The majority of these therapies find their origin in academic research settings[3], and small companies have increasingly been involved. Recently, major pharmaceutical companies have invested in gene and cell-based therapy development as well in both the EU and in the United States[4,5].

Current interest in the (pre)clinical development of these promising products is illustrated by a substantial amount of 12,000 publications in regenerative medicine and tissue engineered products in PubMed between 2012 and 2015 and 15,618 on advanced therapy medicinal products in the last 5 years (PubMed search: “advanced therapy medicinal products OR advanced therapy medicinal products OR gene therapy product OR cell therapy medicinal products OR Tissue engineered products” search performed on 14 August 2016)[6]. However, despite this impressive scientific output, only few of the products have received marketing authorization approval, with the result that there is only limited benefit for patients[6–8]. Inherent product-technical aspects may have hampered clinical development, such as the availability of human starting material, or small-scale or even fully personalized manufacturing strategies[9]. The fact that this is a relatively new field, which used to rely on the academic institutions, also might have impacted this outcome. To be able to explain this disappointing outcome regarding the marketing authorization approvals, first more insight is needed into the clinical development of these products.

Up to now, several attempts were made to analyse the clinical development of gene and cell-based therapies by generating overviews of clinical trials. Maciulaitis *et al.*, generated an overview of the European gene and cell therapy clinical trials based on the European pharmacovigilance database EudraCT in the period of 2004 until 2010[10]. More recently, a global overview of cell therapy clinical trials was generated by Bersenev[11]. However, this latter overview was not peer-reviewed, and was incomplete due to exclusion of gene and tissue engineered therapies[11]. Despite providing an overview of the field, both analytical studies provided limited information on the product-technical aspects, which are of vital importance to identify gene and cell therapy-specific hurdles in clinical development. To be able to identify the reasons for failure of products to achieve marketing authorization in the future, it is important to first have a comprehensive overview of the clinical development of the gene and cell-based therapy products. This overview is also focused on product-technical features, such as product subtype and starting material sources. In this study, we aim to

systematically analyse all EU clinical trials performed in the last decade. Furthermore, our second goal is to establish which factors may influence product design and clinical development.

Materials and Methods

Search strategy EudraCT

On 13 February 2015, a web-based data extraction was executed from the web portal, www.clinicaltrialsregister.eu, of the EudraCT database for pharmacovigilance based on EU Directive 2001/20/EC, using the following queries:

- Public access data: Yes
- Field “Advanced Therapy IMP” OR field “Somatic cell therapy medicinal product” OR field “Gene therapy medicinal product” OR field “Tissue Engineered Product” has to be answered with “YES”

The following data fields, from the EudraCT form, were extracted:

{A.1-Member State submission} {A.2-EudraCT number} {A.3-Full title trial} {A.3.2.-Name of abbreviated title} {A.7-Is the trial part of a PIP?} {A.8-EMEA decision number PIP} {B.3.1/2-Status Sponsor} {B.5-Functional name contact point sponsor} {B.5.3.1 t/m B.5.3.6-Address contact point sponsor} {D.1.1-IMP number} {D.1.2-IMP being tested} {D.1.3-IMP used as a comparator} {D.2.1-Has this IMP to be used in the trial a marketing authorisation?} {D.2.5-Orphan drug designation?} {D.2.5.1-Orphan drug designation number} {D.3.1-Product name} {D.3.2-Product code} {D.3.4-Pharmaceutical form} {D.3.7-Route of administration} {D.3.8-(proposed) INN} {D.3.11.2-Active substance of biological/biotechnological origin (other than ATIMP)?} {D.3.11.3-TIMP?} {D.3.11.3.1-sCTMP?} {GTMP?} {D.3.11.3.3-TEP?} {D.3.11.3.4-Combination ATIMP} {D.3.11.3.5-CAT classification?} {3.11.3.5.1-ATIMP classification number} {D.3.12-Mode of action} {E.1.1-Medical condition(s) to be investigated} {E.1.1.2-Therapeutic area} {E.1.2-MedRA version, level, term, number} {E.1.3-Rare disease?} {E.2.1-Main objective} {E.2.2-Secondary objective} {E.5.1-Primary endpoint} {E.5.2-Secondary endpoint} {E.6.3-Therapy} {E.6.4-Safety} {E.6.5-Efficacy} {E.6.9-Dose Response} {E.7.1-Phase 1} {7.1.1-First administration to humans} {E.7.1.3-Other} {E.7.2-Phase 2} {E.7.3-Phase 3} {E.7.4-Phase 4} {E.8.1-Controlled trial} {E.8.1.1-Randomised trial} {E.8.1.2-Open trial} {E.8.1.3-Single blind trial} {E.8.1.4-Double blind trial} {E.8.1.5-Parallel group} {E.8.1.6-Cross-over} {E.8.2.1-Control group: Other medicinal product} {E.8.2.2-Control group: placebo} {E.8.2.3-Control group: other} {E.8.3-Single site in member State} {E.8.4-Multiple sites in Member State} {E.8.4.1-Numbers of sites} {E.8.5-Multiple Member States} {E.8.5.1-Number of member states in EEA} {E.8.6.1-Trial involving sites within and outside EEA} {E.8.9-Initial estimate of duration trial} {F.1.1-Age trial: Less than 18 years} {F.3.1-Healthy volunteers as subjects} {F.3.2-Patients as subjects} {P – End of trial}.

Selection

The selection based on the queries (see “Search strategy EudraCT”), resulted in 754 trial data records, containing all data fields in a Microsoft Excel 2010 file. Two authors independently classified the products as being a gene therapy product, a cell therapy product or a tissue engineered product, according to the article 17 of regulation (EC) No. 1394/2007[17]. In case of disagreement (29 cases), a third author independently performed the classification, after which the three authors agreed on the classification by consensus. In case a product received a scientific recommendation on classification of the product by the EMA CAT[20], this classification was used. The gene therapy products were divided into two subtypes: in vivo gene therapy products, meaning that genetic material is administered directly into the patient, and ex vivo gene therapy products, when autologous or allogeneic cells are genetically modified ex vivo and (re)administered into the patient. If needed, additional information was collected from websites with information about the clinical trials (e.g., Clinicaltrial.gov), PubMed, and websites from the sponsors.

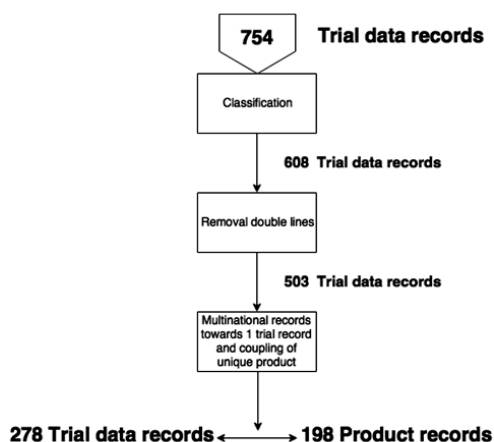
146 trial data records did not meet the gene and cell-based therapy product classification and were deleted. Subsequently, identical trial data records were deleted (105 records) leaving 503 trial data records for analysis. Coupling of the multicentre (multinational) performed trial data records towards one trial data record, corresponding with the same product record, was done based on: product name, product subtype, and sponsor name and resulted in 278 trial data records, corresponding with 198 unique product records (Figure 1a).

To ensure reliability, security, (error) sensitivity with the trial data records and the product data records, a web-based database, Project Manager Internet Server (ProMISe) was used[21]. All data and product records were exported from the Microsoft Excel file towards ProMISe in a specific structure (Figure 1b). Product name (product record) was used as the main record in the ProMISe database, and each product record was linked to one or more trial records (EudraCT numbers). The first four numbers of the EudraCT number correspond with the year in which the EudraCT number was assigned. These year numbers were used for annual overviews.

Classification of the sponsor type was done by one author, based on the SME criteria from regulation (EC) No 726/2004: a company was considered as an SME when <250 staff headcounts AND Turnover ≤ €50 m OR balance sheet total ≤ € 43 m. If a commercial company did not meet the characteristics for a SME, it was classified as being a large company.

Product-technical specifications: product subtypes and starting material sources were classified by three authors independently (Table 1). In case of any disagreement, the product was discussed by the three authors to reach consensus about the product-technical specifications.

a.



b.

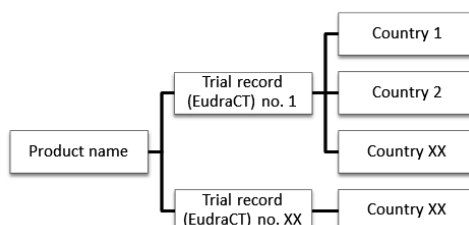


Figure 1. Database record selection and arrangement. (a) A schematic overview of the EudraCT data record selection. Trial data records from the EudraCT queries were reduced towards product records with corresponding clinical trials. (b) A schematic overview on how the database ProMiSe was built, by coupling of clinical trials to the product and coupling of the countries in which the clinical trials have been performed.

Analysis

The data in ProMiSe was analysed in both ProMiSe and Microsoft Access 2010. By generating frequency tables of different variables, cross tables, overviews of the gene and cell-based therapy development in Europe were created. The following variables were analysed: gene and cell-based therapy product type, year of achieving EudraCT number, indication area, country, sponsor type, product subtype, starting material (autologous or allogeneic), and starting material source. See Table 1 for classification of starting material source and product subtype.

Table 3. Gene- and cell-based therapy product type starting material source and product subtypes

Gene and cell based therapy product type	Starting material source	Product subtype
Cell therapy medicinal product (CTMP)	Differentiated tissue	Dendritic Cells
Gene therapy medicinal product (GTMP)	Blood	Differentiated Tissue Cells
Tissue engineered product (TEP)	Bone marrow	GTMP - ex vivo
	Tumour tissue	GTMP - in vivo
	Other	Lymphocytes
		MSC
		Stem cells
		Other

Results

Overview of gene and cell-based therapy clinical trials

From public domain of the EudraCT database (since phase 1 clinical trials are not in the public domain of EudraCT and processing of trials in EudraCT can be delayed, clinical trials may be missing), 278 gene and cell-based therapy clinical trials were identified over the period 2004 until 2014, corresponding with 198 unique gene and cell-based therapy products. The majority of these products was tested in one clinical trial only (75% from total n = 198), while the remaining part was tested in two (17%) or in three or more studies (8%). Half of the products, tested in more than one clinical trial, reached a next clinical trial phase, whereas the other half remained in the same clinical trial phase. The dominant indication areas were cancer (31%), cardiovascular diseases (17%), and skin and connective tissue diseases (11%) (Figure 2a; total n = 278).

The total number of clinical trials increased to maximum numbers between 2007 and 2009, after which the numbers in the database showed a decrease towards 2014 (Figure 2b). Half of the clinical trials were phase 2, while 23 and 19% were phase 1/2 or phase 3 trials, respectively (Figure 2c; total n=278). Since data about phase 1 clinical trials are not available in the public domain of the database, these trials were not included in the analysis. Most trials were performed using cell therapy products (53%).

Country-specific variations in clinical gene and cell-based therapy development

More than half of the clinical trials (65%) were performed in only five of the EU countries (Figure 3a; n = 499). Most trials were performed in Spain (18%), investigating predominantly cell therapy products (71%), and in the United Kingdom (17%), where half of the trials were executed with gene therapy products (Supplementary Figure S1). The other three countries in which there is a clear high clinical activity were Germany (12%), Belgium (11%), and The Netherlands (7%). To further specify these figures, trials with tissue engineered products were mostly performed in Germany (17%). Gene and cell therapy trials contributed less than 1% of the overall clinical trial numbers in the EU (range 0.1–1.6% per country) (Figure 3b).

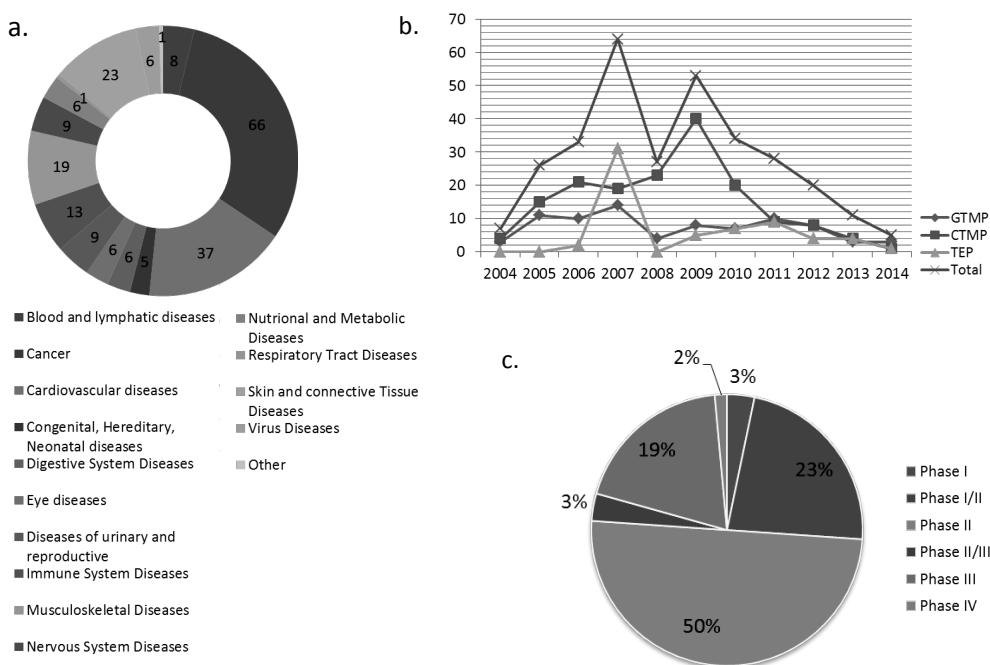


Figure 2. Gene and cell-based therapy landscape. CTMP, cell therapy medicinal product; GTMP, gene therapy medicinal product; SME, small and medium-sized enterprise; TEP, tissue-engineered product. (a) Distribution of the indication areas for the gene- and cell-based therapy, showing absolute numbers derived from the public domain of the EudraCT database*; (b) Absolute numbers of clinical trials with the of gene- and cell-based therapy product types per year; (c) Numbers (represented in percentages, $n = 278$) of different clinical trials study phases performed with gene- and cell-based therapy products. * Since phase 1 clinical trials are not in the public domain of EudraCT and processing of trials in EudraCT can be delayed, clinical trials may be missing.

Sponsor variations in clinical gene and cell-based therapy development

Sponsor types identified were academia, small and medium-sized enterprise (SMEs) and large pharmaceutical companies. More than half of the trials was sponsored by academic institutes (56%), while 36% of the trials was sponsored by SMEs and only 8% by large companies (Figure 4a; total $n = 206$). Most clinical trials sponsored by academic institutes and SMEs, were conducted with cell therapy products (70%; $n = 84$ and 45%; $n = 29$ respectively), and most of these were phase 2 trials (67%; $n = 106$ and 51%; $n = 51$ respectively) (Figure 4b,c and Supplementary Figures S2 and S3). In contrast, large companies focused on clinical trials with in vivo gene therapy products (43%; $n = 9$) and sponsored more than half of the phase 3 trials (54%; $n = 13$). Furthermore, another interesting finding is that single centre and national trials were predominantly sponsored by academic institutes (68%), while nearly all multinational trials were sponsored by SMEs or large companies (94%). Remarkably, for large companies, skin and connective tissue diseases was a relatively prominent indication (26%) (Supplementary Figure S4) ($n = 219$).

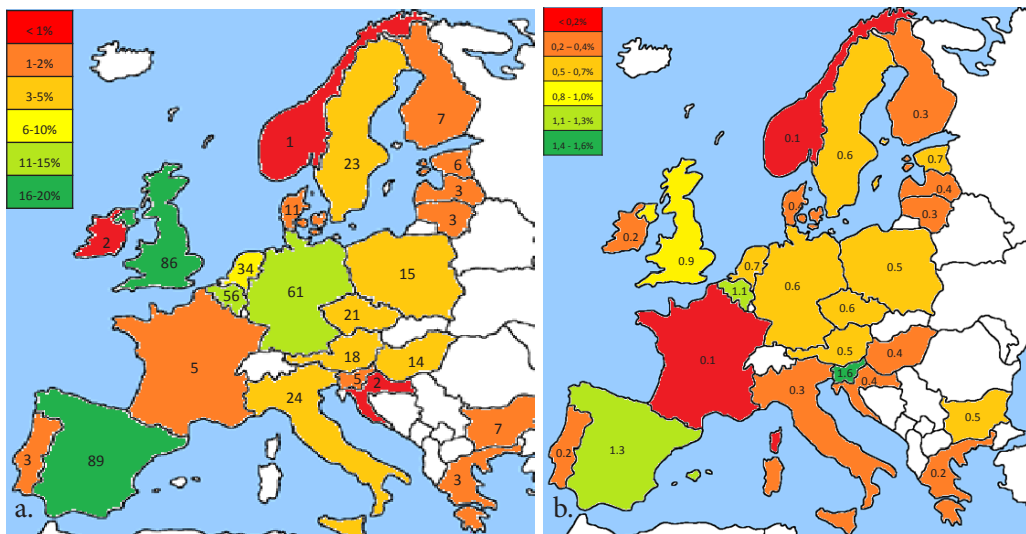


Figure 3. Country-specific variations in gene- and cell-based therapy development. (a) Percentage of clinical trials with gene- and cell-based therapies per country derived from the public domain of the EudraCT database¹ depicted in color and absolute numbers of clinical trials performed per country (written in country). (b) Ratio of the number of clinical trials with gene- and cell-based therapy products performed in a country per the total amount of clinical trials in that country derived from the public domain of the EudraCT database. The white colored countries did not perform any studies with gene- and cell-based therapy products or do not belong to the European Union. (European map adjusted from <http://www.youreuropeamap.com/>).

Product-technical variation in clinical gene and cell-based therapy development

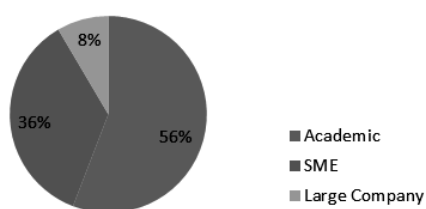
Next, we systematically analysed the product-technical characteristics of gene and cell-based therapy products in clinical development within the EU in more detail.

The major product subtypes were in vivo gene therapy products (22%; n = 44), stem cell products (19%; n = 38) and mesenchymal stromal cells (16%; n = 32). Whereas most of the stem cell products were developed for treating cardiovascular diseases (51%; n = 29) and differentiated tissue cell products for skin and connective tissue diseases (45%; n = 20) (Supplementary Figure S5), most of the dendritic cell products (89%; n = 32), lymphocyte-based products (82%; n = 9), and gene therapy products (52%; n = 43) were designed for cancer treatment. Academic sponsors (total n = 116) mainly performed clinical trials with stem cells, dendritic cells, and mesenchymal stromal cells as largest subtypes (24, 20, and 20%, respectively), while both SMEs (total n = 61) and large companies (total n = 20) performed clinical trials with in vivo gene therapy products as the largest group (31 and 45%, respectively) (Supplementary Figure S6). The majority of the products were produced from

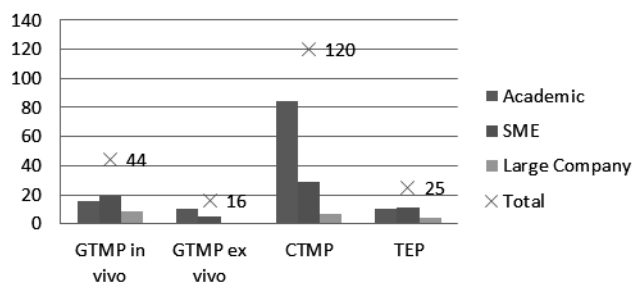
autologous starting material (73%; $n = 117$), of which most often stem cell products were manufactured (31%; $n = 49$) (Figure 4d and (Supplementary Figures S7 and S8). Although in general differentiated tissue was most frequently used as source for starting material (31%; $n = 68$), autologous products were mostly generated using bone marrow derived starting materials (33%; $n = 52$) (Supplementary Figure S9). Academic sponsors and SMEs mainly used autologous starting material for the manufacturing of their products (78%; $n = 80$ and 69%; $n = 31$ respectively), which were most frequently derived from bone marrow in case of academic sponsored studies (29%; $n = 36$) and most frequently from differentiated tissue when sponsored by SMEs (30%, $n = 19$) (Supplementary Figures S7 and S10). Furthermore, autologous starting material is used most often for the production of cancer therapies (31%; $n = 48$) (Supplementary Figure S11). In addition, cancer therapy products were generated from peripheral blood in approximately half of these cases (49%; $n = 45$), whereas the majority of the cardiovascular disease therapy products were generated from autologous bone marrow (63%; $n = 30$) (Supplementary Figure S12).

Most of the allogeneic products were manufactured toward differentiated tissue cells and mesenchymal stromal cells (31%; $n = 19$ each). Half of the products generated by large companies were allogeneic products and were mostly derived from differentiated tissues (23%; $n = 5$). Furthermore, it seems that these allogeneic products were mainly manufactured for treatment of skin and connective tissue diseases (24%; $n = 15$).

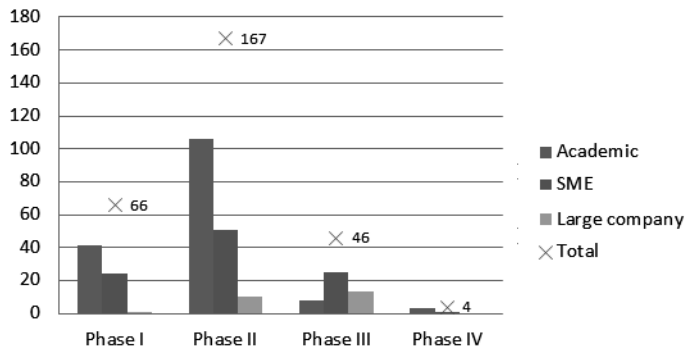
a. Sponsor type ($n=206$)



b. Type gene and cell based therapy per sponsor



c. Study phase per sponsor



d. Starting material per sponsor

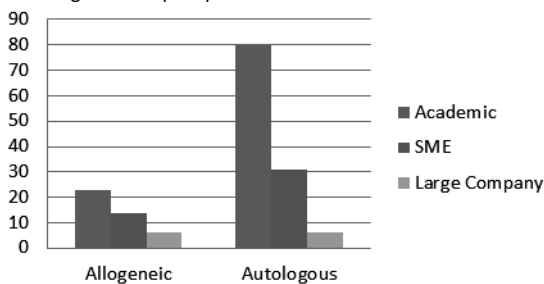


Figure 4. Sponsor type variations in gene- and cell-based therapy development. CTMP, cell therapy medicinal product; GTMP, gene therapy medicinal product; SME, small- and medium-sized enterprise; TEP, tissue-engineered product. (a) Distribution of the different sponsors that performed clinical trials with gene- and cell-based therapies. (b) Absolute numbers of clinical trials performed with gene- and cell-based therapy types per sponsor and the total absolute number of clinical trials with the different gene- and cell-based therapy types. (c) Absolute numbers of clinical trials in different clinical phases per sponsor and the total number of clinical trials per clinical phase. (d) Starting material per sponsor type.

Discussion

This study provides a detailed and comprehensive overview of all clinical trials performed with gene and cell-based therapy products in Europe over the last decade, and represents the current status of gene and cell-based therapy development in Europe. The majority of trials were performed by academic sponsors, most often using autologous starting material and they mostly manufactured stem cell products. Commercial companies performed most studies with in vivo gene therapy products and were nearly always involved in later stage phase 3 clinical trials. Only 11% of these products proceeded toward a clinical trial of the next phase clinical trial, suggesting that clinical development of most products hampered.

The number of clinical trials increased in the period from 2004 to 2010, including two peaks in 2007 and 2009, and thereafter showed a decrease. The first peak, with tissue-engineered products as the major group, might be explained by the fact that the EU directive 2001/83/EC, which defines the gene and cell-based therapy products, was renewed in 2007 adopting tissue-engineered products.¹² The other peak in 2009 might be due to the specific regulation for gene and cell-based therapies (EC)

no 1394/2007 that came into force on 30 December 2008. Most therapies were designed for the treatment of cancer and cardiovascular diseases, which can be explained by the fact that these cause most deaths globally[13]. Therefore, improved clinical development of gene and cell-based therapies may eventually yield clinical benefit for those diseases in particular where there is a high unmet medical need.

Spain and the United Kingdom are the countries in which most of the clinical trials in Europe were performed. Interestingly, gene and cell-based therapy development has been stimulated in these countries by specific initiatives for facilitating financial resources, knowledge and (design of) centralized good manufacturing practice facilities[14,15]. As such, infrastructure appears to have a relevant impact on further development of these promising therapies, regional and national public stakeholders are encouraged to consider similar approaches.

The majority of the products were sponsored by academia, whereas 61% of the clinical trials with conventional medicinal products originated from commercial companies in the European Economic Area (EEA)[16]. From earlier research, the (regulatory) route toward marketing authorization (MA) was found to comprise many hurdles for academic research groups [9]. Indeed, all gene and cell-based therapies that received MA approval were sponsored (in later stages of development) by a commercial party. In our database, it is shown that nearly all phase 3 trials were performed by commercial sponsors, supposing that they have appropriate financial resources and (regulatory) knowledge.

The slight increase (40% to 44%) in commercially sponsored trials from 2010 to 2014, including an increase from 2 to 8% of the large companies involved, suggest increasing interest in gene and cell-based therapy development by the commercial (large company) sector[10]. In comparison, commercial sponsors developed more off-the shelf products, such as allogeneic products and in vivo gene therapy products, compared to academic sponsors. This is to be expected, as late stage off-the-shelf product development is easier and less expensive, because it entails large scale manufacturing and efficient logistics, when compared to personalized autologous or donor-matched manufacturing. However, all cell-based therapies (n=4) with MA approval in Europe were generated from autologous starting material (Chondroelect®, Holoclar®, MACI® (currently suspended), and Provenge® (retracted in 2015)) and had a commercial sponsor, indicating that personalized manufacturing did not hamper their (commercial) development. Due to the potential efficacy and safety of fully personalized therapies, the authors believe that (large) commercial sponsors become more interested in the development of these gene and cell-based therapies toward MA, as seen in the examples of CTL019 and Strimvelis®[4,5]. The growth of investments from large pharmaceutical

companies in gene and cell-based therapy development, is a clear indication of the fact that there is an increasing involvement of the commercial sector in this young field of medicinal products[4,5]. We expect that this trend of more involvement from commercial parties will continue to date. In particular, academic-commercial partnerships may be very efficient to drive the best gene and cell-based products from early academic research toward proper late-stage clinical development. The number of Committee for Advanced Therapies (CAT) classifications and scientific advice applications for gene and cell-based therapy products has increased over the last years. A proactive attitude of regulators, as recommended by Maciulaitis *et al.*, may have contributed to this increase[10]. The involvement of and regulatory advice from the central expertise of the EMA CAT is expected to support increasing numbers of MAs over the next years[8,17,18]. Since gene and cell-based therapies are developed globally, the question is whether their development results more often in MA approval in other jurisdictions. In the United States, Canada, and Japan, whose systems for protection of the public health are corresponding to the European system[19], six, one and two gene and cell-based therapies, respectively received MA approval. This supports the idea, that this lack in further development of these therapies is global. In contrary, South Korea has 18 gene and cell-based therapy products with MA approval[19], suggesting that their specific regulation for these therapies supports development to MA approval.

The largest product group manufactured from autologous starting material was stem cell products. In academic institutes, the autologous products were often derived from bone marrow. This may be explained by the fact that these stem cell products have similarity with hematopoietic stem cells which have already been in use for bone marrow transplantation in these institutes for decades. Furthermore, the autologous products were mostly manufactured for cancer therapy, which might be due to the durable immune stimulatory potential of personalized treatment.

This study provides a comprehensive overview of gene and cell-based therapy product development in the EU. However, since we only had access to the public domain of EudraCT, the phase 1 clinical trials were not included, resulting in an underestimation of the total number of clinical trials and products. Moreover, some clinical trials may not have been included in the public database due to delayed processing of clinical trials into EudraCT.

In order to stimulate clinical development of autologous products toward MA, academic, and commercial parties may collaborate efficiently in public-private partnerships. Furthermore, public stakeholders should consider stimulating efficient development of gene and cell-based therapies toward patient benefit, e.g., via regional or national initiatives.

Based on these results, future studies are necessary to further identify factors associated with success and failure of gene and cell-based therapy development. These insights may help

stakeholders to more effectively use their resources to increase availability of safe and effective gene and cell-based therapies.

Acknowledgement

We thank Paula Vossebeld, PhD, scientific staff member from the Dutch Central Committee on Research Involving Human Subjects (CCMO, The Netherlands), for her help in the EudraCT queries. We also thank Hans Vogelaar, data management information analyst (Leiden University Medical Center), for his contribution in making our data- base in ProMISe. We thank M. Blonk, for her valuable English input.

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Supplementary

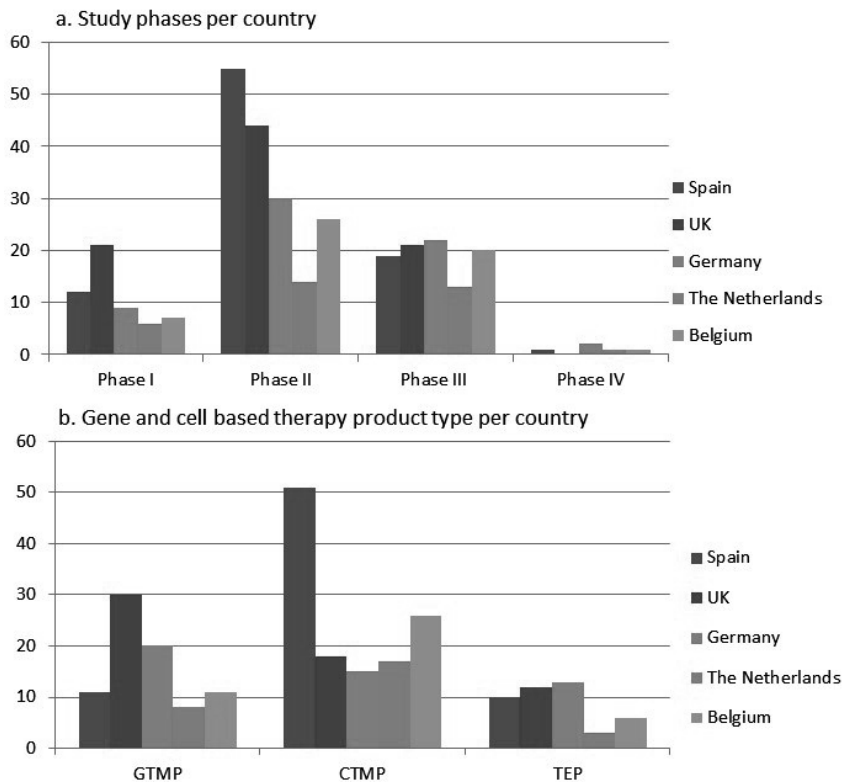


Figure S1. Country-specific clinical trials.

CTMP = cell therapy medicinal product; GTMP = gene therapy medicinal product; TEP = tissue engineered product; UK = United Kingdom (a) Absolute numbers of the clinical trial phases performed in the five main countries. (b) Absolute numbers of clinical trials per gene and cell based product type in the five main countries.

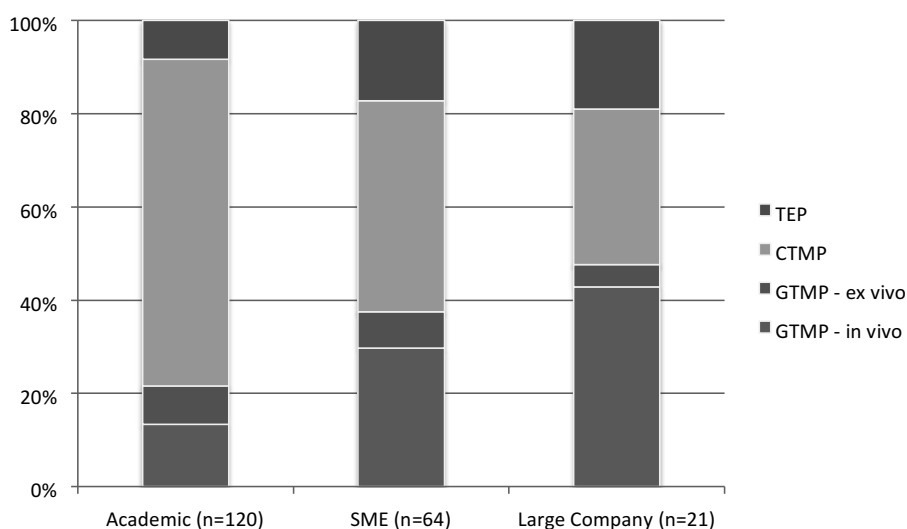


Figure S2. Gene and cell based therapy per sponsor.

CTMP = cell therapy medicinal product; GTMP = gene therapy medicinal product; SME = small and medium-sized enterprise; TEP = tissue-engineered product. The number of gene and cell based product type per sponsors (represented in percentages).

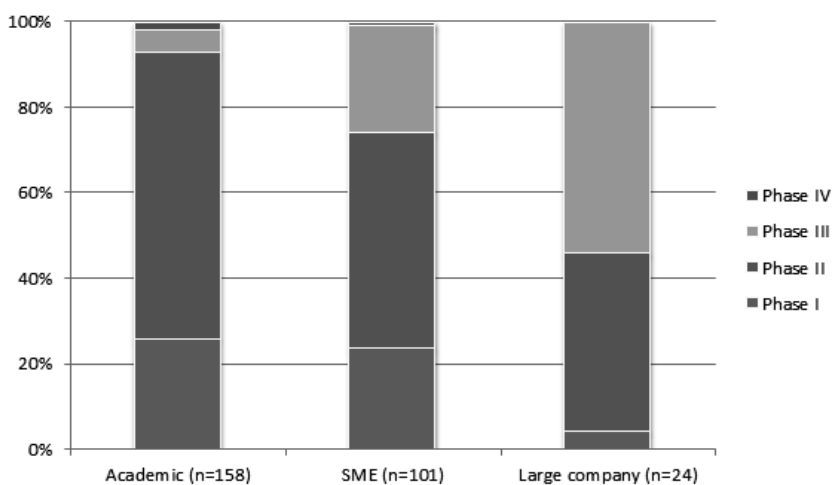


Figure S3. Gene and cell based therapy clinical phase per sponsor.

SME = small and medium-sized enterprise. The number of clinical trial phases performed per sponsor type (represented in percentages).

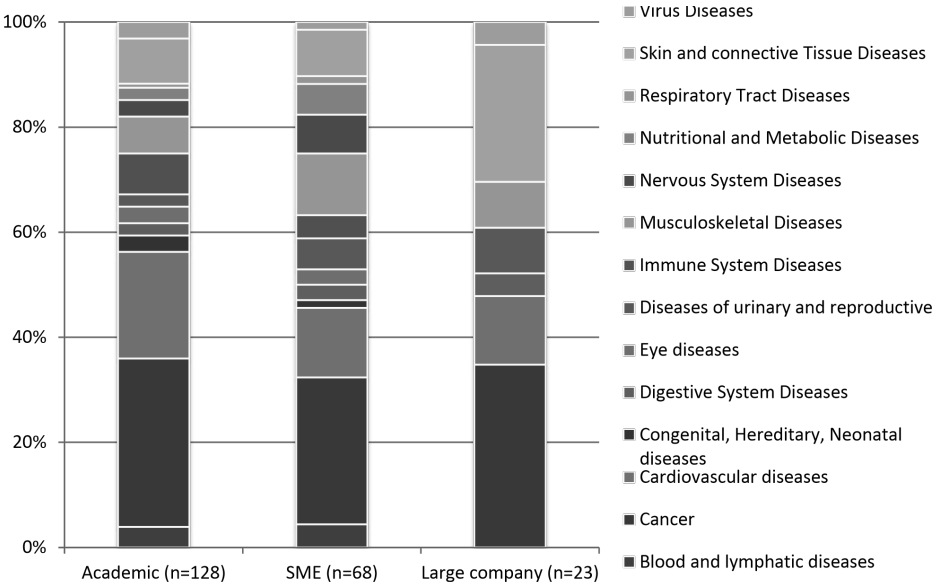


Figure S4. Indication area per sponsor.

SME = small and medium-sized enterprise. Distribution of the different indication areas in which clinical trials were performed per sponsor.

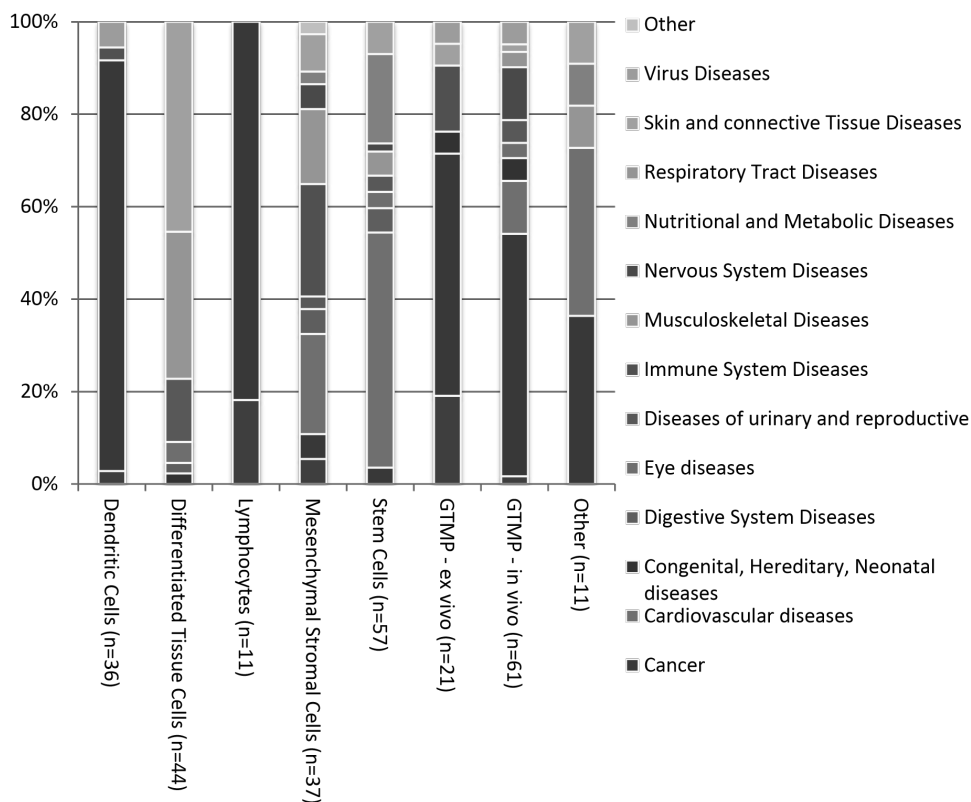


Figure S5. Indication area per subtype of gene and cell based therapies.

GTMP = gene therapy medicinal product; TEP = tissue-engineered product. Distribution of the different indication areas in which clinical trials were performed per product subtype.

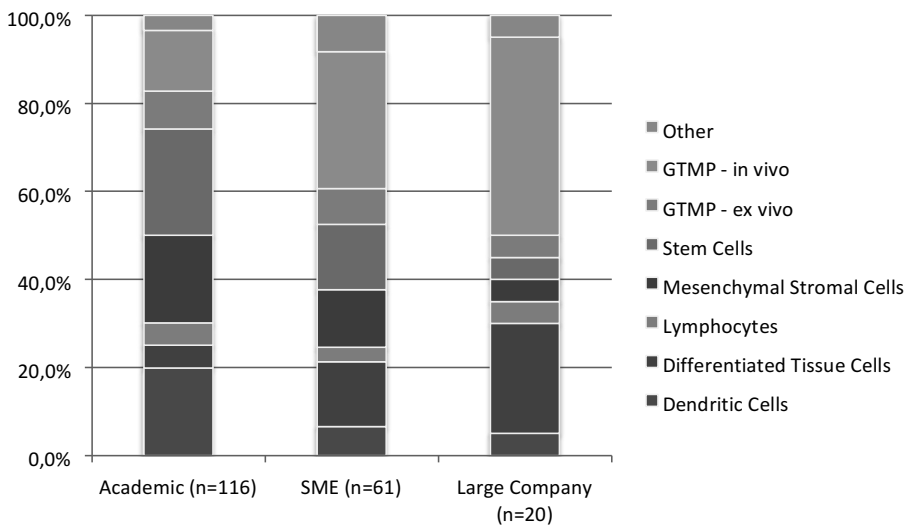


Figure S6. Gene and cell based therapy subtype per sponsor.

CTMP = cell therapy medicinal product; GTMP = gene therapy medicinal product; SME = small and medium-sized enterprise; TEP = tissue-engineered product. Distribution of the gene and cell based therapy product subtype per sponsor.

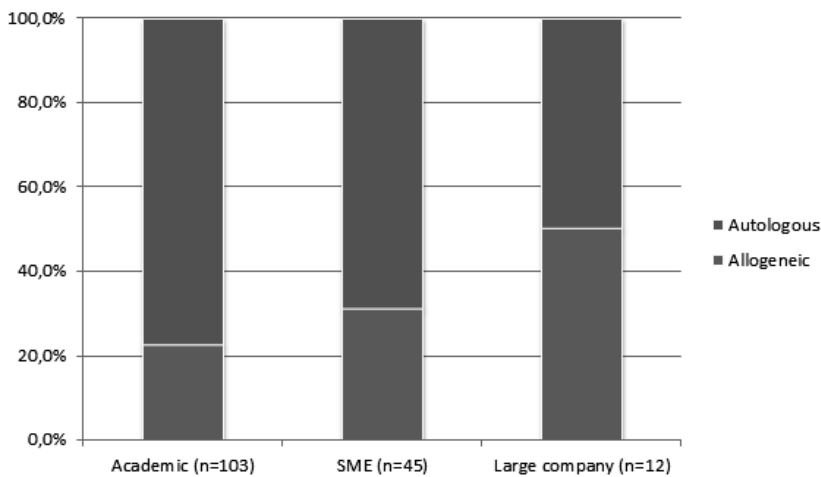


Figure S7. Starting material per sponsor.

SME = small and medium-sized enterprise. Distribution of autologous or allogeneic starting materials used for the gene and cell based therapy per sponsor.

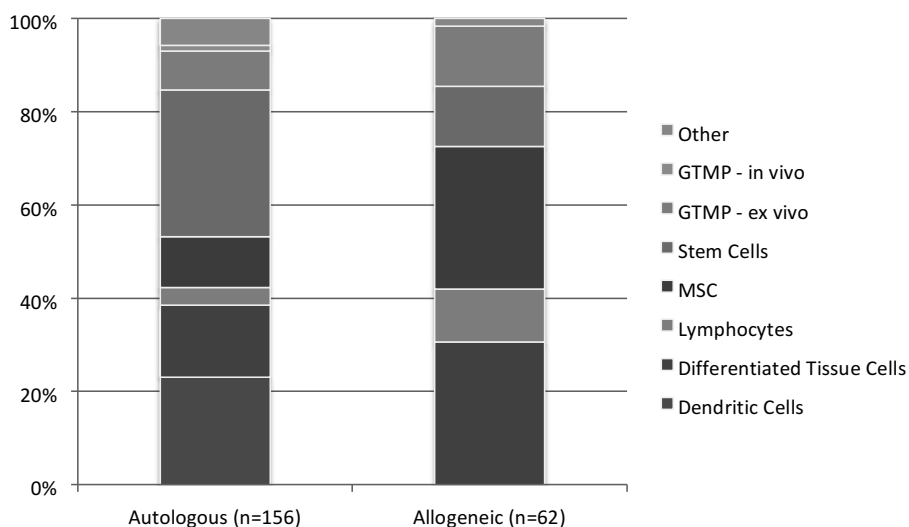


Figure S8. Gene and cell based therapy subtype per starting material.

Distribution of the gene and cell based therapies manufactured from autologous or allogeneic starting material.

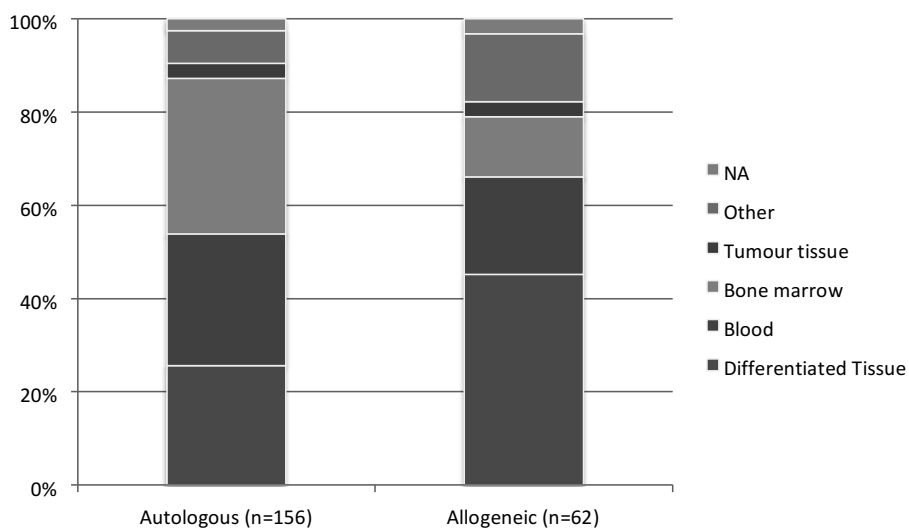


Figure S9. Starting material sources.

Distribution of the starting material sources per autologous or allogeneic derived starting material used for gene and cell based therapy.

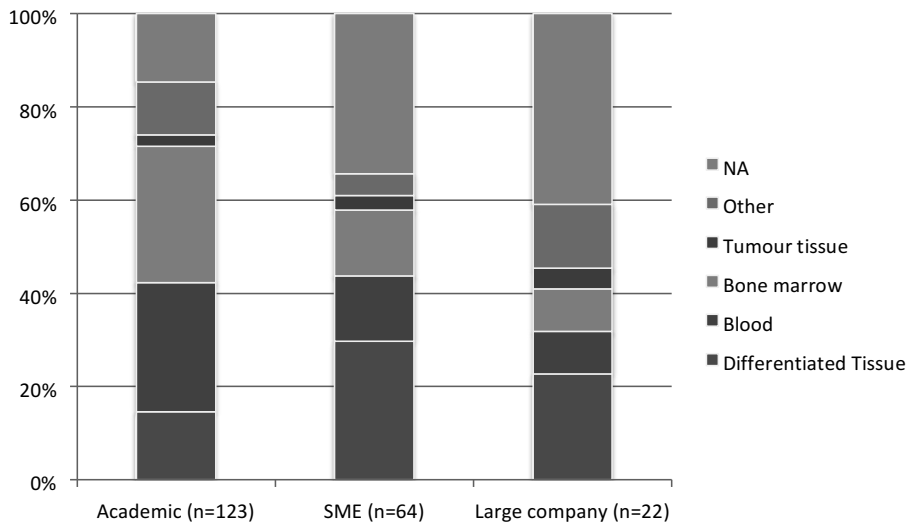


Figure S10. Starting material source per sponsor.
SME = small and medium-sized enterprise. Distribution of the starting materials sources which were used for gene and cell based therapies per sponsor type.

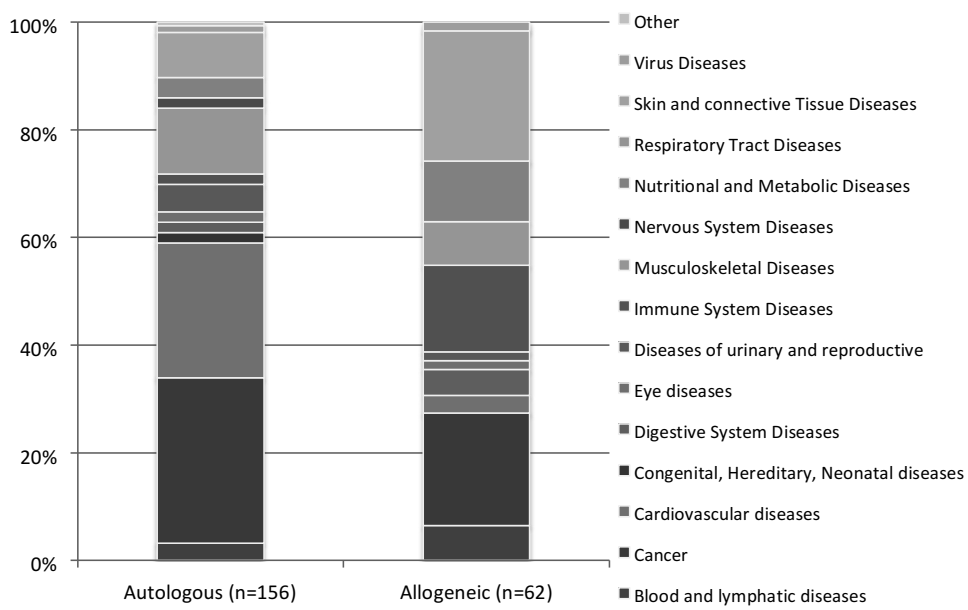


Figure S11. Indication area per starting material.
Distribution of the different indication areas in which clinical trial were performed with gene and cell bases therapy per autologous or allogeneic starting material.

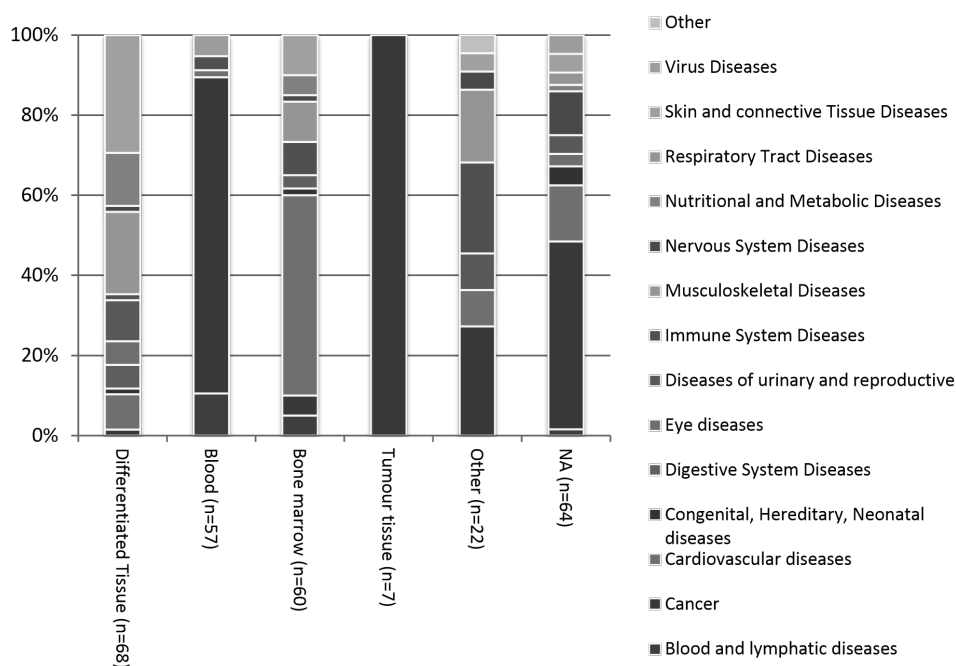


Figure S12. Indication area per starting material source.

Distribution of the different indication areas in which clinical trial were performed with gene and cell bases therapy per starting material source.



CHAPTER 5

Understanding clinical development of chimeric antigen receptor T cell therapies

Sofieke de Wilde, Henk-Jan Guchelaar, Maarten L. Zandvliet and Pauline Meij

Cytotherapy. 2017;19:703-709



Abstract

In the past decade, many clinical trials with gene- and cell-based therapies (GCTs) have been performed. Increased interest in the development of these drug products by various stakeholders has become apparent. Despite this growth in clinical studies, the number of therapies receiving marketing authorization approval (MAA) is lagging behind. To enhance the success rate of GCT development, it is essential to better understand the clinical development of these products. Chimeric antigen receptor (CAR) T cells are a GCT product subtype with promising efficacy in cancer treatment which are tested in many clinical trials, but have not yet received MAA.

We generated an overview of the characteristics of CAR T-cell clinical development in the United States, Canada and Europe. Subsequently, the characteristics of clinical trials with CAR T-cell products that proceeded to a subsequent clinical trial, used as a proxy for success, were compared with those that did not proceed.

From the U.S. and European Union clinical trial databases, 106 CAR T-cell trials were selected, from which 49 were linked to a subsequent trial and 57 were not. The majority of the trials had an academic sponsor from which most did not proceed, whereas most commercially sponsored trials were followed by another clinical trial. Furthermore, trials with a subsequent trial more frequently recruited large patient cohorts and were more often multicentre compared with trials that were not followed up.

These characteristics can be used by investigators to better design clinical trials with CAR T cells. We encourage sponsors to plan clinical development ahead for a higher efficiency of product development and thereby achieving a higher success rate of development towards MAA.

Introduction

Over the past decade, many clinical trials with gene- and cell-based therapies (GCTs) have been performed. Historically, clinical trials with GCTs have primarily been performed by academic institutes, although involvement of commercial companies in clinical development of these medicinal products has rapidly increased[1,2]. In addition, development of these innovative and promising therapies is also receiving increasing interest of other stakeholders, such as regulatory authorities and funding organizations[3]. However, the number of therapies that have reached marketing authorization approval (MAA) is lagging behind[4,5]. Indeed, in Canada, Europe and the United States, only 1, 8 and 6 GCTs, respectively, have been approved. To gain more insight into the low number of MAAs, the clinical development of such products should be investigated. However, predicting a successful development of medicinal products is challenging, even when a medicinal product shows promising results in (pre)clinical trials[6]. Furthermore, the complexity of GCTs makes them more challenging compared with conventional products[6]. Therefore, to better understand this development field, the characteristics of the GCT clinical trials should be analysed and compared to see whether further development of a product can be related to one or more clinical trial characteristics.

Chimeric antigen receptor (CAR) T cells are a GCT product subtype with promising efficacy in cancer treatment that have been tested in many clinical trials globally[6–8]. CARs generally contain two domains, an antigen-recognition and a signalling domain, inserted by gene transfer, through which the T cells can specifically recognize and attack unwanted target cells. These CAR T cells are developed for the treatment of malignancies, with B-cell acute lymphoblastic leukaemia one of the main indications[9]. Despite the demonstrated efficacy, it has not resulted in MAA[10]. Various hurdles are experienced in the clinical development with GCTs in general and with CAR T cells specifically[11,12]. Nevertheless, multiple CAR T-cell products are expected to receive U.S. Food and Drug Administration and European Medicines Agency approval in coming years[13,14]. CD19 targeting CAR T cells are likely to be the first engineered T cells to receive marketing authorization [15].

For this article, we generated an overview of the characteristics of the CAR T-cell clinical development field in Canada, Europe and the United States. Subsequently, the characteristics of CAR T cell clinical trials that developed further were compared with those clinical trials that were not.

Methods

CAR T selection

All clinical trials performed with CAR T cells in open access U.S. and European Union (EU) clinical trial databases were selected in June 2016 from the public websites www.clinicaltrials.gov and www.clinicaltrialsregister.eu. For the European public websites, phase 1 clinical trials are not available for public access. The number of hits per query are shown in Table I. Identical double clinical trial records were removed, resulting in 145 unique clinical trials.

Table I. Queries used in public domain of clinical trial registers in the European Union and United States.

Source	Query	Clinical trials
www.clinicaltrialsregister.eu	"CAR"	4
www.clinicaltrialsregister.eu	"Chimeric antigen receptor"	4
www.clinicaltrials.gov	"CAR"	122
www.clinicaltrials.gov	"Chimeric antigen receptor"	100

Clinical trials that did not involve CAR T cells were removed from the collected data file, resulting in 122 trials. Finally, clinical trials that were performed outside Canada, the United States and Europe were removed, resulting with 93 clinical trials. Canada, the United States and Europe were chosen as main countries because of their similar regulatory frameworks concerning GCTs and because most Canadian, U.S. and European clinical trials are submitted to these databases [4].

In addition, overviews of CAR T-cell clinical trials from the literature and their trial numbers were compared with those in our data file [7,8]. 14 clinical trials from literature that were not present in the data file were added to the remaining 92 clinical trials from the queries, resulting in the final 106 clinical trials with CAR T cells in Canada, Europe and in the United States (Figure 1).

Characteristics of the clinical trials were chosen to describe clinical trial design and product design and were collected from the open access clinical trial databases and from the literature (Table II).

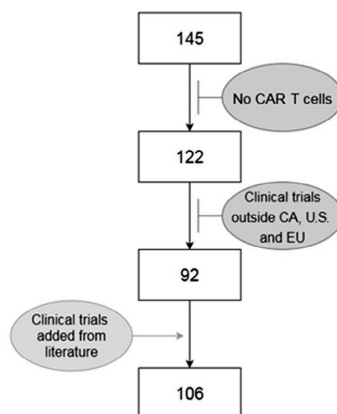


Figure 1. Selection of clinical trials with CAR T cells. CA: Canada.

Definition

Development is considered successful when a product receives MAA. Because no CAR T cells have been submitted for marketing authorization, this definition of success cannot be used at present. Therefore, for each CAR T cell clinical trial, it was determined whether there was a subsequent clinical trial using the same product. This included clinical trials that were followed by another clinical trial in a later stage of the development (e.g., from phase 1 to phase 2) because this was assumed to be a proxy for successful development. In addition, this also included clinical trials with a specific product when they were in the same clinical phase with a parallel study design (e.g., both in phase 1) or for other indications or a different patient cohort. This grading of a clinical trial having a subsequent clinical trial or not was used as a proxy for further clinical development of a CAR T-cell product.

Table II. Determinants used in the analysis.

	Determinants
Drug design	Starting material (autologous/allogeneic)
	Sponsortype (academic/commercial)
Study design	Study phase (phase I/II/III/pilot)
	Primary Endpoint (safety/efficacy/dose/serum concentrations)
	Secondary Endpoint (safety/efficacy/dose/serum concentrations)
	Number of subjects (Small: <17/ Medium: 17-33/ Large: >17)
	Age category (children/adults)
	Multicenter (yes/no)
Study outcome	Multinational (yes/no)
	Followed-up by another clinical trial / approved marketing authorization

Data analysis

All data were collected in IBM SPSS Statistics, version 23, and cross tables and frequency tables were used to create overviews of the overall clinical trial characteristics and subgroup (follow-up trials versus non– follow-up trials) comparisons. Subsequently, the characteristics of the trials without a subsequent trial were compared with the trials with a subsequent clinical trial for early stage trial phases (phase 1 and phase 1/2). Later-stage phases included insufficient numbers (in total 7, 9 and 3 for pilot, phase 2 and phase 2/3) to investigate potential differences among the groups.

Results

Overview of CAR T cell clinical trials

An overview of all characteristics that were scored and their distribution in the 106 CAR T-cell clinical trials that were analysed is shown in Table III. The majority (91%) of the CAR T cells did have an academic sponsor, and most of the trials (68%) were phase 1. For the production of CAR T cells, mainly autologous starting material was used (89%). The number of patients recruited in the clinical trials was equally divided among the different groups (small, medium, large), and most clinical trials were performed with adults as patient cohort (96%). The primary end point most frequently used was safety (51%), and combined end points were defined in 31% of the trials, in which safety was often (85%) included. Secondary end points were often combined (68%), in which efficacy was included for all cases. Approximately a quarter of the clinical trials performed the trial in more than one center, and a small portion (6%) executed multinational trials.

Table III. Distribution of determinants from CAR T-cell clinical trials.

Determinant		Number	(%)
Sponsor type	Academic	96	(91%)
	Commercial	10	(9%)
Study phase	Pilot	7	(7%)
	Phase 1	72	(68 %)
	Phase 2	9	(9%)
	Phase 1/2	15	(14%)
	Phase 2/3	3	(3%)
Starting Material	Autologous	96	(89%)
	Allogeneic	12	(9%)
	Autologous & Allogeneic	2	(2%)
Number of patients recruited	<17	34	(32,1%)
	17-33	34	(32,1%)
	>33	37	(34,9%)
Trial Design - Centres	Single centre	76	(72%)
	Multicentre	30	(28%)
Trial Design – Countries	Single country	100	(94%)
	Multinational	6	(6%)
Patient cohort	Children	4	(4%)
	Adults	67	(63%)
	Adults/children	35	(33%)
Primary Endpoint	Efficacy	7	(7%)
	Safety	54	(51%)
	Serum concentrations ^a	-	-
	Dose ^b	12	(11%)
	Combined	33	(31%)
Secondary Endpoint	Efficacy	28	(26%)
	Safety	11	(1%)
	Serum concentrations ^a	4	(4%)
	Dose ^b	1	(1%)
	Combined	72	(68%)

^aSerum concentration: e.g., T-cell persistence, Pharmacokinetic/ Pharmacodynamic measures, serum cytokine levels.

^bDose: e.g., escalating dose, maximum tolerated dose, dose limiting toxicity.

Characteristics related to further clinical trial development

From the 106 clinical trials with CAR T cells, 49 had a subsequent clinical trial, and 57 did not. From the 57 clinical trials without a subsequent clinical trial, 54% was still open for recruitment; this was the case in a slightly lower percentage (45%) of the trials with a subsequent clinical trial (Figure 2A). The clinical trials that were terminated were more frequently seen in the group without a subsequent trial (16%) compared with the trials with a subsequent trial (6%). From the subsequently followed-up trials, one trial was terminated and incorporated into another clinical trial, and two trials did not reach the recruitment deadline. However, these two are currently still open for recruitment. In contrast, nine clinical trials without a subsequent trial failed in recruitment before the indicated deadline or were stopped. From these nine trials, four were still open for recruitment, others were terminated due to safety issues or unknown reasons. As shown in Figure 2B, there was no difference in the number of clinical trials with or without a subsequent clinical trial per trial phase. The phase 2/3 clinical trials were still in the recruitment phase and were not yet further developed.

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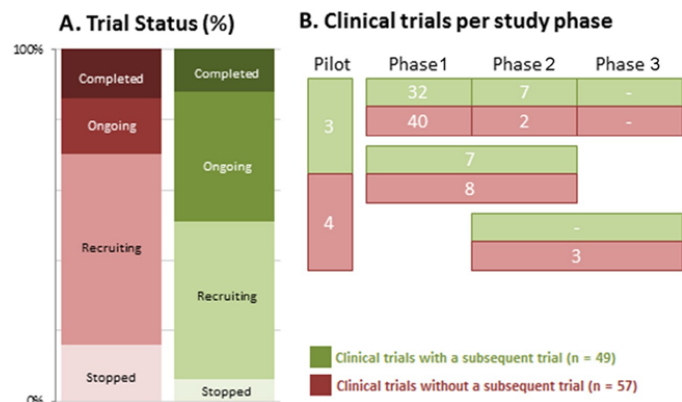


Figure 2. Trial status and clinical phase of the CAR T-cell clinical trials. (A) Status of CAR T-cell clinical trials at point of data collection. Ongoing: recruitment has ended, trial is ongoing. (B) Clinical phases of the CAR T-cell clinical trials.

Next, we analysed whether the clinical trial characteristics, as defined, differed between the clinical trials with and without subsequent trials, which was used as a proxy for the successful clinical development of the CAR T-cell products. As shown in Figure 3A, most studies without a subsequent clinical trial had an academic sponsor (97%), whereas this percentage is lower in the clinical trials with a follow-up clinical trial (84%).

Clinical trials without a subsequent clinical trial more frequently used allogeneic material (14%)

trials (35% versus 29%, respectively; see Figure 3C). In addition, as shown in Figure 3D, multicentre designed clinical trials were more frequently seen in the trials with a subsequent trial (41%) compared with the trials without succession (18%). Furthermore, trials in which children comprised the patient cohort did not have follow-up trials (Figure 3E).

No substantial differences in the primary end points between the two groups were seen (Figure 3F). For the secondary end points, efficacy was more frequently defined in the trials with subsequent trials (37%) compared with the group without a subsequent trial (18%) (Figure 3G). Furthermore, a combination of secondary end points was seen more often (75%) in the trials without follow-up trials compared with the group with a follow-up trial (59%).

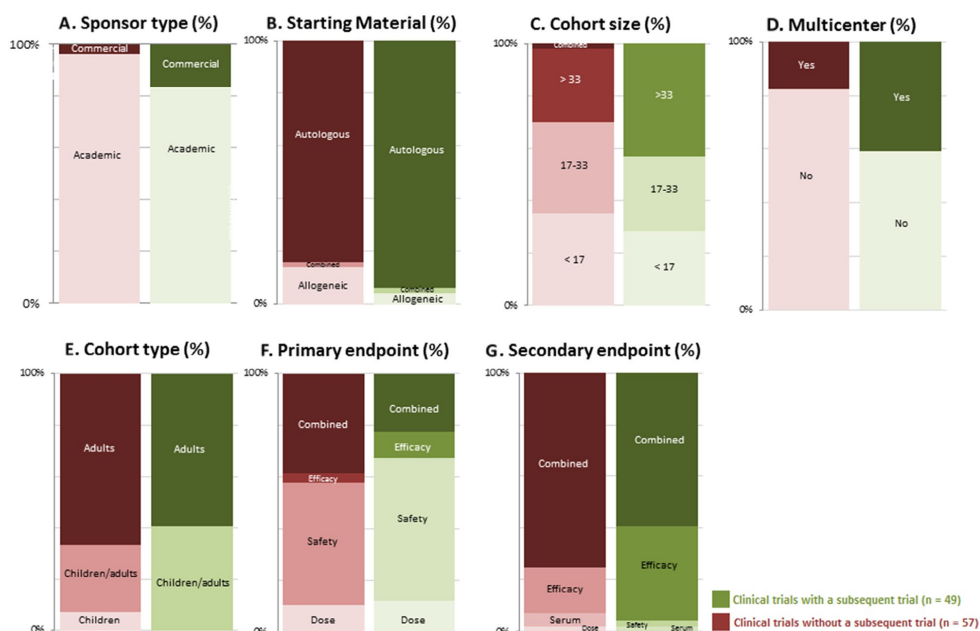


Figure 3. Comparison of clinical trial characteristics between trials with or without a subsequent trial. (A) Sponsor type per trial. (B) Starting material used for the CAR T-cell products. (C) Cohort sizes of the clinical trials. (D) Multicenter or single-center-designed trials. (E) Patient cohort. (F) Defined primary end point in the trial. (G) Defined secondary end points in the trials: serum = end point based on measurements in the serum.

Characteristics related to clinical study phase

It was determined whether the substantial differences seen between the clinical characteristics were related to the study phase of the clinical trial. Due to insufficient numbers in the pilot, phase 2 and phase 2/3 groups, this was only done for the phase 1 and the phase 1/2 group (Figure 2B). No substantial differences were seen between clinical trials with or without a subsequent trial in phase 1 clinical trials. Focusing on the phase 1/2 trials, there were more commercial sponsors in the trials with a subsequent study were shown, and the group without a next-stage trial more frequently had small subject recruitment. Finally, allogeneic starting material was used more frequently in the trials without follow-up compared with those with follow-up trials.

Discussion

In this study, an overview of characteristics of clinical trials performed with CAR T cells in Canada, Europe and the United States was created. The clinical trials were divided in clinical trials with or without a subsequent clinical trial to compare the clinical trial designs. At the time of data collection, based on 106 clinical trials, 57 were not followed up, and 49 had a follow-up clinical trial. The majority of the trials had an academic sponsor, from which most did not proceed to a subsequent trial; most commercially sponsored trials were followed up with another clinical trial. In addition, trials with a subsequent trial more frequently recruited large patient cohorts and were more often multicentre compared with the non-followed up trials. This difference was more pronounced in the phase 1/2 trials compared with phase 1 trials.

The trials sponsored by commercial companies were both early and late stage clinical trials (phase 1, 1/2, 2 and 2/3), suggesting commercial involvement from phase 1 to MAA. Interestingly, for all commercially sponsored, followed-up clinical trials, the same three companies were involved. CAR T-cell products from these companies are expected to be submitted for MAA in Europe and the United States in coming years [13,14]. After phase 1 trials, the majority of the academic-sponsored trials did not have a subsequent clinical trial. This can be explained by various reasons, including that the focus in academic institutions is not product-driven and that there is often lack of sufficient financial support and regulatory knowledge [16].

The first CAR T cell clinical trials sponsored by academia were begun in 1998; since 2015, commercial companies have begun sponsoring the CAR T-cell trials. This difference explains why there are more completed trials among the academic sponsors compared with the commercially sponsored trials, which are all still recruiting. In this study, the end term of having a subsequent clinical trial was used as a proxy for successful product development. It must be noted that trials with a subsequent clinical trial also include those that were started later and are in the same clinical phase (e.g., from phase 1

to phase 1 with a slightly different design, such as another patient cohort or a different clinical indication). This differs in the definition of further development from trials that were followed-up with a clinical trial in a later phase (e.g., from phase 1 to phase 2). However, because we assume that using another indication as broadening the indication for that product and another patient cohort can also extend the population for which the product can be used once licensed, this is also considered further development. The majority of the clinical trials, both for followed up and non-followed up trials, use CAR T cells from autologous, rather than allogeneic, starting material. An important aspect that has to be taken into account concerning the allogeneic starting material is that it can be derived from the donor from whom the patient received a hematopoietic stem cell transplantation (HSCT) if HSCT patients are included in the trial. Therefore, a difference should be noted in non-personalized and personalized (HSCT-donor-derived) allogeneic starting material. Personalized allogeneic starting material is most frequently used for CAR T-cell products. When autologous or personalized allogeneic starting material is used, a specific product has to be manufactured for every patient, and large-scale manufacturing is not possible; this leads to logistic challenges and suggests a more time-consuming and expensive procedure. Interestingly, most GCTs with MAA from the European Medicines Agency and U.S. Food and Drug Administration and are generated from autologous starting material [17,18].

A clinical trial design with more than 33 patients recruited was seen more often in the followed-up clinical trials. When a larger number of subjects is recruited for a clinical trial, there is greater incentive for other parties to collaborate. That most clinical trials (~60%) are performed with smaller (≤ 33) patient groups can be explained by the fact that most of these studies are in phase 1/2 clinical development and for small (orphan) indications. These (very) small patient numbers may lead to suboptimal clinical design to distinguish reliable effect(s) of the product, which may lead to less frequent follow-up with a subsequent trial.

Clinical trials with multicentre design were also more often in the group with follow-up trials compared with single center clinical trials. Phase 2 clinical trials that were followed up were mostly designed with more than 33 patients recruited and were multi center. The majority of the followed-up clinical trials in phase 1 were also multicentre. This strengthens the idea that multicentre trials might have a superior clinical trial design because experts from more than centre are involved [19]; this results in a better chance of a follow-up trial. Some of the differences found in this study might be self-explanatory, such as greater success among large patient cohort and multicentre designed clinical trials, both of which may lead to a higher chance of a subsequent clinical trial. However, from

the 37 trials with large patient cohorts and the 30 multi center designed clinical trials, only 12 trials were both multicentre and included a large patient cohort. This illustrates that a multicentre design does not always include a large patient cohort or vice versa.

Combined defined primary and secondary end points were more frequently used in the non-followed-up clinical trials. Efficacy was more often defined as secondary end point in the followed-up clinical trial group. In this study, we were not able to use the results of these end points because many were ongoing and/ or did not yet have published results. In general, as expected, safety was the most frequently defined primary end point in the phase 1 clinical trials because most phase 1 clinical trials determine the safety of a medicinal product.

From the queries performed in the public U.S. and EU clinical trial registers, the EU database retrieved only eight hits, likely because phase 1 clinical trials are not for public access in the EU. However, as supported in the literature, we included the majority of all CAR T-cell clinical trials that were performed in Canada, Europe and United States [7–9].

Because of the large variety of the GCT subtypes, we focused on the promising CAR T cells. The overviews provided a general impression of the CAR T-cell field and some trends for what may lead to subsequent clinical trials, such as multicentre design, larger patient cohorts and having a commercial sponsor. It should be investigated whether these variables also apply to other GCT subtypes. A recommendation for investigators would be to take these variables into account when designing clinical trials with CAR T-cell products, starting from phase 1/2. For the regulatory authorities that approve clinical trials, we recommend that they take a critical look at clinical trial designs with attention to the potential for further development of a product. This would encourage investigators to think about the product's future development and perhaps lead to a higher success rate in the progression toward MAA.

Acknowledgement

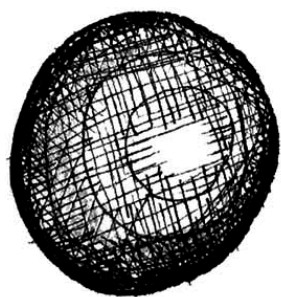
We thank Dr. E.R. Koomen and Dr. M. Teichert for their helpful input on the data presentation.

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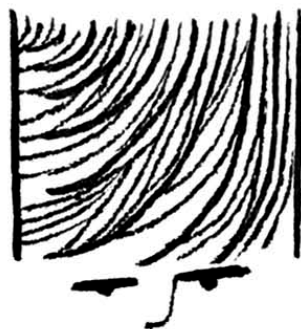
CHAPTER 6

EU decision-making for marketing authorization of Advanced Therapy Medicinal Products

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Submitted



Abstract

In recent years there has been increased interest in the development of advanced therapy medicinal products (ATMPs) towards marketing authorization (MA). In the EU a special regulation came into force in 2009 to regulate ATMPs. However, systemic insight into decision-making for approval is limited. Therefore, we aim to evaluate how EU regulators reached opinions on benefit/risk for ATMPs based on product profiles, scientific evidence and within the context of a regulatory process. European public assessments report (EPARs) of submitted and evaluated ATMPs for MA between 2009 and December 2016, were analysed using a mixed quantitative-qualitative study design to compare different regulatory opinions: standard approval, expedited approval, or non-approval. Analysis consisted of 3 steps: (1) descriptive quantitative cohort analysis of product profile, scientific evidence and regulatory processes, (2) qualitative analysis of major scientific issues and (3) qualitative analysis of the benefit/risk-assessments conducted by the Committee for Medicinal Products for Human Use (CHMP) of the EMA.

Relevant quality issues were raised in all assessment procedures. Most robust clinical trial design and clinical outcomes were evident for standard approved ATMPs (n=5). All expedited approvals were granted for orphan ATMPs, for which considerations of unmet medical need counterbalanced clinical uncertainties and risks. For non-approved ATMPs lack of clinical efficacy and severe safety risks were decisive for negative benefit/risk opinions.

Our findings suggest that setting appropriate standards for ATMP approval in Europe, like elsewhere, is a learning experience. The experimental characteristics of approved ATMPs urge regulators, industry and clinical practice to pay accurate attention to post-marketing surveillance and risk-minimization measures to limit patient risk. Methodologies to evaluate ATMPs and regulations need to be continuously monitored and improved for the field to flourish.

Introduction

In the last decade there has been increased interest in the development of advanced therapy medicinal products (ATMPs) towards marketing authorization. In 2009, Regulation EC No.1394/2007 came into force as the first specific regulatory framework approval of this potentially new class of medicinal products in the European Union (EU)[1,2]. Due to the novelty and complexity of ATMPs, a special Committee for Advanced Therapies (CAT) was founded by the European Medicines Agency (EMA) to support the Committee for Medicinal Products for Human use (CHMP) in benefit/risk assessments, to stimulate early dialogues between the developers and the authorities and to encourage the development of these promising medicinal products towards marketing authorization[2,3]. The CAT advises the CHMP on benefit/risk, who in turn makes a recommendation for centralized approval by the European Committee (EC)[1],[4]. By August 2017 the number of ATMP regulatory procedures for marketing authorization was 16, a number that has been coined as relatively low given the recent impressive advances in basic molecular and clinical science in the field of ATMPs[5–7].

It is well known that ATMP developers face various scientific and technological challenges ranging from manufacturing and quality issues[8] to preclinical and clinical efficacy and safety issues[9]. Moreover, additional hurdles in the trajectory towards approval are experienced by academic developers, such as a lack of regulatory knowledge, insufficient financial support and clinical trial related problems, such as recruitment[10]. Regulation EC No. 1394/2007 includes high-level requirements for approval, however, as the field is rapidly evolving, standardization of regulatory requirements for approval is difficult and perhaps undesirable. Consequently, decision-making for approval of ATMPs largely occurs on a case-by-case basis[11]. Considering these developmental and regulatory complexities, scientific uncertainties during benefit/risk assessments are highly prevalent. In this study we aim to provide insight into decision-making for approval of ATMPs in Europe between 2009-2016. We compare 1) product profiles, scientific evidence and regulatory procedures, 2) scientific issues that were interpreted as critical in the assessment procedure and 3) how EU regulators reached decisions on benefit/risk profiles for ATMPs under both standard and expedited pathways and for non-approved ATMPs.

Methods

Information on assessments procedures for marketing authorization of ATMPs were obtained from the EMA website, using the European Public Assessment reports (EPARs)[12]. Since 2009, 16 applications were submitted in the EU, of which eight procedures led to approval by the EC. Seven applications were either rejected by the authorities (n=3) or withdrawn by the applicants (n=4)

before regulatory decision-making[13]. Two non-approved applications for one product (Cerepro) were analysed at final decision as one assessment procedure, because the initial scientific evidence was only substituted in the second application. In 2017, the CHMP recommended approval of Spherox®, however, because it is not yet approved by the EC, this assessment procedure was excluded. In total, eight approved and six non-approved ATMPs were included for analysis.

Drawing from previous work[14–16], a preliminary set of variables was designed to characterize assessment procedures based on the three elements (product profile, scientific evidence, and regulatory procedures). This set was tested in a pilot study. Consequently, additional variables were added to optimize specificity for assessment procedures for ATMPs from all included assessment procedures, see supplementary 1, table 1. Scientific evidence was divided into four categories: quality, preclinical studies, clinical trial design, and clinical outcome. These variables were used to perform the three steps of the mixed quantitative-qualitative analysis, as described below, in order to compare the various regulatory outcomes (standard approval, expedited approval ('conditional approval' and 'approval under exceptional circumstances (UEC)') and non-approval).

Step 1: Descriptive cohort analysis

A comparison of the characteristics of each regulatory outcome was performed. Two authors (SdW and DC) independently scored the characteristics of each ATMP. In case of disagreement a discussion was held until the final score by consensus. In case of uncertainty, a third independent author (PM) was asked to score independently the specific characteristic. Data were stratified according to regulatory outcome to reveal associations with product profile, scientific evidence and regulatory process using IBM SPSS Statistics 23.

Step 2: Qualitative analysis of major issues

Major objections, major concerns, major deficiencies and grounds for refusal were collected from the EPARs in order to identify scientific issues that were interpreted as critical in the assessment process. Similar to step 1, this collection was independently performed by two authors (SdW and DC), using the search function (eg, 'objections', 'concerns', 'deficiencies') and by distinguishing major from non-major. Also, whether regulators considered such major issue to be resolved or not was identified. Obtained text elements from the EPARs were qualitatively coded in NVivo 11.4.1.1064 Pro. Codes were linked to the corresponding scientific evidence category (quality, preclinical, clinical trial design and clinical outcome) to facilitate categorization of the major issues. Codes were compared between authors, and in case of disagreement a discussion was held until consensus.

Step 3: Qualitative analysis of benefit/risk-assessment

For each scientific evidence category (quality, preclinical, clinical trial design, clinical outcome), relevant text elements were extracted from the 'benefit/risk-balance' and 'recommendation'

sections of the EPARs in order to identify the decisive determinants for positive and negative final regulatory outcomes (approval versus non-approval). For each assessment procedure, variables that were mentioned in the 'benefit/risk-balance' and/or 'recommendation' section and major issues or uncertainties mentioned by regulators were identified and coded in NVivo 11.4.1.1064 Pro. Regulatory interpretations on scientific evidence were included in codes, for example whether scientific evidence category was deemed satisfactory, uncertain or considered to be a major objection.

Per scientific evidence category, codes were transferred to scores ranging from unsatisfactory (--), to neutral (+/-), to satisfactory (++) to depict regulatory consideration of decisive elements and outcome per benefit/risk-assessment. Uncertainty in long-term efficacy/safety was not shown, because these applied for all products and had to be resolved post-marketing according to the regulators.

Results

Step 1: Descriptive cohort analysis

From the 14 included ATMPs, 5 were standard approvals, 3 were approved via the expedited pathway, and 6 were non-approved. In table 1, the product profiles of all assessed ATMPs are shown. Characteristics such as ATMP subtype, starting material, administration route and storage conditions were diverse for the different regulatory outcomes. Orphan drug designation was assigned to all expedited approved products, whereas only 1 (out of 5) standard approved product and half (n=3 out of 6) of the non-approved products were designated orphan drugs. For the expedited approved products no alternative treatment was available, whereas this applied only to 1 out of 5 standard approved products and 2 (out of 6) non-approved products.

Potency assays were part of all the applications. All standard approvals were tested as being according to standards on sterility, purity and viability upon release. However, for the expedited approvals these release tests were not always discussed in the EPARs (available release tests: sterility (n=1 out of 3), purity (n=1 out of 3) and viability (n=2 out of 3)). This also applied to the non-approved products (available release tests: sterility (n=4 out of 6), purity (n=4 out of 6) and viability (n=2 out of 6)). Remarkable is the unspecified shelf-life and storage condition for non-approved products (n=4 out of 6).

Design of pivotal clinical trials were more robust for standard versus expedited approved and non-approved products. For the majority (n=4 out of 5) of the standard approvals a randomized controlled phase III clinical trial was performed. In contrast, for all expedited approved products non-randomized controlled data were submitted. For only 2 (out of 6) of the non-approved products

randomized controlled data were in the dossier. The number of patients recruited was substantial higher for the standard approved products (mean: 244 patients, range: 12-341) compared to non-approved products (mean: 120 patients, range: 26-241) and expedited approved products (mean: 57 patients, range: 14-106). The defined primary endpoints were considered clinically relevant by the regulators for all standard approved products, for some expedited approved ATMPs (n=2 out of 3) and for half (n=3 out of 6) of the non-approved products.

A significant effect on the primary endpoint was demonstrated for all standard approved products. In contrast, significant effects were not demonstrated in 2 (out of 3) expedited approved products and in 5 (out of 6) non-approved products. No added clinical benefit was demonstrated for most of the standard approved (n=4 out of 5) and for all the non-approved products (n=6 out of 6). For all expedited approved products (n=3 out of 3) added clinical benefit was demonstrated due to the lack of alternative therapies.

Table 1. Elements with its variables scored per marketing approval type. Per element, variables are scored for each (non-) approval type of the ATMPs.

		SA (n=5)	CA (n=2)	UEC (n=1)	NA (n=6)
1. Product profile					
Product Type	<i>GTMP</i>	2	0	1	3
	<i>CTMP</i>	1	1	0	1
	<i>TEP</i>	1	1	0	2
	<i>Combined</i>	1	0	0	0
Starting Material	<i>Autologous</i>	4	1	0	2
	<i>Allogeneic</i>	0	1	0	1
	<i>Not applicable</i>	1	0	1	3
End product	<i>Refrigerated</i>	2	0	0	0
	<i>Room Temperature</i>	2	1	0	0
	<i>Nitrogen-cryopreserved</i>	0	1	0	1
	<i>Other-cryopreserved</i>	1	0	1	1
	<i>Unspecified</i>	0	0	0	4
Previous approved in other jurisdictions	<i>Yes</i>	3	0	0	0
Indication area	<i>Cancer</i>	2	0	0	2
	<i>Congenital, hereditary, neonatal diseases</i>	1	0	1	2
	<i>Eye diseases</i>	0	1	0	1
	<i>Immune system diseases</i>	0	1	0	0
	<i>Musculoskeletal diseases</i>	2	0	0	1
	<i>Yes</i>	1	2	1	2
Lack alternative treatment	<i>Yes</i>	1	2	1	2
Orphan drug designation	<i>Yes</i>	1	2	1	3
2. Scientific evidence					
Quality	<i>Potency assay</i>	5	2	1	6
	<i>Release - sterility</i>	5	1	0	4
	<i>Release - Purity</i>	5	1	0	4
	<i>Release - Viability</i>	5	2	0	2
	<i>Release - activity</i>	3	1	1	3
Preclinical	<i>Toxicity</i>	4	2	1	6
	<i>Efficacy</i>	5	1	1	6
	<i>Dose</i>	3	1	1	6
Pivotal trial Design	<i>RCT</i>	4	0	0	2
	<i>Clinical prim. EP</i>	5	1	0	4
	<i>Clinical Relevance prim. EP</i>	5	2	0	3
	<i>Significant Outcome</i>	5	1	0	1
Clinical Outcome	<i>Significant primary EP</i>	5	1	0	1
	<i>Beneficial Effect</i>	1	2	1	0
	<i>Scientific advice</i>	5	2	1	4
3. Regulatory process					
	<i>Restricted Labelling</i>	5	1	1	0

ATMP = advanced therapy medicinal product, CA = conditional approved, CTMP = cell therapy medicinal product, EP = endpoint, GTMP = gene therapy medicinal product, NA = non-approved, RCT = randomized controlled trial, SA = standard approved, TEP = tissue engineering product, UEC = under exceptional circumstances

The CAT consulted expert panels for advice on clinical relevance of outcomes in 3 assessment procedures (standard approval: n=2 out of 5 and non-approval: n=1 out of 6). Scientific advice was provided for almost all applications (n=13 out of 15), but for only 4 (3 approved and 1 non-approved) applications the first interaction between developer and regulators was before the start of the clinical trials. The time between submission and final decision, including clock-stop time, was comparable for standard approved (mean: 633 days, range: 371-857 days) and non-approved products (mean: 668 days, range: 321-1538 days). However, this duration was substantial longer for expedited approvals (mean: 882 days, range: 713-1037 days). Labels were restricted to either reflect

trial populations correctly or to reflect the observed clinical outcomes for subgroups of patients for all approved products, except for 1 (out of 3) expedited approved product.

Step 2: Qualitative analysis of major issues

Major issues were evaluated across assessment procedures, regardless of final regulatory opinion (table 2), for detailed descriptions see supplementary 2, table 1.

For quality, major issues were noted for all products, i.e. the vector (expedited approval n=1 out of 3, non-approved: n=2 out of 6), GMP facility (non-approved: n=3 out of 6), GMO test (non-approved: n=1 out of 6), in-process-controls (standard approved: n=1 out of 5, non-approved: n=2 out of 6), release specifications (standard approved: n=1 out of 5) and specific release tests (standard approved: n=1 out of 5, expedited approved: n=3 out of 3, non-approved: n=5 out of 6). While developers of the approved products were able to resolve the objections before final regulatory decision-making, only one major issue raised for a non-approved product was resolved at time of final regulatory decision-making.

Most of the major issues related to preclinical studies were raised for non-approved products (Table 2). These concerned animal models (n=1 out of 6), plus toxicology (n=4 out of 6) and efficacy studies (n=1 out of 6). On the contrary, no major issues were noted for the approved products, except for 1 (out of 3) expedited approved product, which concerned toxicology and was unresolved upon final decision-making. Nevertheless, it was agreed on the applicant that no suitable animal model was available and the discussed literature was sufficient for approval UEC. In contrast, major issues indicated for non-approved products were still unresolved at time of final decision-making.

For clinical trial design, most major issues were also raised for non-approved products (Table 2). These issues concerned methodological issues or invalid clinical trial design (n=5 out of 6) and change of endpoints or uncertain clinical relevance of an endpoint (n=2 out of 6). A change of endpoints was also noted as major issue for 1 (out of 5) standard approved product and 1 (out of 3) expedited approved product. For the approved products, the major concerns were considered resolved, whereas all major issues on clinical trial design for the non-approved products were unresolved upon final decision-making.

Table 2. Major issues mentioned in the assessment reports for marketing authorization. Per category (quality, preclinical, clinical trial design, and clinical outcome) the major issues including the number of products for which that major objection was raised is mentioned. Light grey = resolved at time of final decision; grey = acceptable at time of final decision; dark grey = unresolved at time of final decision.

		Quality	Preclinical	Clinical trial design	Clinical Outcome
Approved (n=8)	<i>Standard (n = 5)</i>	In process control (1)		Endpoint (1)	
		Release specification (1)			
		Specific release test (1)			
	<i>Conditional (n=2)</i>	Specific release test (2)			
Non-approved (n=6)	<i>UEC (n=1)</i>	Vector (1)	Toxicology (1)	Endpoint (1)	Efficacy (1)
		Specific release test (1)			Safety (1)
		Vector (2)	Toxicology (4)	Design (5)	PD (2)
		GMP Facility (3)	Animal model (1)	Endpoint (2)	GCP (3)
		In process control (2)	Efficacy (1)		Efficacy (6)
		GMO test (1)			Safety (5)
		Starting material (1)			
		Specific Release Test (1)			
		Specific release test (4)			

UEC = under exceptional circumstances; GMO = genetically modified organism; GCP = good clinical practice; PD = pharmacodynamics

Major issues related to clinical outcomes were raised for all non-approved products and for Glybera®, one of the approved products. A lack of favourable clinical outcomes for non-approved products related to both efficacy (n=6 out of 6) and safety (n=5 out of 6). Furthermore, good clinical practice (GCP) was an issue in 3 (out of 6) dossiers and pharmacodynamics data were too limited in 2 (out of 6) non-approved products.

Step 3: Qualitative analysis of benefit/risk-assessment

All benefit/risk-assessments are represented in table 3. In general, approval was not recommended when clinical outcomes were judged as unsatisfactory (--). Unmet medical need did not outweigh unsatisfactory clinical outcomes. The benefit/risk-assessments per regulatory outcome are described below.

Table 3. Benefit/risk-assessment per category. Unsatisfactory, unresolved major objections (--); uncertainty, concerns and risks, trend towards unsatisfactory (-); neutral, mentioned but no clear judgement (+/-); uncertainty, trend towards satisfactory (+); satisfactory (++), not mentioned (empty box), unmet medical need considered in benefit/risk-assessment (▲);

	Quality	Preclinical	Design	Efficacy	Safety	Unmet Medical Need	Benefit - Risk
Standard approval							
Chondroelect[®]	++	+/-	--	+	++		++
Imlygic[®]			-	+	+		+
MACI[®]	++		++	++	++		++
Provenge[®]	--		+/-	++	-	▲	+
Strimvelis[®]			+/-	++	-	▲	++
Conditional approval							
Holocl[®]	-		+/-	+	+	▲	++
Zalmoxis[®]			+/-	+/-	-	▲	+
Under exceptional circumstances							
Glybera[®]	--		+/-	+/-	+/-	▲	+
Non-approval							
Advexin	--	--	--	--	--		--
CLG	--	--		--	--		--
Cerepro	+	+	--	--	--		--
Heparesc			--	--	+/-		-
Hyalograft	--	--	--	+/-	--		--
OraNera	--	--	--	--	--		--

CLG = contusogene ladenovec genodux.

For standard approved ATMPs, benefit-risk balances were mainly based on clinical efficacy results. The beneficial efficacy outcomes and favourable safety profile, resulted in a positive opinion for MACI[®]. The beneficial efficacy trend for Chondroelect[®] and Imlygic[®] combined with satisfactory safety profiles resulted in standard approval, despite ample regulatory discussion about the clinical trial design. Significant and clinically relevant efficacy of Provenge[®] combined with the acknowledged unmet medical need for the target indication (oncology), outweighed the risks and uncertainties related to the safety profile. Compelling efficacy outcomes for Strimvelis[®] demonstrated in clinical practice, with the acknowledged unmet medical need (lack of alternative pharmacological treatment for a life-threatening disease) outweighed risks and uncertainties surrounding latent severe adverse events[17]. Despite these favourable regulatory opinions, divergent positions were submitted for 2 approved products (Imlygic[®]: n=1 ; Provenge[®]: n=13).

As conditional approval pathways prerequisite, the body of evidence is overall less robust and associated with more uncertainty compared to standard approved ATMPs. Uncertainties have to be resolved or managed through post-marketing obligations. Considerations of unmet medical need were part of all decision-making under conditional approval. Uncertainty on significant clinical benefits for Holocl[®] was recognized due to the retrospective, non-randomised, uncontrolled observational study design. Yet, this was outweighed by the manageable risks and acknowledged unmet medical need. Unmet medical need outweighed non-confirmatory clinical benefit and safety due to uncertainty in clinical trial design for Zalmoxis[®]. In response to this positive opinion, a

divergent position was undersigned by 3 member of the CHMP.

Glybera® was the only ATMP approved UEC after a long and extensive assessment procedure, involving many re-evaluations by the CAT and CHMP[18]. Many uncertainties on quality, efficacy and safety led to unfavourable recommendations for approval twice. Before the final re-examination, after previous negative recommendations, lack of robust efficacy outcomes was considered as a major concern. Yet, a post-hoc analysis revealed a beneficial effect with Glybera® for lipoprotein lipase (LPL) deficient patients (n=5). The unmet medical need for this subgroup was crucial to reach approval UEC, taking the ultra-orphan status into consideration. Consequently, the label was restricted to this patient group. The final CHMP opinion was not supported by 16 members who undersigned a divergent positions.

Non-approval of ATMPs was associated with numerous scientific deficiencies. More specifically, 3 (out of 6) non-approved products had an unsatisfactory profile for all scientific evidence elements: quality, preclinical studies, clinical trial design and clinical efficacy and safety. For all non-approved products the clinical trial design was regarded as unsatisfactory which hindered regulators to evaluate the clinical data. Positive results related to quality and preclinical studies were demonstrated for Cerepro. However, unsatisfactory clinical trial design and clinical outcomes resulted in non-approval. For Heparesc, the clinical safety profile was acceptable, but the clinical trial design and clinical efficacy were judged to be unsatisfactory. For Hyalograft only clinical efficacy was acceptable, but other aspects were unsatisfactory. For 4 (out of 6) non-approved products, unmet medical need was acknowledged, but not being sufficient to outweigh scientific deficiencies.

Discussion

In this study we demonstrated how characteristics related to ATMP product profiles, scientific evidence and regulatory processes were considered in the regulatory assessment of the first cohort of ATMPs under the Regulation EC No. 1394/2007. Our results suggest that EU regulators are currently exploring an appropriate regulatory standard for ATMPs, i.e. we are learning to implement this regulation in the most appropriate way. Unmet medical need has been often considered to outweigh scientific uncertainties. In particular this was the case for expedited approved ATMPs, which were all orphan drugs. Non-approval was associated with a lack of clinical efficacy and identified severe safety risks. Moreover, the numerous scientific issues related to pharmaceutical quality demonstrate that this domain remains problematic in the ATMP field[8].

A main pharmaceutical quality issue in the submitted applications concerned the level of validation of release testing conform quality control (QC) for different clinical trial stages and for approval. EU

GMP requirements are more stringent compared to other jurisdictions and may impose development hurdles. For example, in the USA, GMP requirements for gene and cell products increase as the product continues towards a later stage clinical trial[19]. However, the disadvantage of this concept is that GMP adherence may be insufficient upon approval, in particular when phase III clinical trials are not conducted. EU regulators are also searching for justified flexibility for GMP compliance for ATMPs, which is illustrated by the development of a new GMP guideline for ATMPs[20].

Potency also frequently raised major objections for both approved and non-approved ATMPs. ATMP developers experience difficulties in proper potency testing, due to the lack of suitable animal models, little or even lacking knowledge about the mechanism of action, and therefore also lack of validated biomarkers. Developers may prevent failure in late stage development through early investment in potency evaluation[21]. Vector-related problems of in vivo gene therapy medicinal products (GTMPs), such as unaddressed functionality, and dissatisfactory assay replications, belong to the fundamental development aspects of such product and should have been resolved before submission for approval. This also accounts for non-defined end product storage conditions and shelf-life, which are all associated with negative opinions for approval.

In contrast to the early days of the ATMP regulation, it is nowadays possible to conditionally release a product by using a rapid-release test. The final release of fresh products on small scale occurs after administration of the product. Our findings indeed demonstrate that a lack of a final release test was often resolved by the development of a rapid-release test for approved ATMPs. Furthermore, incomparability of the commercial product and clinical trial product also raised major objections. This should and could be avoided by considering future aspects of development already in early stages of ATMP development and proper clinical trial design[10,22].

The observed suboptimal clinical trial designs that create uncertainty on clinical outcomes are in line with earlier reports of development hurdles experienced in the field[7,23]. Only for one approved ATMP the clinical trial design was considered satisfactory. Yet, half of currently approved ATMPs target orphan diseases for which robust clinical trial design is not always possible as a result of small patient populations or a lack of alternative treatment[7,24,25]. Our observations of suboptimal study designs under expedited approval are also in line with findings for conditionally approved products in the EU. For example, RCTs are not commonly conducted under conditional approval[16].

Here, a relatively high proportion of orphan drugs among the approved ATMPs skews the level of scientific evidence to a non-confirmatory nature. There is ample concern that in the field of orphan drugs, but also of targeted oncology products, the non-confirmatory nature of the evidence becomes less confirmatory with the use of non-randomized data and surrogate endpoints[26]. The relatively large ratio of orphan ATMPs will impact the regulatory considerations for marketing approval in the future[27]. Unmet medical need plays an important role in decision-making for approval of ATMPs, provided that the data should at least show some beneficial trends of efficacy or a favorable safety profile to receive approval. This feature is also seen in the field of regulating orphan drugs[14]. Yet, considerations of unmet medical need did not lead to a higher rate of positive opinions on orphan drug approval compared to treatments without unmet medical need[15]. Surprisingly, conditional approval and approval UEC for orphan ATMPs is not primarily initiated by the developers, but by the regulators. In line with previous work, our findings suggest that conditional approval is frequently used as a rescue option for approval[16].

Some major concerns related to clinical trial design, such as a change of primary endpoint, were also raised for standard approved ATMPs. Yet, regulators evaluated scientific evidence as sufficient for standard approval. In addition, unmet medical need was acknowledged and taken into account for decision-making, also for standard approval, such as for Strimvelis®[17]. In contrast, a robust clinical trial design and clinical outcomes are mandatory for standard approval of conventional products [15]. This suggests that EU regulators are exploring an appropriate regulatory standard for ATMPs, , where conventional products may be used as a useful reference. By all means it remains crucial that developers adequately design their clinical trials prospectively to reduce the risk that major issues are identified during marketing authorization assessment. Early scientific advice in this context is recommended, for which under certain conditions fee reductions are in place for ATMP developers [28].

Our findings indicate that the process of decision-making leading to non-approval is similar between ATMPs and conventional medicinal products. Earlier research on regulatory assessment procedures of conventional medicinal products shows that major issues that were unresolved at time of final decision often led to withdrawal by the applicant[23]. Applications for most of the non-approved ATMPs were withdrawn after a negative opinion as a result of major issues. Furthermore, earlier research on conventional medicinal products showed that beneficial, clinically relevant efficacy outcomes are determinants for approval[14]. Strikingly, scientific evidence for non-approved ATMPs was unsatisfactory to great extent as a result of unresolved major issues related to quality, efficacy and safety. These findings underline the challenges in development of ATMPs[8,9,21]. Glybera® is

the only approved product that appears to be an exception to the rule to be approved despite of its uncertain benefit/risk profile. It was approved after a long regulatory process with a restricted label and many uncertainties. In a recent post-hoc analysis only a marginal trend of efficacy was found [29]. Currently, the product is withdrawn by the marketing authorization holder.

The current centralized system for ATMPs, including CAT experts and a wide range of advantages for ATMP developers, creates opportunity to learn and gain experience with these innovative products as well as the underlying science and technology[28]. As the field develops, it is important that regulatory standards (incrementally) co-evolve to tailor procedures and decision-making for these ATMPs. There are in fact numerous regulatory adaptations that are to be implemented soon (e.g. the new Clinical Trial Regulation) in the EU. For sure, these will also affect ATMP development[30]. Others have been recently implemented, such as the new regulatory pathway for priority medicines (PRIME). Many of the investigational medicines that were included in the PRIME scheme are ATMPs [31]. Development efforts are rapidly evolving as well. The ATMPs discussed here reflect a tip of a huge clinical development pipeline [5–7,30], for which applications for approval will be filed in due time. Thus the current analysis reflects decision-making for a small sample of first generation ATMPs, making it difficult to draw generalizable conclusions for the future. It is possible that some observations are driven by product specificity and/or disease characteristics instead of regulatory approval pathways. Therefore, it is crucial to continue to monitor regulatory outcomes and evaluate the ATMP regulatory framework.

In conclusion, EU regulators are making important steps in the field of ATMPs by balancing medical needs and critical scientific uncertainties that may hamper marketing approval. In this context, defining appropriate regulatory standards taking into account the complexities inherent to these products is critical. The development, regulation and clinical application of most ATMPs are still experimental. As long as the risks are acceptable, this seems the way forward. Regulators, industry and clinical practice need to pay accurate attention to post-marketing surveillance and risk-minimization measures of such products to limit possible patient risks. For the field to flourish, developers and regulators need to collaborate to continuously monitor and evolve methodologies and regulations for ATMPs.

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Supplementary 1.

Table 1. Set of variables per element to characterize assessment procedures.

Category	Variable	Scores
1. Product profile		
Profile	<i>Product type</i>	Gene therapy, cell therapy, tissue engineered product
	<i>Product subtype</i>	Dendritic cells, differentiated tissue cells, lymphocytes, MSC, stem cells, ex-vivo gene therapy
	<i>Administration route</i>	Local application, systemical application
	<i>Starting material</i>	Autologous, allogeneic
	<i>Starting material subtype</i>	Differentiated tissues, blood, tumor tissue, other
	<i>End product</i>	Fresh (2-8°C), fresh (18-24°C), cryopreserved nitrogen (-196°C), cryopreserved (-80°C)
	<i>Previous approval in other jurisdictions</i>	Yes, No
	<i>Indication</i>	Oncology, cardiovascular disease, congenital/ hereditary/ neonatal disease, eye disease, immune system disease, musculoskeletal disease, skin and connective tissue disease
Target population	<i>Lack of alternative therapy</i>	Yes (no specific medicinal product treatment available – including standard care), No
	<i>Orphan designation</i>	Yes, No
	<i>Severity of disease</i>	Yes (considered serious, life-threatening, or severely debilitating), No (including not mentioned)
2. Scientific evidence		
Quality	<i>Potency</i>	
	- <i>Available</i>	In process control, release test
	- <i>Release testing</i>	Yes, No
	<i>Release test</i>	
	- <i>Sterility</i>	Yes, No
	- <i>Purity</i>	Yes, No
	- <i>Viability</i>	Yes, No
	- <i>Activity</i>	Yes, No
	<i>Shelf-life</i>	[Time period]
Preclinical	<i>Preclinical data</i>	
	- <i>Toxicity</i>	Yes (studies performed), No
	- <i>Efficacy</i>	Yes (studies performed), No
	- <i>Dose</i>	Yes (studies performed), No
Clinical development plan	<i>Dose-finding studies</i>	Yes (studies performed), No
	<i>Pivotal trial(s)</i>	
	- <i>Number pivotal trials</i>	Number of pivotal trials
	- <i>Number patients</i>	Number of patients (total, all arms)
	- <i>RCT design</i>	Yes, No (single arm, observational)
	- <i>Blinded</i>	Yes, No
	- <i>Comparator</i>	Yes (active comparator, placebo), No (single arm, historical control)
	- <i>Primary endpoint(s)</i>	Clinical, surrogate endpoint
	- <i>Secondary endpoint(s)</i>	Clinical, surrogate endpoint
	- <i>Multicenter</i>	Yes, No
	- <i>Multinational</i>	Yes, No
	<i>Clinically relevant primary endpoint</i>	Yes, No
	<i>Clinically relevant secondary endpoint(s)</i>	Yes, No
	<i>Significant outcome on primary endpoint</i>	Yes, No (trend, no effect)
	<i>Significant outcome(s) on secondary endpoint(s)</i>	Yes, No (trend, no effect)
	<i>Safety concerns/uncertainties</i>	Identified safety concerns, uncertainty due to small sample, uncertainties due to lack of appropriate Methodology/ technology, unexplored safety concerns, concerns due to study design
	<i>Added clinical benefit</i>	Yes (superiority over alternative treatment, first available treatment), No (superiority not shown or not tested)
3. Regulatory process		
	<i>Sponsor type</i>	Non-profit, small or medium sized enterprise, large private company
	<i>Country sponsor</i>	[Country]
	<i>External influence on MA advice</i>	Yes (decision-making by regulators influenced by experts or patient representatives), No
	<i>Regulatory approval pathway</i>	Standard approval, expedited approval
	<i>Scientific advice</i>	Yes, No
	<i>Time to decision</i>	Days between application and decision
	<i>Special requests</i>	Special requests by developer
4. Outcome	<i>Restricted labeling</i>	Yes (label restricted by regulator compared to requested label by sponsor to specific patient groups), No

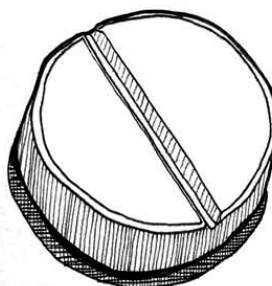
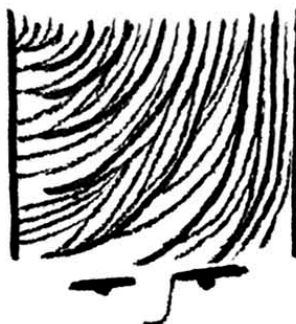
RCT = randomized controlled trial

Supplementary 2

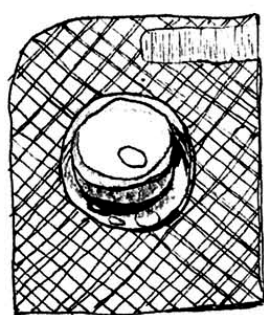
Table 1. Major issues per category discussed in the assessment reports.

Category	Topic	Category uncertainties/objections
SA	Quality	IPC
		Release specification
		Specific Release Test
		Specific Release Test
	Design	Specific Release Test
CA	Quality	Endpoint
		Potency release test insufficient
		Purity not demonstrated (non-proliferation of target cell not demonstrated)
UEC	Quality	No rapid microbial quality control due short shelf-life
		Comparability commercial product and trial product unclear
		Unvalidated potency assay
		Oncogenicity due to structure
		Impurity due to residual viral DNA
NA	Preclinical	Lack of replication assay for release
		Potency specification unacceptable
		Toxicology
		Change of endpoint
		Efficacy
	Design	Lack of robust efficacy outcomes
		Uncertainty severe adverse event
		Safety
		Functionality replicant competent vector unaddressed
		Assay replication competent vector dissatisfactory
	Outcome	Risk associated with structure of vector
		Inconsistency of batches
		Multiple unvalidated release testing
		Lack GMP certification and import license
		Inconsistency of batches
	Preclinical	Impurity/contamination insufficient controlled
		IPC
		Insufficient in-process controls
		GMO Test
		Environmental risk analysis lacking
		Starting material
		Uncertain impact of reagent
		Specific Release Test
		Unvalidated potency assay
		Specific Release Test
		Insufficiently specified potency assay
		Facility
		Lack of manufacturing site
		Limitations of toxicology studies
		Inadequate biodistribution study
	Design	Potential dissimilarity animal and human
		Mechanism of action and benefit not established
		Risk of adverse events
		Methodological issues and invalid study designs
		Bias due to change of endpoints
	Outcome	Uncertain clinical relevance
		No efficacy (benefit)
		Uncertain clinical outcomes
		Unclear clinical pharmacodynamics
		GCP non compliance
	Safety	Insufficient safety reporting
		Risk of severe adverse events

CA = conditional approval; CLG = contusugene ladenovec gendux; GCP = Good Clinical Practice; GMO = Genetically modified organism; IPC = in-process-control; NA = non-approved; SA = standard approved; UEC = under exceptional circumstances. Light grey = resolved, dark grey = unresolved, grey = considered acceptable, although unresolved



PART II - UNLICENSED PHARMACEUTICAL PREPARATIONS



CHAPTER 7

Unlicensed pharmaceutical preparations for clinical patient care: ensuring safety

Sofieke de Wilde, Maria G.H. de Jong, Paul P.H. Le Brun, Henk-Jan Guchelaar, Kirsten J.M. Schimmel
Pharmacoepidemiology and drug safety. 2017 October 19



Abstract

Most medicinal products dispensed to patients have marketing authorization (MA) to ensure high quality of the product, safety, and efficacy. However, in daily practice, to treat patients adequately, there is a medical need for drugs that do not hold MA. To meet this medical need, medicinal products are used in clinical care without MA (unlicensed), such as products prepared by (local) pharmacies: the pharmaceutical preparations. Three types of pharmaceutical preparations are distinguished: (i) reconstitution in excess of summary of product characteristics; (ii) adaptation of a licensed medicinal product (outside its official labelling); (iii) medicinal products from an active pharmaceutical ingredient. Although unlicensed, patients may expect the same quality for these unlicensed pharmaceutical preparations as for the licensed medicinal products. To assure this quality, a proper risk-benefit assessment and proper documentation in (centralized) patient registries and linking to a national pharmacovigilance database should be in place. Based on a risk assessment matrix, requirements for quality assurance can be determined, which has impact on the level of documentation of a pharmaceutical preparation.

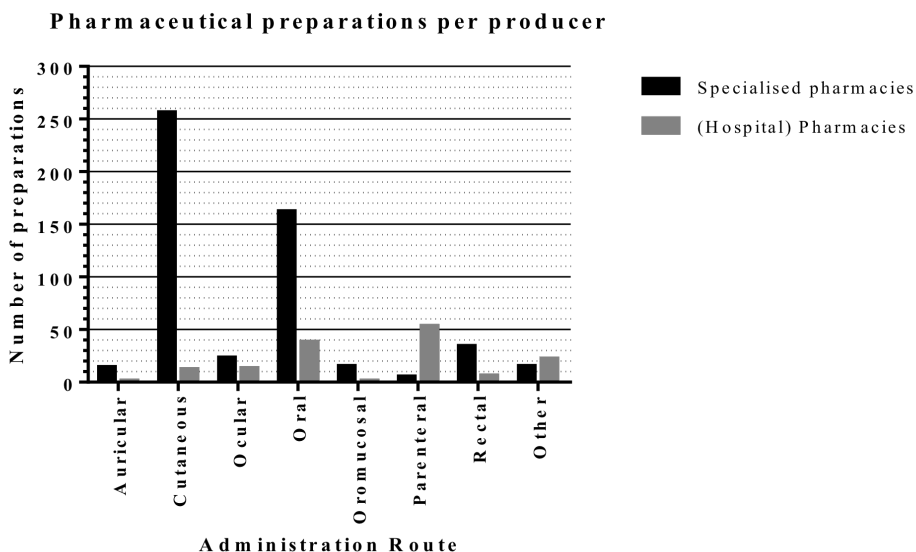
In this paper, the approach for good documentation including quality assurance and benefit-risk assessment will be discussed and possibilities for patient registries are described to make these crucial preparations available for regular patient care.

1 Introduction

In the ideal world, all medicinal products dispensed to patients have marketing authorization (MA) to ensure high quality of the product, safety, and efficacy. However, in daily practice, it turns out that there is a medical need for medicinal products which are not licensed. To meet this medical need, medicinal products are used in clinical care without gained MA (unlicensed), such as off-label use of licensed medicinal products[1], licensed medicinal products which are imported from other countries[2,3], and products prepared by (local) pharmacies: the pharmaceutical preparations[4,5]. This last category is commonly used in regular clinical care; for example in The Netherlands, approximately 300 unlicensed active pharmaceutical ingredients (API) preparations are listed in the Dutch drug database. An illustration of the various administration routes of the pharmaceutical preparations adopted in this Dutch Drug Database per producer type is shown in box 1.

Box 1. Overview of the unlicensed pharmaceutical preparation adopted in the Dutch Drug Database

In the Netherlands, approximately 700 unlicensed pharmaceutical preparations, from which 300 are APIs, are adopted in the Dutch Drug Database, enabling pharmacovigilance. Most unlicensed pharmaceutical products in the Dutch Drug Database are prepared by specialized pharmacies with large production facilities. Mostly, these facilities produce low-risk preparations for cutaneous and oral administration for large indication areas in primary care. In contrary, the (hospital) pharmacies have fewer preparations adopted in this drug database; most frequently, high-risk preparations, eg, intravenous administration, are produced compared with the company preparations. The category “other” includes low numbers of products per administration route, such as inhalation and vaginal administration.



Although pharmaceutical preparations have not been officially approved, patients may expect the same quality as the licensed medicinal products. However, there has not been a formal benefit-risk assessment for these unlicensed products[3]. In this paper, we discuss the different types of pharmaceutical preparations and describe the possibilities to ensure safe use of these products by adequate quality and an appropriate benefit-risk assessment focused on Europe and The Netherlands (see box 2 for a short description of the situation in the United States). Subsequently, the approach for good documentation will be discussed and the possible use of patient registries is described with the aim to make these essential pharmaceutical preparations available for clinical patient care.

2 Unlicensed pharmaceutical preparations

Unlicensed pharmaceutical preparations, are defined in the European Pharmacopeia and Directive 2001/83/EC, and can be prepared at two different scales: Magistral formulas and larger batches for stock.[6–8]

Box 2. Pharmaceutical compounding drugs in the USA

In the USA a magistral formula is defined as pharmaceutical compounding drug, which is described in the US Pharmacopoeia as a preparation produced based on a prescription of a physician or based on the ‘practitioner-patient-pharmacist-compounder relationship’⁶. To ensure safety and quality of these compounding drugs the so-called ‘Pharmaceutical Quality, Security and Accountability Act’ was initiated by the Senate and House committees of the USA[6]. Up to now, the assurance of drug quality, safety, and efficacy has to be performed in accordance with the federal quality standards, which is not verified by the Food and Drug Administration (FDA)[31]. However, the FDA wants pharmacies to register themselves, to ensure safe use of these compounding drugs by being able to perform FDA inspections according to good manufacturing[32].

Magistral formulas, also known as extemporaneous preparations, are formulas prepared in a pharmacy on prescription by a physician[9]. The prescribed medicinal product is for individual use, and no commercial product is available or sufficiently effective. Before preparation, a risk assessment on the pharmacotherapeutic field is executed by the producer and documented to perform a decision based on efficacy and safety of the preparation for treatment of the patient. Finally, pharmaceutical quality assurance of the preparation is performed, as described in the Resolution CM/RES(2016)[8].

2.1 Pharmaceutical quality assurance

The different types of pharmaceutical preparations are accompanied by different aims of quality levels depending on the associated risk. Whereas uniformity of these aims was lacking for the member states of the EU, recently, the Resolution CM/ResAP(2011)1[10] was adapted into the CM/Res(2016)1 to assure pharmaceutical quality and estimate the risk of unlicensed pharmaceutical preparations using a risk assessment matrix[8,10]. In case of high-risk pharmaceutical preparations, quality has to be guaranteed by meeting with good manufacturing practices (GMP)[8]. The pharmaceutical quality of low-risk medicinal products can be assured by using the Pharmaceutical Inspection Co-operation Scheme Good Preparation Practices (PIC/S GPP) guide[8,11]. A drawback of the resolution is that the focus is on the product quality only and patient need is not considered.

2.2 Pharmacovigilance

While health practitioners are obliged to report adverse events of both licensed and unlicensed medicinal products, there is no systematic check on safety, efficacy, and pharmacovigilance for the unlicensed products. According to a review from the European Medicines Agency (EMA), it turned out that adverse events of unlicensed (and off-label used) medicinal products were under registered[1,12]. Furthermore, in cases of registered adverse events, unlicensed medicinal products were more frequently associated with adverse events than licensed medicinal products[1,12]. To ensure safety for these patients the adverse events of unlicensed medicinal products should be documented. This is in line with Regulation (EU) No 1027/2012, which states that the producer of the unlicensed medicinal products is responsible for documentation of the prescribing physician, patients and adverse events[13,14].

2.3 Documentation

Ensuring full documentation, by completing all topics of the product dossier, is not always possible because it may cause a delay in delivery of the medicinal product with unmet medical need.[8] For such individual cases, both the prescriber and the preparing pharmacist have an important role in ensuring quality and safety of the product and informing the patient. There should be a good balance between the benefit of the magistral formulas and the risk of receiving a product with lower quality assurance than a product with MA. Finally, pharmaceutical quality and safety of pharmaceutical preparations practice should be verified via inspections executed by the national healthcare inspectorate or other competent authorities[8].

Whereas magistral formulas are based on physician's prescriptions and intended for individual patients, for-stock pharmaceutical preparations can be prepared for a small (in-house) patient cohort[6]. These for-stock unlicensed medicinal products are prepared by pharmacists or other institutions with a "license for manufacturing"[8]. In these cases, licensing of the individual products

is not required[9,15].

The requirements for magistral and stock preparations are the same; however, for for-stock preparations more controls (eg, analytic end control) are needed compared with the magistral formulas. For such preparations, documentation is required in a format of a product dossier as described in Resolution CM/Res(2016)1[8], which is more extensive than for magistral formulas[15]. For example, information about the release quality control (QC), validation, and stability should be included[15]. Also, for these products, national competent authorities will execute more extensive inspections of the quality and safety of the pharmaceutical process[8].

2.4 Pharmaceutical preparation types

Although there is 1 definition of these pharmaceutical preparations in the EU, there is no uniformity in the interpretation of these preparations among all the countries because it is mostly regulated by national authorities[6,8]. Here, we provide an overview of the different types of pharmaceutical preparations including their requirements and practical elaboration of these requirements for quality assurance and benefit-risk assessments, see figure 1, consisting of reconstitution in excess of SmPC preparation instructions, adaptation of a licensed medicinal product, and medicinal products from an API[15,16].

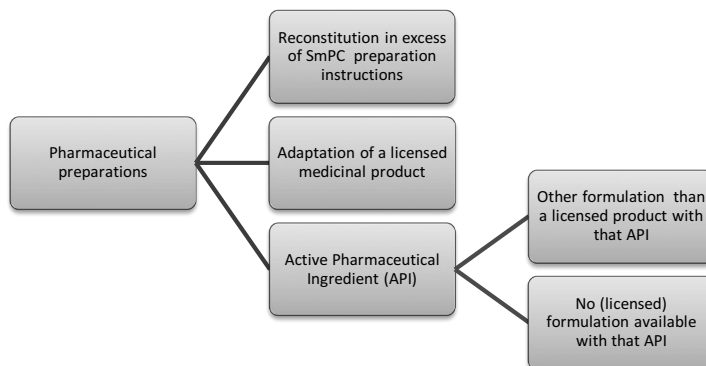


Figure 1. Schematic overview of pharmaceutical preparations. Pharmaceutical preparations can be divided into three different types: reconstitution in excess of SmPC preparation instructions, adaptation of a licensed medicinal product, and medicinal product from an active pharmaceutical ingredient. API = active pharmaceutical ingredient, SmPC = Summary of Product Characteristics.

2.5 Reconstitution in excess of SmPC preparation instructions

Reconstitution can be defined as “manipulation to enable the use or administration of a medicinal product for products with a marketing authorisation issued by any competent medicines regulatory authority, the reconstitution is carried out in accordance with the instructions given in the SmPC or the package leaflet”, according to the European Directorate of Quality of Medicines (EDQM)[8]. Meaning, a preparation of a licensed medicinal product according to the SmPC via good nursing

practice[15–17]. In practice, reconstitution can be done in a more efficient way by preparing products on a larger scale in central units; eg, ready-to-administer syringes can be used as service products by various departments in the hospital. These pharmaceutical preparations are graded as high risk[8]. Like the magistral formulas, these preparations are based on the SmPC of a product and reconstitution by the pharmacy reduces risks of miscalculations and contamination[18,19]. Reconstitution can be executed conform good nursing practice in clinical areas, where upscaling above a certain volume leads to increasing risks because a deficient product may affect the health of a considerable number of patients. This requires enhanced quality assurance via release controls and an increased level of documentation in the product dossier. Due to production of batches, the preservability of the products must be extended. Microbiological validation will require several actions such as process validation and environmental monitoring[20]. Because these manipulations are executed with licensed medicinal products, pharmacovigilance would be possible. It is possible to submit pharmaceutical preparations to a (national) database for pharmacovigilance, and in case this preparation is based on a licensed product, the pharmacovigilance information is already available and can be used in the database. However, it comes under the responsibility of the producer instead of the MA holder.

2.6 Adaptation of licensed medicinal products

Sometimes, administration of licensed formulations may not be possible. In that case, adaptations of medicinal products take place outside the official labelling, eg, phenprocoumon oral suspension 1 mg/ml prepared from 3-mg licensed tablets[21]. An example is amending the dissolution stated in the SmPC or changing the concentration when needed to adequately treat a patient. To ensure patient safety, a concise product dossier, including a substantiated rationale, should be prepared. Furthermore, it is necessary to evaluate efficacy and safety of such manipulations and add this information to the product dossier[15]. When there is a frequent need for this manipulation of an existing product, it can be modified from magistral to for stock preparation. This will lead to more extensive QC and documentation. Based on documentation in the product dossier of magistral formulas, data are available to endorse safety and efficacy of such preparations. Pharmacovigilance can be performed based on the information from the SmPC of the licensed formulation, which is again the responsibility of the producer.

2.7 Active pharmaceutical ingredient

For some patients, preparing from APIs can be necessary[21]. Examples of these products are polymyxin-neomycin tablets and isoniazid injections[22]. As described in section 2.6, for these unlicensed APIs, a concise product dossier to ensure safety is necessary. Results from studies investigating efficacy and safety can improve such dossier[15]. Moreover, risk assessment will decide

whether GPP is enough or if preparation conform to GMP is necessary. Upon upscaling of these individual active ingredients, expansion of the dossier and QC is necessary[8].

3 Pharmaceutical preparations toward marketing authorization approval

There are some examples of (orphan) APIs which used to be prepared by a (hospital) pharmacy, after which a pharmaceutical company converted these preparations into licensed medicinal products.

Interestingly, the prices of these medicinal products sometimes increased excessively, e.g. amifampridine for Lambert-Eaton-myasthenic syndrome (LEMS) and zinc acetate for Wilson's disease[23]. For such pharmaceutical preparations, it may be interesting to assess the possibility to start an MA process in a not-for-profit organisation, based on data from experience in regular care and through a well-established use procedure. However, currently for the MA process, a well-designed clinical trial is preferred showing safety and efficacy. This may give rise to ethical dilemmas because once the medicinal product is already in use in patient care it is difficult to setup a placebo-controlled trial. Furthermore, acquiring MA of pharmaceutical preparations may not be considered in scope of academic institutions[24]. Box 3 describes an example of how the available data of the pharmaceutical preparation for LEMS differed from data used for obtaining MA of the licensed formulation.

4 Ensuring safety

Currently, there are national formularies that provide guidance for quality and rationality for usage of pharmaceutical preparations by standardization of a series of pharmaceutical preparations[25], eg, the German Formulary (NRF) and the formulary of Dutch pharmacists (FNA)[15]. In the Dutch situation, the acronym "FNA" can be used when a preparation conforms to FNA requirements. But when the preparations are distributed toward (other) pharmacies, the official FNA license has to be retrieved provided by the overarching "LNA (Laboratory of Dutch Pharmacists)." Subsequently, these FNA licenses are adopted in the Netherlands Pharmacovigilance Centre Lareb database, monitoring adverse events and safety issues. This example from the Netherlands shows that there are possibilities of performing pharmacovigilance with unlicensed pharmaceutical preparations.

Currently, international organisations are also initiated to collect and analyze adverse drug events, such as the worldwide Uppsala Monitoring Centre set up by the World Health Organization (WHO)[26]. By combining these, the quality assurance, and pharmacovigilance database, safe use of products is well monitored.

Unfortunately, for active pharmaceutical preparations indicated for (ultra) orphan indications such

FNA license is often not available, due to small patient numbers and centralized treatment. Thus, quality and a proper benefit-risk assessments should be ensured by good documentation of the preparing pharmacy. Furthermore, pharmacotherapy control and pharmacovigilance are not yet standard available for APIs. Pharmaceutical preparations with a long history of use and for (ultra) orphan indications, such as 3,4-DAP (see box 3), should leverage on the available documentation in patient files covering information of the treatment, including preparation batches, adverse events, and efficacy data. By collecting more data from clinical experience, eg, in patient registries, an appropriate benefit-risk assessment can be made, which also generates more possibilities in pharmacovigilance for these products.

Nowadays, patient registries are available in all different formats and can be organised by different organizations and/or different parties such as healthcare practitioners (including researchers) or patients, resulting in nonuniform data collections[27]. By creating a (central) patient registry for specific orphan medicinal conditions, the effectiveness of treatments can be collected and safety data can be assessed after a specific time of use[28]. Patient-powered patient registries are mostly controlled by patients and/or their family and cannot be filled in by all patients correctly, for example, due to limited education and understanding of medical terms[29]. Nevertheless, such design led to good uniformity of self-reporting compared to an electronic medical data[30]. On the contrary, when a patient registry is controlled by healthcare practitioners, more representative data and medically validated effects of a pharmaceutical preparation can be collected[30]. Once a patient registry is well designed, it can be linked to a monitoring database, such as the Uppsala Monitoring Centre, which creates opportunities to increase the pharmacovigilance for orphan unlicensed medicinal products.

In conclusion, ensuring pharmaceutical quality and performing a proper benefit-risk assessment, followed by good documentation will guarantee safe use of pharmaceutical preparations. While national formulary labels confirm quality and have implemented pharmacovigilance of the products, this license is mostly unavailable for ultra-orphan preparations. Therefore, good documentation of these treatments can be collected in centralized patient registries and should be combined with existing information in (inter)national databases and self-reflection of patients. Such registries will enable pharmacovigilance and control of the usage of these medicinal products. Linking these patient registries to a centralized database for adverse drug events is highly recommended as it increases safety control of the (ultra) orphan pharmaceutical preparations. Follow-up of a recently started patient registry for LEMS and Myasthenia Gravis patients is an interesting development to monitor the safe use of 3,4-DAP. This approach provides a solution to ensure safe use of

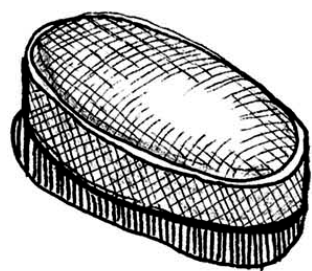
pharmaceutical preparations and at the same time prevents unacceptable high costs charged by the pharmaceutical industry for products which are already used in clinical care and have a proven record regarding safety and efficacy.

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CHAPTER 8

The possibility of obtaining marketing authorization of orphan pharmaceutical compounding preparations: 3,4-DAP for Lambert-Eaton Myasthenic Syndrome

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Abstract

Pharmaceutical preparations, produced by (hospital) pharmacies, usually do not have marketing authorization. As a consequence, some of these pharmaceutical preparations can be picked-up by a pharmaceutical company to retrieve marketing authorization, often leading to price increases. An example is the 3,4-diaminopyridine slow release (3,4-DAP SR) tablets for Lambert-Eaton Myasthenic Syndrome (LEMS). In 2009 marketing authorization was given for the commercial immediate release phosphate salt of the drug, including a fifty-fold price increase compared to the pharmaceutical preparation. Obtaining marketing authorization for 3,4-DAP SR by academia might have been a solution to prevent this price increase. To determine whether the available data of a pharmaceutical preparation with long-term experience in regular care are adequate to retrieve marketing authorization, 3,4-DAP SR is used as a case study.

A retrospective qualitative case-study was performed. Initially, document analysis was executed by collecting the required data for marketing authorization in general and whether data of Firdapse® and 3,4-DAP SR met these requirements. Secondly, the (non-) available data of the two formulations were compared with each other to determine the differences in availability.

At the time of approval, almost all data were available for both Firdapse® and 3,4-DAP SR. Conversely, much of the data used for the approval of Firdapse® originated from the 3,4-DAP immediate release (3,4-DAP IR) formulation. Only two bioequivalence studies and one pharmacology safety study was performed with Firdapse® before marketing authorization application.

In conclusion, at time Firdapse® retrieved approval, the data available did not differ substantially from 3,4-DAP SR, indicating that approval with 3,4-DAP SR would have been possible. We make a plea for approval of orphan medicinal products developed and manufactured by academic institutions as to keep utilization of these products affordable.

Introduction

The Lambert-Eaton Myasthenic Syndrome (LEMS) is an ultra-orphan autoimmune disease of the neuromuscular junction[1,2] with a prevalence of 0.35:100 000[3,4]. Currently, due to lacking curing treatment of LEMS, symptoms can be relieved by preferably symptomatic or immunomodulating treatment[5]. 3,4-Diaminopyridine (3,4-DAP) is the most frequently prescribed symptomatic treatment and is used globally[6].

Until 2009, two formulations of 3,4-DAP tablets used to be available as pharmaceutical preparations: 3,4-DAP base immediate release (3,4-DAP IR) and 3,4-DAP base slow release (3,4-DAP SR). However, in 2009 a third type of 3,4-DAP received marketing authorization in Europe, Firdapse®[7], an immediate release phosphate salt, see table 1. Due to the licensed status of Firdapse® and the obtained orphan designation status, including ten years of market exclusivity, the two other 3,4-DAP formulations were not allowed anymore for treating LEMS in most countries despite the fact that before the licensed Firdapse® appeared, 3,4-DAP IR had obtained long-term experience in LEMS patients[8,9]. Likewise, the SR variant of 3,4-DAP has been produced and used for over 20 years at the Leiden University Medical Center (LUMC) in The Netherlands.

Table 1. Different formulations of 3,4-diaminopyridine. 3,4-DAP IR = 3,4-diaminopyridine immediate release, 3,4-DAP SR = 3,4-diaminopyridine slow release

Name	Base/phosphate	Immediate/slow release	Trade Name
3,4-DAP IR	Base	Immediate	NA (pharmaceutical preparation)
3,4-DAP SR	Base	Slow	NA (pharmaceutical preparation)
3,4-DAP phosphate	Phosphate	Immediate	Firdapse®

For Firdapse®, obtaining complete data for marketing authorization submission was not possible due to the rarity of the disease. Therefore, this medicinal product is approved ‘under exceptional circumstances’[7]. After the approval of Firdapse®, a substantial increase in pricing occurred compared to the costs for the available pharmaceutical preparations 3,4-DAP SR and IR[10]. This rise in costs negatively influenced regular LEMS patient care: e.g. in the United Kingdom, due to the 50-fold increase in costs, health care insurances were not willing to pay these extra costs, while the pharmaceutical formulations were forbidden to be provided to patients, resulting in inaccessibility of 3,4-DAP as a treatment for LEMS patients[11,12]. Alternatively, in The Netherlands the Dutch Minister of Health, Welfare and Sport decided that due to the modified release profile of the SR formulation and the undesirable additional costs of Firdapse®, estimated at €1.8 million per year for the 40-70 treated patients, 3,4-DAP SR was still allowed for the treatment of LEMS patients[10].

Several pharmaceutical preparations, such as 3,4-DAP IR and SR, are produced in the (fully Good Manufacturing Practices (GMP) licensed hospital) pharmacies. In most cases, these are medicinal products for (ultra-) orphan diseases and arise from *ad hoc* preparations. Sometimes, in case such *ad hoc* preparation is prescribed more frequently, these preparations can be scaled up to (small) for-

hoc preparation is prescribed more frequently, these preparations can be scaled up to (small) for-stock preparations[13]. These for-stock preparations increase the requirements for documentation of the product and its quality assurance and lead to substantial experience with such medicinal products in regular care “Unpublished Observations, S. de Wilde *et al.*”[13]. However, these unlicensed pharmaceutical preparations can easily be picked up by the pharmaceutical industry, and in some cases receive a license with a substantially higher price tag in comparison with the pharmaceutical preparation formulation[12]. 3,4-DAP SR is an example of such pharmaceutical preparation which was picked-up by the industry and for which the costs increased tremendously, but other examples exist, such as ibuprofen for neonatal patent ductus arteriosus and zinc acetate for Wilson's disease[14].

Licensing of a medicinal product guarantees a level of quality, efficacy, and safety of the product. Moreover, industrial production is more rigidly monitored compared to pharmaceutical preparations[13]. Due to this extra monitoring, it is reasonable that the costs for treatment increase compared to the regular therapy with pharmaceutical preparations. However, due to the ten years market exclusivity and the small market size, prices for (ultra-) orphan drugs often rise more than desired[15,16]. In some cases, the increase can be disproportionate to the limited efforts required for authorization[17], especially when (hardly) no original research is performed by the pharmaceutical company to obtain marketing authorization.

To determine whether the available data of a pharmaceutical preparation with long-term experience in regular clinical care are sufficient to apply for marketing authorization, 3,4-DAP by LEMS is used as a case study. The available data of 3,4-DAP SR will be compared with the data of the licensed Firdapse[®], to investigate whether 3,4-DAP SR could have been licensed at the same time as Firdapse[®] did and/or which additional studies are still required to retrieve marketing authorization with 3,4-DAP SR. The goal of investigating marketing authorization possibilities for the pharmaceutical preparation 3,4-DAP SR is to guarantee regular patient care at a reasonable price. Recommendations will be provided to ensure reasonable pricing and possibilities of pharmaceutical preparations towards marketing authorization.

Methods

Study design

A retrospective qualitative case-study was performed with 3,4-DAP SR and Firdapse®. Initially, a document analysis was conducted to collect the required data for marketing authorization and whether Firdapse® and 3,4-DAP SR met these requirements. Secondly, the available data for the two formulations were compared with each other, to determine at which points the data of 3,4-DAP SR differed from the data of Firdapse®.

Processing and analysis of the data

Based on the requirements for an assessment report (AR)[18–20], data of Firdapse® in the AR were scored on availability[7]. When data were adopted in the AR, a check on the origin of the data was performed, including whether data came from the phosphate salt (Firdapse®) or from the 3,4-DAP IR. In case data were not available but were required after approval by the European Medicines Agency (EMA), this was also scored.

Above described method was also used for the unlicensed 3,4-DAP SR. Not only the pharmaceutical product dossier of 3,4-DAP SR was examined “Unpublished observations, M.G.H. de Jong, S de Wilde, K.J.M. Schimmel” but also the sources PubMed and Scopus were used to search for additional data, such as non-clinical and clinical pharmacokinetics and non-clinical toxicology.

Finally, data for both formulations were compared to determine whether the available data of 3,4-DAP SR differed from the data used for licensing of Firdapse®. Eventually, it was determined whether additional research would have been necessary for marketing authorization of 3,4-DAP SR, see figure 1. The scored data were subcategorized in quality (see supplementary 1), non-clinical (see supplementary 2) and clinical aspects (see supplementary 3) like the AR of Firdapse®.

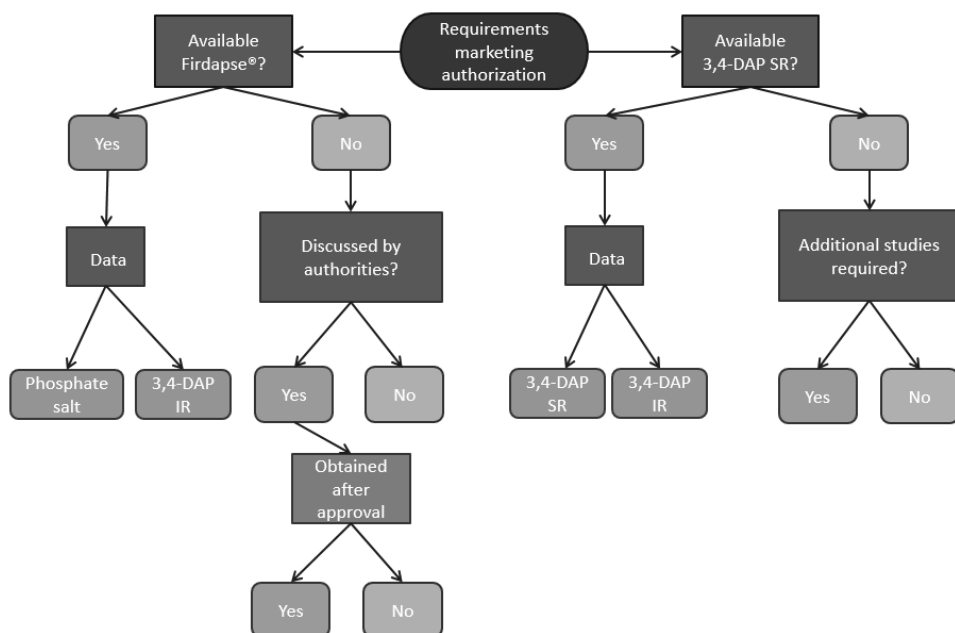


Figure 1. Schematic overview of the methodological analysis. 3,4-DAP = 3,4-diaminopyridine; IR = immediate release; SR = slow release.

Results

Overviews of the available data of Firdapse® in the AR and of 3,4-DAP in the product dossiers are listed in appendices 1-3, and a summary of missing data for both products is shown in table 2.

Quality

All required quality data, according to the requirements for marketing authorization, were available for both Firdapse® and 3,4-DAP SR (see supplementary 1). For 3,4-DAP SR, the data were less extensively described compared to Firdapse® but the data met the requirements (see supplementary 1).

Table 2. Missing data of Firdapse® and 3,4-DAP SR in the EPAR or product dossier. 3,4-DAP = 3,4-diaminopyridine; EPAR = European public assessment report; IR = immediate release; SR = slow release.

Missing data			
		Firdapse®	3,4-DAP SR
Quality		-	-
Non-clinical	<i>Pharmacology</i>		Safety pharmacology programme
		Pharmacodynamic drug interactions	Pharmacodynamic drug interactions
	<i>Pharmacokinetics</i>		Distribution
		Metabolism	Metabolism
		Excretion	Excretion
		Pharmacokinetic drug interactions	Pharmacokinetic drug interactions
	<i>Toxicology</i>	Carcinogenicity	Carcinogenicity Reproduction toxicity Toxicokinetic
Clinical	<i>Pharmacokinetics</i>	Data obtained after approval	No data
	<i>Pharmacodynamics</i>	Secondary pharmacology	Secondary pharmacology
	<i>Efficacy and safety</i>	Available data and 3,4-DAP IR data	Available data and 3,4-DAP IR data

Non-clinical

The primary and secondary pharmacodynamic data were available for both formulations. However, data about the pharmacodynamic drug interactions for both medicinal products were lacking, see supplementary 2. Moreover, for 3,4-DAP SR the safety pharmacology programme was also missing. For both medicinal products data were adopted from the IR formulation of 3,4-DAP and both in vitro data and secondary pharmacodynamic data acquired from 3,4-DAP IR were described in the AR of Firdapse® and could be extended for 3,4-DAP SR. Also, data from 3,4-DAP IR, obtained from literature, was used for the in vivo data of 3,4-DAP SR[21,22].

Limited pharmacokinetic data were available for both product formulations, and absorption data were available for both medicinal products, see additional file 2. As for metabolism and excretion, no studies have been performed. Distribution data were only available for Firdapse®.

For Firdapse®, only carcinogenicity data were lacking from the toxicology data. On the contrary, since 3,4-DAP SR did not contain much toxicology data, data were adopted from the IR formulation, like for Firdapse®. The genotoxicity data were conducted from studies with 3,4-DAP IR and given in the AR of Firdapse®. The lacking data about the single-dose toxicity of 3,4-DAP SR were obtained from literature[23]. The pharmaceutical company of Firdapse® conducted the reproduction toxicity study after approval; this toxicity study was a requirement of approval along with the carcinogenicity study (see supplementary 2).

The ecotoxicity/environmental risk assessment for both medicinal products was acquired from 3,4-DAP IR (see supplementary 2). The results of this study were presented in the AR of Firdapse®.

Clinical

Overall, the clinical data for both Firdapse[®] and 3,4-DAP SR also contained data adopted from 3,4-DAP IR. A pharmacokinetic study in healthy volunteers was conducted after approval of Firdapse[®] and published in 2014[24], see supplementary 3. At the time of approval, these data were not yet provided, thus the available data were similar to 3,4-DAP SR. Data about the pharmacokinetic interactions and pharmacokinetics using human biomaterials were not available for both products. The presented pharmacodynamic data of 3,4-DAP SR were the same as Firdapse[®] (see supplementary 3). The primary pharmacology, the relation between plasma concentration and effect, and the pharmacodynamic interactions with other medicinal products or substances were acquired from 3,4-DAP IR for both products. For the clinical efficacy and safety almost all required data were available for both Firdapse[®] and 3,4-DAP SR, with the exception of data for special populations, such as patients with hepatic or renal impairment (see supplementary 3). Due to the long-term availability of 3,4-DAP SR, more experience in patients has been established compared to Firdapse[®].

Discussion

In this study, the AR of the licensed Firdapse[®] and the product dossier of the pharmaceutical preparation 3,4-DAP SR were analysed to investigate whether data fulfilled the requirements for marketing authorization as described by the EMA or which studies should be initiated to complete the lacking data. Since not all required data were available at the time of marketing authorization, due to the small LEMS patient cohort, Firdapse[®] was approved 'under exceptional circumstances'[7]. At the time of approval, most of the data were equally available for both Firdapse[®] and 3,4-DAP SR. Furthermore, most of the data used for the approval of Firdapse[®] originated from 3,4-DAP IR[10].

Firdapse[®]

Only two medium-sized bioequivalence studies (one in animals and one in healthy volunteers) and one small pharmacology safety study was performed with Firdapse[®] before applying for marketing authorization[7]. Due to the demonstrated bioequivalence studies, with equal areas under the curves (AUC) for both Firdapse[®] and 3,4-DAP IR, bridging of (non-) clinical data from 3,4-DAP IR was justified for Firdapse[®]. The equal AUCs support the assumption that efficacy between those two medicinal products is identical[25].

After marketing authorization approval, additional studies were required by the EMA. For non-clinical data, a carcinogenicity and a reproduction toxicity study still had to be performed. Furthermore, a clinical pharmacokinetic study, concerning the effects of food intake[26] and genetic variation in aryl N-acetyltransferase[24], was required. All required additional studies were

conducted, except for the non-clinical carcinogenicity study[7]. At last, more data about the clinical efficacy and safety had to be obtained, which was achieved by executing a phase III, randomised, double-blinded clinical trial[27], on the company's own initiative, and by the establishment of an LEMS patient registry in Europe[28]. With the patient registry, additional long-term efficacy and safety data is provided and the exposure to Firdapse® can be monitored[28]. Furthermore, this patient registry may collect additional data about special populations, such as patients with hepatic or renal impairment[7,28].

3,4-DAP SR

Many characteristics of 3,4-DAP SR originated from the IR, like Firdapse®. Data from 3,4-DAP IR can be used for the SR formulation, since both pharmaceutical formulations contain the same active ingredient, as shown in figure 2. It is also expected that the exposure is the same as 3,4-DAP IR (in case the active ingredient is completely absorbed)[25,29]. To confirm these assumptions, a pharmacokinetic study should be conducted to determine whether the AUC of 3,4-DAP SR equals the AUC of Firdapse®, and thus 3,4-DAP IR. By using the same study design as the pharmacokinetic study of Firdapse®[26], the results can be compared without using the expensive medicinal product in a study design. By using this strategy, no study is required that directly compares the pharmacokinetics of Firdapse® with 3,4-DAP SR. In case the AUC of 3,4-DAP SR equals the AUCs of the IR and Firdapse®, non-clinical data of Firdapse® can be used for 3,4-DAP SR as well.

3,4-DAP SR has been used for over 20 years in regular clinical care in The Netherlands, which means long-term experience in patients. Up to now, no severe, likely related adverse events have been reported at the Dutch pharmacovigilance database (Lareb) taking into account that no official pharmacovigilance has been performed yet.

Scoring of the availability of the aspects, “yes” or “no”, in the AR or in the product dossier do not reflect the extensiveness of the available data. An extensive amount of the required data for marketing authorization was discussed in the AR of Firdapse®, but sometimes the data were only briefly described. Also for 3,4-DAP SR, not all the data are comprehensively described, for example, the quality part is not as extensively described as Firdapse®. Whereas parts of the guideline are very descriptive about the requirements of quality, non-clinical and clinical aspects of the marketing authorisation application, these requirements were not always met by Firdapse® (and 3,4-DAP SR). Still, our analysis provides a good overview of the data required for approval and which data can be collected after approval for 3,4-DAP SR.

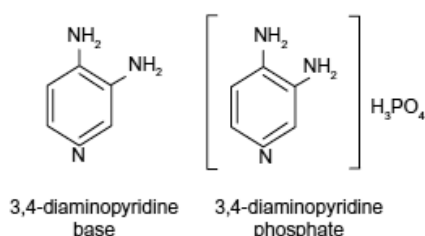


Figure 2. Chemical structures of 3,4-diaminopyridine base and 3,4-diaminopyridine phosphate (Firdapse®). Figure adapted from Lindquist, 2011[34]. Both 3,4-DAP base and 3,4-DAP phosphate (Firdapse®) contain the same active ingredient. 3,4-DAP = 3,4-diaminopyridine; SR = Slow release.

Furthermore, we have to keep in mind that the Firdapse® and 3,4-DAP SR is a specific case of a pharmaceutical preparation, and in order to apply for licensing a high level of documentation is needed. However, we think that this example clarifies the possibilities of pharmaceutical preparations towards licensing as a possibility to keep treatment available at reasonable costs.

Another possibility to avoid tremendous increases in pricing after licensing former pharmaceutical preparations can be established by more involvement from the government in protecting the purpose of the (ultra-) orphan drug designation. For example, in case the (ultra-)orphan medicinal product exceeds the number of 50 000 patients using it[4], the qualification of an (ultra-) orphan drug expires and the exclusivity period can be decreased[30]. In Japan, pharmaceutical companies pay a 1% sales tax on orphan drugs with annual profits exceeding 100 million Japanese yen (approximately €900 000,-)[30]. Moreover, the price transparency can be increased. In the EU, the pricing of (ultra-) orphan drugs is completely confidential which leads to unanswered questions[31]. Increased supervision of the Health Technology Assessment (HTA) might also positively influence the price tag[32]. The HTA should supervise the data on which a product received marketing authorization. In the case of a sudden and extreme price increase, without significant research performed by the pharmaceutical company to justify this increase in pricing, it is advisable that the HTA can impose restrictions to stop the tremendous price increase.

Since the available data from 3,4-DAP SR did not differ substantially from Firdapse® at the time of approval, there is a possibility that academic institutions can retrieve marketing authorization for pharmaceutical preparations after long-term use. As shown in the case of Firdapse®, a medicinal product can receive marketing authorization with hardly any original research and some small additional studies. However, in academic institutions, applying for marketing authorization is not a priority: since the focus is more science and care-driven instead of product-driven[33]. A commencement can be made by ensuring good documentation and quality controls to guarantee safety of the product for the patients. Subsequently, registration of all safety and efficacy data can

be obtained via good documentation, such as an LEMS patient registry, and can be used for applying for marketing authorization with such a product. Another possibility is to collaborate with a pharmaceutical company, to ensure safety for patients against affordable prices.

Conclusions

In conclusion, at time Firdapse® retrieved marketing authorization approval, the available data did not differ much from 3,4-DAP SR, indicating that marketing authorization approval with 3,4-DAP SR would have been possible, most likely 'Under Exceptional Circumstances'. Such approval requires post-marketing additional studies like it was the case for Firdapse®. To license 3,4-DAP SR, a pharmacokinetic study in healthy volunteers is necessary and investigation of long-term safety and efficacy could be established by collecting data in a patient registry. To avoid the tremendous price increases of pharmaceutical preparations like 3,4-DAP SR, the involvement of the government and HTA can lead to more control over the data used for marketing authorization by a commercial company. Furthermore, 3,4-DAP shows the possibility of retrieving marketing authorization with a pharmaceutical preparation by academic GMP licensed institutions.

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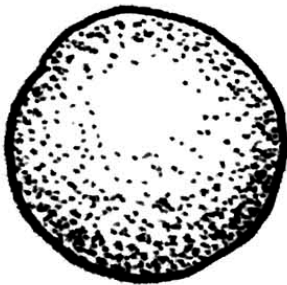
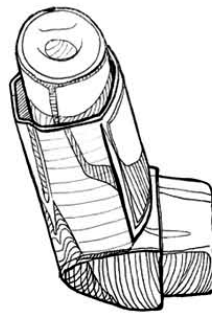
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Supplementary 3

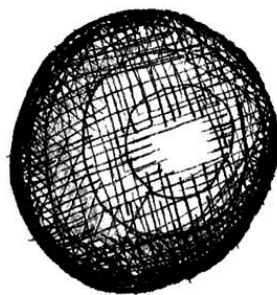
Table 1. Available data on clinical aspects for Firdapse^{*} and 3,4-diaminopyridine slow release (3,4-DAP SR)

Clinical aspects		Firdapse		3,4-DAP SR	
		Data (Yes/No)	available	Data (Yes/No)	available
Introduction		Yes		Yes	
GCP		Yes		Yes	
Pharmacokinetics					
Absorption	Bioequivalence	Yes		Yes ^{*1}	
	Bioavailability	Yes ^{*2}		No	
Distribution and elimination	Metabolism	Yes ^{*2}		No	
	Dose proportionality and time dependencies	Yes ^{*2}		No	
	Intra- and inter-individual variability	Yes ^{*2}		No	
	Special populations	Yes ^{*2}		No	
	Pharmacokinetic interaction studies	No		No	
	Pharmacokinetics using human biomaterials	No		No	
Discussion on pharmacokinetics		Yes		Yes	
Pharmacodynamics		Yes		Yes	
Mechanism of action		Yes		Yes	
Pharmacology	Primary pharmacology	Yes ^{*1}		Yes ^{*1}	
	Secondary pharmacology	No		No	
	Relation between plasma concentration and effect	Yes ^{*1}		Yes ^{*1}	
	Pharmacodynamic interactions with other medicinal products or substances	Yes ^{*1}		Yes ^{*1}	
Discussion on pharmacodynamics		Yes		Yes	
Clinical efficacy	Clinical efficacy	Yes ^{*1,3}		Yes ^{*1}	
	Clinical studies in special populations	No		No	
Discussion on clinical efficacy	Supportive studies	Yes ^{*1}		Yes ^{*1}	
		Yes		Yes	
	Patient exposure	Yes ^{*1,3}		Yes ^{*1,3}	
	Adverse events	Yes ^{*1,3}		Yes ^{*1,3}	
	Serious adverse event/deaths/other significant events	Yes ^{*1,3}		Yes ^{*1,3}	
Clinical safety	Laboratory findings	Yes ^{*1}		Yes ^{*1}	
	Safety in special populations	No		No	
	Safety related to drug-drug interactions and other interactions	Yes ^{*1}		Yes ^{*1}	
	Discontinuation due to adverse events	Yes ^{*1,3}		Yes ^{*1,3}	
	Post-marketing experience	Yes		Yes	
		Yes		Yes	
Discussion on clinical safety		Yes		Yes	

^{*1} Data from 3,4-DAP IR; ^{*2} Data obtained after approval of Firdapse[®]; ^{*3} limited data about the medicinal product itself.



PART III - DISCUSSION, CONCLUDING REMARKS AND SUMMARIES



CHAPTER 9

General discussion



Problem statement

This thesis focuses on drug development and drug manufacturing for special (small) patient populations in academic institutions. Reaching the patient via the commercial route of marketing approval (licensing) does mostly not apply to these academic products. The first category of these drugs, the advanced therapy medicinal products (ATMPs), belongs to a new complex group of medicinal products, of which the process of acquiring marketing authorization is relatively unexplored. The second category is the unlicensed tailor made pharmaceutical preparations, which have been used in clinical care in hospitals for decades. Despite long-term experience, it seems that commercialization of these pharmaceutical preparations, via licensing, has never been the main goal for academia.

The aim of this thesis is to explore the development field of these academic medicinal products and the role of the academic developers and manufacturers for providing these products for regular patient care whether commercialized or not.

The path to reach the patient: current status

ATMPs

The mainly academic origin of ATMPs[1], as confirmed in **Chapter 4**, can be explained by the fact that academic institutions have many strengths in stimulating early development of these products, such as high pathophysiological knowledge of diseases and availability of human derived materials for different purposes (for example biobanks, disease models and starting material; **Chapter 2**). However, besides these strengths in academia during the initial stages of basic research and early clinical development, many hurdles can be identified in the trajectory from later stage clinical development via marketing authorization towards regular patient care. These hurdles, experienced in later stage clinical development and marketing authorization, are confirmed by the different stakeholders, including academic researchers, as described in **Chapter 3**. In the last decade, the number of clinical trials concerning ATMPs has increased in Europe[1,2] (currently, estimated at ≥ 300 clinical trials), which supports the promising nature of these products. In Europe, the main countries that performed clinical trials (and adopted it in the European clinical trials database) with ATMPs were Spain and the United Kingdom (UK). Also, The Netherlands belongs to the top 5 countries with most conducted ATMP clinical trials, as shown in **Chapter 4**.

As described in **Chapter 2**, it is to be expected that, due to the patient care that takes place in the academic institutions, direct patient access would lead to easy patient recruitment and enrolment in the clinical trials. However, from **Chapter 3**, it becomes clear that some of the academic researchers experience difficulties in recruiting patients. This challenge in recruiting may be explained by the fact

that ATMPs are frequently developed for orphan patient groups, meaning that the patient cohorts are small. As a consequence, this insufficient patient recruitment can affect the feasibility of (meeting the deadline for) completing the trial. Indeed, due to insufficient recruitment, some chimeric antigen receptor T-cells (CAR T-cells) trials failed to be completed before the stated deadline, as shown in **Chapter 5**. Also here, academic sponsors appeared to have problems with recruitment more frequently compared to commercial sponsors. A solution for this problem is creating public databases for patients, showing the clinical trials that are open for recruitment of specific patient groups, as described in **Chapter 3**. Patient organisations should help by publishing such databases.

After phase I clinical trials, the majority of the academic sponsored trials were not followed up by a subsequent clinical trial. An explanation may be that academic sponsors are not product-driven, have less financial support and lack in regulatory knowledge, as described in **Chapter 2 and Chapter 3**. Furthermore, the clinical trial design itself seems to have an impact on whether trials are being followed up by subsequent trials: recruitment of large patient numbers and execution of a multicentre clinical trial may have a positive influence on a clinical trial being followed up or not (**Chapter 5**). Proper clinical trial design forces investigators to consider the ultimate objective of their product, especially when combined with a target product profile (TPP), which can be a start for collaborations with commercial parties.

Finally, lack of sufficient financial support, especially in later stage clinical trials, contributes to the reluctance of retrieving marketing authorization for the investigational product for the not-for-profit setting. This lack in financial support during later stage clinical trials can be explained by the fact that funding agencies do not, in general, supply grants for later stage clinical development, nor do they provide support for the expensive steps towards marketing authorization. Obviously, the later phases of clinical trials are more expensive than early stage clinical trials, due to the fact that later phases of clinical trials involve studies that require extra time and larger patient cohorts. Currently, this transition from innovation of conventional products to marketing authorization is estimated at \$2.8 billion[3], demonstrating the tremendous investments that are necessary. Also, it explains that all ATMP submissions in Europe are currently submitted by commercial companies[4]. Factors, such as lack of financial support and lack in regulatory knowledge, may impact the likelihood of obtaining marketing authorization or receiving reimbursement after approval.

In **Chapter 6** it was explored how the decision-making on marketing authorization was established for the ATMPs. Here, it demonstrated that regulators adjusted the approval procedure of these products, taking into account unmet medical needs. Limited comprehensive evidence on the clinical outcome (efficacy and safety) was demonstrated, supporting the experimental and new

characteristics of these products. However, at least a trend of efficacy and safety profiles has to be demonstrated before products were even being considered for approval. In case no beneficial trend and/or a worsened safety profile was shown, unmet medical need did not influence the final decision-making. Remarkably, the quality profile of all submitted ATMPs raised major concerns for both the approved and non-approved groups at time of approval. This confirms the complexity of these products and the difference in quality management compared to industrially originated 'conventional' medicinal products.

Pharmaceutical preparations

For pharmaceutical preparations, long-term experience in regular patient care has often already been achieved, as described in **Chapter 7** and **Chapter 8**. However, there is no guarantee that these preparations remain available for these patients at an affordable price, since there is the risk of being taken up by commercial companies. The same hurdles as seen with the ATMPs (such as not product-driven, less financial support, lack in regulatory knowledge) might play a role for the pharmaceutical preparations with an academic origin. In case of commercialization, collaboration with those involved in regular patient care is often lacking and there is a strong risk of a considerable raise in prices for licensed formulation of the products. In **Chapter 8**, a case study demonstrates the possibility of a pharmaceutical preparation acquiring approval, if the preparations would not have been adopted and licensed by a commercial company. It is questionable whether marketing authorization is necessary and achievable for all these pharmaceutical preparations. Also, pharmaceutical preparations without marketing authorization may provide an excellent opportunity to treat individual patients with (orphan) unmet medical needs against affordable prices[5]. To be able to provide the service of pharmaceutical preparations, without presenting unacceptable risks to the patients[5], it is important to provide good documentation and to guarantee safety of the product for the patient, as summarized in **Chapter 7**.

After acquiring marketing authorization

In Europe, various collaborations between academia (and/or universities) and commercial partners led to the approval of nine ATMPs (a ninth product is recommended by the CAT and CHMP, August 2017). Alarmingly, despite having been granted marketing authorization, a majority of these ATMPs are not reimbursed in the different member states, leading to inaccessibility of treatment for patients[6–8]. Apparently, the health technology assessment (HTA) discussions for ATMPs are challenging, due to the uncertainty in efficacy (and/or safety) and costs[9]. In case of unmet medical need, a product can succeed in the marketing authorization procedure after demonstrating (a trend in) efficacy[10]. However, HTAs base their decision not only on the proven beneficial effect, but on an assessment of cost-effectiveness as well[10]. Therefore, the results of the non-comparability

trials conducted with ATMPs make it difficult for the performance of such HTA processes[8]. Globally, various HTAs are investigating the use of 'real world data' to demonstrate efficacy for products that receive marketing authorization without performance of a randomized controlled trial (RCT)[11]. Using real world data for HTA discussions can help in the accessibility of treatment in patients. This also applies to the pharmaceutical preparations, since clinical data are based on real world data. Another possibility to collect data based on orphan patient cohorts is to make use of the so-called 'n-of-one trials'. In such a clinical trial design, a cross-over RCT is performed per patient, for example ephedrine for myasthenia gravis and a specific cough technique for cystic fibrosis, in different treatment cycles [12,13]. Of course, due to the small number of patients involved, such a clinical trial design can only show a trend of clinical outcomes rather than comprehensive data [12,14].

Currently, four of the marketing authorization approved ATMPs in Europe have been suspended or withdrawn and are thus no longer available to patients due to commercial reasons (Chondrocelect®, MACI®, Provenge® and Glybera®). The high costs of Provenge® were considered not proportional to the average survival prolongation of four months. For Chondrocelect®, the autologous manufacturing procedure was withdrawn to focus on the allogeneic starting materials as it was commercially more sustainable[8]. MACI® was suspended due to the disappointing commercial performance, like it was for Provenge®. Finally, the last withdrawal was Glybera®, the first gene therapy medicinal product which was approved in 2012 and which was used only for one patient in Germany. As is shown in **Chapter 6**, this poor performance is caused by the high price tag on the product in combination with the uncertain efficacy and safety profile of the product. Based on this and the recent withdrawal of the product by the company[15], Glybera® can be considered as another commercial failure[16]. To increase the likelihood for reimbursement a money back payment-guarantee model was negotiated in the HTA discussion for Strimvelis®, due to the high price (€594,000 per patient, for one treatment): in case the product is not effective, the money will be returned by the company[17].

The fact that relatively many ATMPs are withdrawn raises the question how feasible it is to reach the patient with an ATMP after obtaining marketing approval. Based on the current situation it can be concluded that this approval does not directly lead to treatment in regular patient care. In **Chapter 6**, the uncertainty of long term safety and efficacy was considered as one of the main uncertainties mentioned in all applications. However, these long-term efficacy and safety uncertainties can often be resolved via patient registry risk minimisation and/or post-marketing (observational) clinical trials.

Finally, once approved, and in case reimbursement is arranged, the ATMP has to be prescribed by a

physician. This differs from the conventional products, since for the ATMPs success of the treatment can be dependent on the skills of the surgeon or other physician, for example for MACI® and ChondroCelect®[8]. In case of commercialization of products, the expertise of physicians in the clinic plays a very important part in the products actually reaching the patients and public-private partnership is essential[8,18]. Clinicians need to be familiar with the procedures, which is the start of prescribing such complex medicinal product. Therefore, the development and use of ATMPs should be applied in specialized academic institutions. Such complexity in administration of a product generally does not apply for the unlicensed pharmaceutical preparations.

Smoothening the path to reach the patient

Although the number of ATMPs with granted marketing approval is disappointing, it has to be stated that the ATMPs belong to a group of new medicinal products. Therefore, it is difficult to conclude at this stage whether the development of ATMPs is staggering or not. For example, the development of the monoclonal antibodies (MAb) resulted in the first licensed product (by the Food and Drug Administration (FDA)) in 1986. Only 11 years after this first marketing authorized MAb, an exponential increase was shown in the clinical trials conducted with these MABs[19]. Until now, this has resulted in no less than 30 approved MABs by the FDA[20]. This example clearly illustrates that a new technology or medicinal product group needs time to reach success as acquiring marketing authorization. This trend observed for the MABs, offers hope for the development of ATMPs. However, if the ATMPs are to be successfully developed, involvement of commercial companies and good clinical trial design have proven to be essential.

Hospital exemption

A way to reach the patient with ATMPs in Europe without marketing authorization is the hospital exemption, stating that use of that product is allowed solely in the hospital that developed that specific product. Hospital exemption is only allowed when used on a non-routine basis, based on a prescription, with specific quality criteria, under responsibility of the physician[21]. In The Netherlands, the national healthcare inspectorate judges the hospital exemption application. Hospital exemption is restricted for an established number of treatments with that ATMP after which (or on annual basis) the healthcare inspectorate re-examines the hospital exemption for the following year or for a new number of treatments. Hospital exemption is a solution especially for these ATMPs that are unattractive for commercial companies to be taken over and/or not intended to be placed on the market[22]. For example, ATMPs for ultra-orphan indications (<2 patients treated a year), or with extremely complex manufacturing procedures.

Patient registries

Use of unlicensed academic medicinal products in regular care should be combined with a (national) centralized patient registry. Such registry can be used as an alternative way of collecting data, compared to the conventional RCTs, to apply for marketing authorization. Holoclar® is an example of a product that is approved based on retrospective data, well collected and documented in a registry. For the organisation of such registries, the main responsibility of data collection relies on the manufacturers of the academic medicinal products, including documentation of product specific information, such as batch numbers, dose and quality assurance. Furthermore, physicians also play a very important role in supplying information of the clinical safety and efficacy data for these registries. Subsequently, these registries need to be linked to centralized pharmacovigilance databases on a national level. In the future, it should be possible to automatically link the prescription system to the centralized pharmacovigilance database. Thereby, also the patients themselves have to be able to put data of usage experience in such registries. The patients can be reached via both the physician and the patient organisations. However, for the management of these registries, (financial) stimulation by the government and funding agencies is necessary.

Currently, patient registries are often required for orphan approved medicinal products to collect post-marketing comprehensive clinical data on efficacy and safety. However, commercial companies experience difficulties in collecting high quality post-marketing data and struggle in the performance of independent analyses of the clinical outcome data[5]. Such patient registry is more feasible for academic medicinal preparations, which is the result of direct involvement of patients, physicians and pharmacists in treating the patient[5]. Such close collaborations and interaction may be a considerable contribution for collecting high quality data.

Currently, the price tag on academic medicinal products is based on the production costs, including starting material and manpower used for the production, analysis and for the facilities. Once a patient registry is required for such preparations and the responsibility for data input lies at the producer, the price tag should be able to increase. The government should initiate a pilot for the set-up of such patient registry. For example, for starting a patient registry it is necessary to have a guideline for the set-up and maintenance of such registry. Also, linking of a registry to the (Dutch) pharmacovigilance database needs to be smoothened. And finally, the possibility of granting marketing authorization based on (long-term) collected data from these patient registries has to be explored.

Public-private partnerships

The fact that academic institutions are more involved in the early stage development and that commercial companies are more involved in the process of late stage development towards marketing authorization, creates opportunities for collaboration of both stakeholders, the so-called

public-private partnerships. Combining the strengths of both partners can synergize the development, which could lead to a higher likelihood of bringing academic medicinal products towards regular patient care. However, when the interests of both partners are conflicting (for example profit versus not-for-profit), collaboration can often be difficult. In addition, even though it is said that owning intellectual property is not required for public-private partnerships, cases in the recent past have shown that owning intellectual property helps in negotiations between academia and commercial companies[23]. Subsequently, owning intellectual property on a product or on a product specific manufacturing procedure can improve the bargaining power to control the final costs of a product and finally, to keep these products affordable.

Due to the insufficient financial resources in academia for late stage product development, commercial companies play an important role in the existence of ATMPs. The uncertainty of return on investments is an important factor that can limit the willingness from industry to invest in such products. The fact that reaching the patient with an academic product in development is difficult without collaborating with commercial companies should encourage the (academic) investigators even more to think properly about the future of a product. A TPP can help the investigator with the design of a feasible clinical trial, which can be even further improved when the regulatory authorities, who judge (ethical) aspects of clinical trials, also take the future perspective of a product into account when assessing the clinical trial. Furthermore, the better the TPP is elaborated, the more realistic establishing a development plan becomes. And this, in turn may influence the late stage funding, from governmental resources or via other more voluntary resources, such as philanthropic funders or crowd funding. Since academic (early) development is often funded by agencies and governmental subsidiaries, it is recommended that all this public funding invested in developing products should be taken in consideration when negotiating with interested commercial parties.

In the last decade, a slight increase of involvement of the (large) commercial companies in ATMP clinical development has been observed. Especially in the late stage phase III clinical trials, most of the (large) commercial companies are now involved, as shown in **Chapter 4**. However, when looking at the CAR T-cell products in **Chapter 5**, large companies also appear to be increasingly getting involved during early stage clinical trials. The fact that commercial companies increase their involvement at all stage of research is promising: apparently, companies now come to realize that ATMPs show commercial promise.

Regulatory authority stimulation and collaboration

Despite the fact that, so far, only a small number of products are being used in regular clinical care, different authorities foresee a sanguine prospective for these ATMPs. To be more precise, some

legal instruments exist to facilitate ATMP development in an academic setting, such as the certification procedure for small and medium sized enterprises (SMEs), which is a label on quality and non-clinical data that judges whether the development and/or the manufacturing procedures are corresponding with the regulations[4,24,25]. This was initiated by the European Commission, due to the hurdles experienced with quality and preclinical data with ATMPs for SMEs. However, since an academic institution is classified as a large company, based on the EMA classification[26], academic developers cannot submit their quality and non-clinical data for a certification procedure unless they start a spin-off. Inclusion of academic institutions, due to their not-for-profit status, as an exemption on the SME classification would be helpful for the early development of these academic products.

Not-for-profit status' of academic institutions stimulates the possibility for early dialogues with the regulatory authority, for instance in order to obtain scientific advice. In such a dialogue, the developer has the opportunity to discuss the development of a product, such as quality and (pre)clinical aspects, with the CAT. In case of a large enterprise status, the costs are high for such scientific advice, which is often not available in academic institutions.

The different milestones in a development trajectory are focused on diverse aspects. And each stakeholder has a different role to play. For example, a (national) ethics committee judges on whether a clinical trial design is ethical to conduct, whereas the regulatory authorities evaluate the beneficial efficacy and safety aspects (including quality of a product). Involvement of the regulatory authority in the ethical committee discussion for approval of clinical trial design, such as in Italy, may be helpful at the end of the clinical development to proceed faster towards the clinical data during evaluation for marketing authorization, since early discussions on e.g. quality already have been performed. On the contrary, this collaboration delays the early clinical development. The fact that stakeholders have different aims and perspectives contributes to the difficulties often experienced during the development trajectory and may therefore be one of the main causes why promising medicinal products do not become available for patients in regular clinical care.

Collaboration with HTAs during the clinical development process, aimed at marketing authorization, would also be advisable for academic drugs. For example, in The Netherlands, the Dutch Medicines Evaluation Board started with a 'tailored scientific advice', which offers early informal dialogues with regulatory authorities, including the HTA, for academic institutions. Such an initiative can help academic research groups in their design of clinical trials, but also in the trajectory of a product towards marketing authorization. Furthermore, a dialogue during the early stages of development between an academic research group and the regulatory authorities, including HTA involvement, can also be useful for the opportunity to collaborate with companies.

Also on a centralized level, a special scheme was launched by the EMA in 2016, entitled PRIME (priority medicine). This scheme is used to support the development of medicinal products that are considered promising, often for unmet medical needs and to do so by opening possibilities for having early dialogues for all authorities involved[27]. Scientific advice on (preliminary) early clinical outcomes is made available for all companies. Subsequently, for the academic institutions and SMEs earlier dialogues, concerning non-clinical data, are also possible.[27] In these (early) dialogues, all authoritative bodies can be involved, including the HTA, in order to improve the development plans, including high quality of the applications for marketing authorization[27]. Therefore, it would be interesting to see whether having the PRIME scheme in place actually does improve the development of (academic) ATMPs towards marketing authorization and whether this does indeed increase the chance of ATMPs eventually being used in regular patient care.

Another new and promising initiative has been introduced in The Netherlands: “the Dutch conditionally approval trajectory”, which supports further collaboration between all parties involved, such as investigators, regulators, HTAs and health care insurances. Currently, two ATMPs, which are still in the investigational phase, are used in this Dutch conditional approval trajectory. In this trajectory, the use of developmental ATMPs in phase III clinical trials is reimbursed by the health care insurances for maximum duration of 3,5 years to investigate whether that product can demonstrate efficacy with regards to “state of the science and practice”[28]. In case of demonstrated efficacy and safety, this may lead to granting marketing approval. Further study in order to follow up on these two ATMPs currently in the Dutch conditionally approval trajectory is recommended.

The initiatives mentioned above are more focused on the development pathway of ATMPs than on the unlicensed pharmaceutical preparations. Since these pharmaceutical preparations are already used in clinical care, good documentation including initiatives for patient registries is most important. For these patient registries, which also applies for ATMPs used via hospital exemption, awareness from the different authorities and stimulation from these bodies are important for the implementation of the patient registries and for linking with the pharmacovigilance databases. Involvement from the regulatory bodies could eventually lead to real world data that can be used for the applications for marketing authorization and also for HTA discussions. Therefore, it is important that the authorities are getting familiar with this type of data collecting.

Also, there is a strong belief that more stimulation in development of ATMPs is necessary, involving all different stakeholders: (academic) developers, commercial companies, ethical committees, regulatory authority and HTA bodies. New programs to stimulate the development are starting in Europe. Therefore, it would be interesting to investigate the status of the developed ATMPs in the five years to come. Getting large companies involved may increase the development trajectories.

Also, considering the fact that unmet medical need is important for these ATMPs, it can be assumed that an increased number of ATMPs can obtain conditional approval, instead of follow the standard and complicated route towards marketing authorization.

Furthermore, hospital exemption can impact the approved products, since in case of good documentation and in case a format of a patient registry is set up, these data can be used more frequently in applying for marketing authorization. The main focus of this thesis is on the ATMP development in the EU, but it would be interesting to see how the regulatory authorities of other jurisdictions (such as USA, Japan) are involved in the development of the ATMPs and whether they have a special framework like the EU for the ATMPs.

The role of the ‘academic pharma’

This thesis demonstrates that academic institutions play an important role in the discovery and development of specific medicinal products, such as ATMPs and pharmaceutical preparations for special patient populations. In this regard, academic institutions are essential drug manufacturers providing specialized and orphan drugs for treatment of patients. In our studies, we have shown that – until now – mostly these academic medicinal product do not hold marketing authorization and commercialization of these products does not take place and is perhaps in several cases not even preferred. Especially, for products related to ultra-orphan diseases, in which case conventional phase III clinical trials are not feasible, (late stage) data collection on efficacy should be collected for example via hospital exemption. For the pharmaceutical preparations it was explored that acquiring approval is possible, however, the cost-effectiveness of such preparations is uncertain. This raises the question how feasible it is for preparations, used for ultra-orphan patient cohorts combined with relatively easy manufacturing procedures, to be commercialized.

For both types of academic medicinal products it is important to guarantee safety and have good documentation. Via databases, such as patient registries, good documentation is provided in a structural manner. Furthermore it is important to take pharmacovigilance to a next (more professional) level, which can be achieved by linking patient registries with centralized pharmacovigilance databases. It is considered the responsibility of the academic institutions as an ‘academic pharma’ to set up and maintain good drug product files and safe use of these academic medicinal products in regular patient care. The government and regulatory authorities should stimulate and embrace the ‘academic pharma’ to keep developing and manufacturing academic medicinal products in order to enable treatment of the special (ultra-) orphan patients for an affordable price. Finally, academic pharma is stimulated to acknowledge their essential role in drug discovery and development in current healthcare.

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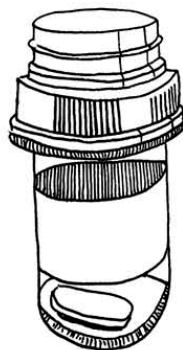
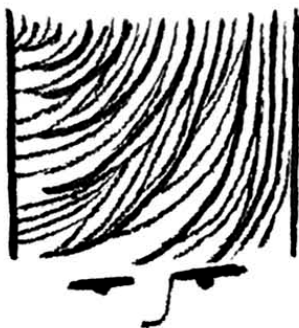
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CHAPTER 10

Summary



The wide variety of licensed medicinal products, mainly produced by the pharmaceutical industry, offers many patients a treatment for their disease. However, not everyone benefits from conventional licensed medicinal products. For these patients, so-called academic medicinal products developed in academic setting or manufactured by (hospital) pharmacies often offer a better alternative. In this thesis, the focus is on the discovery and development of academic medicinal products, more specifically on: advanced therapy medicinal products (ATMPs, Part I) and unlicensed pharmaceutical preparations (Part II).

ATMPs are considered as innovative and complex medicinal products which differ from conventional products in their characteristics and manufacturing. These ATMPs are medicinal products mostly derived from human cells obtained from either the patient (autologous) or a donor (allogeneic). These cells are hence substantially manipulated or the cells received a different function in the recipient compared to the original function (non-homologous use). In case these cells are used in diagnosis, prevention or treatment they are classified as cell therapy medicinal products (CTMPs). On the other hand when the purpose of these cells is to regenerate, repair or replace tissue (such as skin) they are classified as tissue engineered products (TEPs). Finally, the third category of ATMPs is the gene therapy medicinal products (GTMPs), which include genes for diagnostic, prophylactic or therapeutic purposes.

Since the European special Regulation (EC) No. 1394/2007 was imposed in 2009, a centralized regulatory framework for these products was established. In general, the Committee for Medicinal Products for Human Use (CHMP) is responsible for the evaluation of quality, safety and efficacy of all medicinal products in the centralized procedures. However, due to this new complex group of medicinal products, a group of experts was established by the European Medicines Agency (EMA) to support the CHMP, the Committee for Advanced Therapies (CAT). After the scientific assessment evaluation by the CAT, the CHMP provides a recommendation for marketing authorization, which is hence followed by a final decision of the European Commission (EC).

Increasing numbers of clinical trials with ATMPs are performed globally and improved involvement of commercial companies in the clinical development was established. However, this led to only nine licensed ATMPs that are currently available commercially. It is important to determine the cause of this meagre progress; whether this is caused by the fact that these products are relatively new in the medicinal product field and thus need more time, or whether the current system is not suitable for these ATMPs leading to hurdles in the development route. Knowledge on this will support understanding the yet limited number of approved ATMPs and could help in the future to increase the number of these products and thus to be able to treat more patients.

In contrast to ATMPs, unlicensed pharmaceutical preparations have usually already been used in regular patient care for years or even decades. Three different types of pharmaceutical preparations can be distinguished:

1. reconstitution in excess of summary of product characteristics,
2. adaptation of a licensed medicinal product (outside its official labelling)
3. medicinal products from an active pharmaceutical ingredient.

Mostly, these preparations are manufactured for orphan indications (<5 patients per 10,000 humans). Although unlicensed, they should guarantee safety similar to the licensed medicinal products. Since these products are unlicensed, there is a risk that pharmaceutical preparations from an active pharmaceutical ingredient are detected by the industry which hence can apply for marketing authorization and imply a tremendously higher price tag on the licensed product. Such increase in price can lead to inaccessible treatment for patients. It would be unethical that price increases would lead to non-refunded treatment for patients with a long history of treatment with specific unlicensed pharmaceutical preparations. Understanding pharmaceutical preparations including the safety requirements and proper documentation can facilitate these pharmaceutical preparations to patients in need.

The general aim of this thesis is to investigate how academic medicinal products reach clinical patient care. This was explored by investigating the ATMP development field from hurdles experienced in early clinical development towards the decision-making by authorities of these products (Part I) and by describing how unlicensed pharmaceutical preparations should reach the patient in regular clinical care with guaranteed safety and against an affordable price (Part II).

Part I – Advanced therapy medicinal products

In **Chapter 2** we outlined the strengths and hurdles that apply to the development of ATMPs containing cells (CTMPs, TEPs, and GTMPs – *ex vivo*) in academic institutions. The academic strengths rely mainly on the beginning of the development of these products in the trajectory from basic research until licensing and marketing. These strengths start with the fact that there is disease-specific expertise in the academic institutions. Furthermore, there is direct access to human samples for research *in vitro* and if possible *in vivo* disease models but also for cell banks. In addition there is direct access to human starting material for these CTMPs and TEPs, including a rapid and direct organized logistic process from manufacturing until treatment within an institution. Finally, patient enrolment and follow up is facilitated in the academic setting by the fact that patients already undergo their medical treatment at academic institutions. In contrast, limitations have a higher impact towards late phase clinical development, such as lack of regulatory knowledge. This can be

explained as most academic institutions are science-driven rather than product-driven which includes the output system of academic institutions mainly being driven by peer-reviewed scientific publications. Also, the lack of long-term goals on product development shows that academic institutions are mostly not product-driven. In addition, the lack of sufficient funding also negatively influences performance of phase III clinical trials and the ability to apply for marketing authorization. Hurdles experienced by different stakeholders in The Netherlands during clinical development of ATMPs were investigated in **Chapter 3**. More than half (56% of 45) of the principal investigators from academic institutions planned to reach patients in clinical care after successful clinical trials via marketing authorization and/or via hospital exemption. The other part of principal investigators were planning on reaching clinical care with ATMPs via other routes, such as the Tissues and Cells Directive (n=12) and a fifth did not have a future plan for implementation in clinical care yet. One year after the interviews, an increased number of principal investigators intended to reach clinical care after successful clinical development via either marketing authorization and/or hospital exemption. All other stakeholders perceived that only hospital exemption and marketing authorization were the possibilities of reaching clinical care. The main hurdles in ATMP development identified by the stakeholders included: inadequate financial support, rapid evolving field, study-related problems (such as limited availability of human starting material or patient enrolment), lack of regulatory knowledge and problems in collaborations and responsibilities.

To better understand the clinical development field of the ATMPs in the EU, **Chapter 4** describes a comprehensive overview of the clinical trials with ATMPs that have been performed in Europe in the period of 2004 until 2014. 278 clinical trials, corresponding with 198 unique ATMPs, were identified from the public domain of the European clinical trial database (EudraCT), which did not contain non-public data of phase I clinical trials. Half of the trials were phase II trials, a quarter were phase I/II combined trials and the rest were phase III trials. More than half of the trials (56%) were sponsored by academic institutions. However, the part of clinical trials with commercial sponsors involved, increased slightly in 2014 compared to 2010, including an increase of involvement of large commercial companies (8% in 2014 versus 4% in 2010). The main characteristics of academic and commercial sponsored trials differ as academic sponsors mostly used autologous derived starting material (78%), of which most from bone marrow (29%), while commercial sponsors' main focus has been the GTMPs – *in vivo* (46%) and almost all were part of the later stage phase III clinical trials. From all included clinical trials approximately one in ten proceeded towards a clinical trial in the next clinical trial phase.

Chapter 5 describes the field of a specific subtype of the ATMPs, the Chimeric Antigen Receptor (CAR) T-cells. The goal was to investigate whether characteristics of clinical trials show trends in

successful development of CAR T-cell trials performed in Europe and USA until 2016. Successful development was defined as a clinical trial that did have a subsequent clinical trial in either a next phase clinical trial (e.g. from phase I towards phase II) or a clinical trial with a specific product in the same clinical phase with parallel study design, for other indications and/or a different patient cohort. From the 106 clinical trials with CAR-T cells performed in Canada, Europe and USA, the majority of trials had an academic sponsor, and more than half were in phase I. Furthermore, autologous starting material was used most frequently. Clinical trials with CAR-T cells were more likely to have a subsequent clinical trial when commercially sponsored, recruiting a large number of patients ($n > 33$) or when it's design was multicentre.

The regulatory decision-making on marketing authorization of all ATMP assessment reports for marketing authorization in Europe was investigated in **Chapter 6**. Of the 14 investigated ATMPs, 5 were approved according to standard procedure, 3 were approved via the expedited pathway (2 conditional approval and 1 approval under exceptional circumstances) and 6 were not approved. Major issues in quality, for example vector-related and release tests, were raised in all assessment procedures, demonstrating that this domain is an important issue in the ATMP field. Whereas for the approved products most of these quality issues were considered to be resolved (for example by post-marketing requirements) the objections for the non-approved products were considered unresolved at time of final decision by the regulators. The most robust clinical trial design and clinical outcomes were evident for the standard approved ATMPs, compared to expedited approvals. All expedited approvals were granted for orphan ATMPs, for which considerations of unmet medical need counterbalanced clinical uncertainties and risks. For non-approved ATMPs lack of clinical efficacy and severe safety risks were decisive for negative benefit/risk opinions.

Part II – Unlicensed pharmaceutical preparations

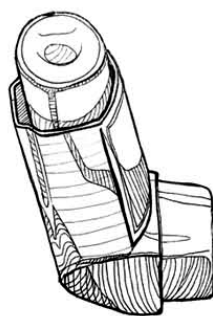
Chapter 7 presents an overview of the different unlicensed pharmaceutical preparations for small (in-house) patient cohorts. Also, requirements for pharmaceutical quality assurance and the level of documentation for each preparation type is discussed. Performing a benefit/risk assessment matrix for pharmaceutical quality assurance, as described in the Resolution (CM/RES(2016)), will distinguish the level of risk linked to the pharmaceutical preparation, that has consequences for the level of documentation. In case of low risk, quality assurance has to be performed according to the Pharmaceutical Inspection Co-operation Scheme Good Preparation Practices (PIC/S GPP), whereas for high risk preparations, quality is guaranteed by meeting with Good Manufacturing Practices (GMP). Furthermore, pharmacovigilance of these pharmaceutical preparations are the responsibility of the (hospital)pharmacy and should be well-documented, including documentation provided by

the prescribing physician, information about the patients and specific attention to any adverse events that may occur or have occurred. Especially for the active pharmaceutical ingredient (API) a concise product dossier with data on efficacy and safety is important since no available information on these aspects exists. The product dossiers of preparations adapted from licensed medicinal products need to contain a substantiated rationale besides safety and efficacy data from these preparations. The reconstituted preparations are executed with licensed medicinal products, allowing pharmacovigilance conform the licensed individual reconstitution.

In **Chapter 8**, the unlicensed pharmaceutical preparation 3,4-diaminopyridine was used as a case study to compare the available data of the preparation with the licensed formulation Firdapse®. Mostly, the manufacturer of Firdapse® used data from pharmaceutical preparations for the licensing of their product. Only two bioequivalence studies and one pharmacology study were performed with the licensed formulation by the company. It questioned the tremendous price increase for Firdapse® compared to the price of the pharmaceutical preparations. Furthermore, it showed that pharmaceutical preparations developed and manufactured by (hospital) pharmacies had opportunities for obtaining marketing authorization.

The role of the ‘academic pharma’

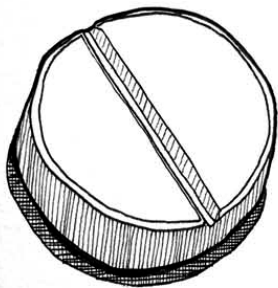
Finally, in **Chapter 9**, all study results are discussed and concluding remarks on the role of the ‘academic pharma’ are posed. Academic institutions are essential drug manufacturers providing specialized and orphan drugs for treatment of patients. Until now, most of these academic products do not hold marketing authorization and commercialization of these products does not take place and is perhaps in several cases not even preferred. For both types of academic medicinal products it is important to guarantee safety and have good documentation. Via databases, such as patient registries, good documentation is provided in a structural manner. Furthermore, increased (professional) pharmacovigilance should be achieved by linking patient registries with centralized pharmacovigilance databases. It is considered the responsibility of the academic institutions as an ‘academic pharma’ to set up and maintain proper drug product files and ensure safe use of these academic medicinal products in regular patient care. The government and regulatory authorities should stimulate and embrace the ‘academic pharma’ to keep developing and manufacturing academic medicinal products in order to enable treatment of the special (ultra-) orphan patients for an affordable price. Finally, ‘academic pharma’ is stimulated to acknowledge their essential role in drug discovery and development in current healthcare.



CHAPTER 11

Nederlandse samenvatting

Illustration of a pill with a diagonal line.



Vandaag de dag bestaat er een grote variëteit van geregistreerde geneesmiddelen, meestal geproduceerd door de farmaceutische industrie. Helaas kunnen niet alle patiënten worden behandeld met deze beschikbare, geregistreerde, conventionele producten. Academische geneesmiddelen zouden de oplossing kunnen zijn voor die patiënten voor wie geen beschikbare geneesmiddelen op de markt zijn. In dit proefschrift ligt de focus op het proces van de ontdekking en ontwikkeling van academische geneesmiddelen, in het bijzonder van de (I) geavanceerde therapieën en (II) de niet-geregistreerde farmaceutische bereidingen.

Geavanceerde therapieën zijn geneesmiddelen die bestaan uit cellen, afkomstig van de patiënt zelf (autoloog) of van een donor (allogeen), die ofwel 'substantieel' gemanipuleerd zijn, ofwel een andere functie hebben dan de originele functie van de cellen (niet-homoloog, bijvoorbeeld stam cellen uit beenmerg die dienen voor reparatie van het hart). Als deze cellen worden toegepast voor diagnose, preventie of behandeling behoren ze tot de celtherapieën. Echter wanneer de toepassing van deze cellen is om te regenereren, repareren of om weefsel te vervangen (bijvoorbeeld huid) worden deze cellen weefselproducten genoemd. De laatste subcategorie zijn de gentherapie producten, deze producten bevatten een gen dat een diagnosticerende, profylactische, of therapeutische functie heeft.

De geavanceerde therapieën worden gezien als innovatieve, complexe geneesmiddelen die anders zijn dan de conventionele geneesmiddelen, zoals de productkarakteristieken en de bereidingsprocessen. Sinds 2009 is er een speciale Europese regelgeving van kracht, (EC) No. 1394/2007, voor de geavanceerde therapieën. Ondanks het toenemende aantal klinische studies dat wordt uitgevoerd met deze geneesmiddelen, zijn er tot nu toe slechts 9 geavanceerde therapieën op de markt gekomen in Europa. Dat het aantal goedgekeurde producten zo laag is, kan liggen aan het feit dat het om relatief nieuwe geneesmiddelen gaat, waardoor meer tijd nodig is om te zien of de ontwikkeling daadwerkelijk succesvol is of niet. Een andere oorzaak kan zijn dat het huidige systeem nog niet goed is ingericht op deze groep geneesmiddelen, wat kan leiden tot obstakels tijdens het ontwikkelingsproces.

Daar waar de geavanceerde therapieën nog in ontwikkeling zijn, worden de niet-geregistreerde farmaceutische bereidingen vaak al jaren gebruikt in de patiëntenzorg. Deze farmaceutische bereidingen zijn geneesmiddelen die vaak ontstaan als een bereiding voor de individuele patiënt (*ad hoc*). Als deze bereiding uiteindelijk vaker moeten worden gemaakt, kan worden overwogen om over te gaan op (kleine) voorraadbereidingen. Vaak worden ze gemaakt door (ziekenhuis)apotheken voor zeldzame ziektes (<5 patiënten per 10.000 mensen in Europa). Ondanks het feit dat deze geneesmiddelen niet geregistreerd zijn, moet de kwaliteit en veiligheid van het product en de veiligheid voor de patiënt wel gegarandeerd kunnen worden, net zoals bij de geregistreerde

geneesmiddelen.

Het doel van dit proefschrift is om te onderzoeken hoe de twee bovengenoemde typen academische geneesmiddelen de patiënt bereiken. Dit is gedaan door allereerst het ontwikkelingsveld van de geavanceerde therapieën te onderzoeken, vanaf de knelpunten die ervaren worden in een vroeg stadium van de ontwikkeling tot de besluitvorming voor registratie door de regulatoire autoriteiten (Deel I). Vervolgens wordt beschreven hoe de niet-geregistreerde farmaceutische bereidingen veilig beschikbaar zouden moeten komen tegen een betaalbare prijs (Deel II).

Deel I – Geavanceerde therapieën

In **Hoofdstuk 2** is een overzicht gegeven van de sterke en zwakke punten van de ontwikkeling van geavanceerde (cel)therapieën die plaatsvindt in de academische centra. Met name in de vroege ontwikkeling van een product zijn er grote voordelen in een academische setting, zoals de aanwezigheid van ziekte specifieke expertise. Daarbij is er directe toegang tot menselijk materiaal, zoals menselijke cellen of weefsels, dat niet alleen gebruikt kan worden voor ziektemodellen, maar ook voor celbanken. Bovendien kan dergelijk menselijk materiaal gebruikt worden als startmateriaal voor de celtherapieën en weefselproducten. Naast de toegang tot menselijk materiaal, is het logistieke proces in de academische centra snel en direct aangezien het plaatsvindt op één locatie. Ook zal de inclusie en opvolging van patiënten in klinische studies goed te organiseren zijn in de academie, vanwege de directe patiëntenzorg die plaatsvindt in dat centrum. Hier staat tegenover dat hoe verder het ontwikkeltraject voortschrijdt, op weg naar registratie, er meer obstakels ontstaan waar de academische centra tegenaanlopen. Bovendien krijgen academische onderzoekers vaak te maken met het feit dat de regulatoire kennis, wat nodig is voor registratie, ontbreekt. De meeste academische onderzoekers worden gedreven door de wetenschap en niet door het ontwikkelen van een product. Het output systeem van academische centra draagt hier ook aan bij, aangezien het in de meeste gevallen gaat om het publiceren van artikelen. Het (veelal) ontbreken van lange-termijn doelen in een product-ontwikkeltraject bevestigt dat de focus niet is gericht op de echte ontwikkeling van een product. Tot slot kan nog worden toegevoegd dat het ontbreken van voldoende financiële ondersteuning negatieve invloed heeft op de mogelijkheid om een (goede) fase III klinische studie uit te kunnen voeren, of om het product te registreren.

Diverse stakeholders (hoofdonderzoekers van geavanceerde therapieën in academische centra, patiënt organisaties, de Centrale Commissie Mensgebonden Onderzoek (CCMO), het College ter Beoordeling van Geneesmiddelen (CBG), Zorginstituut Nederland, een zorgverzekeraar en drie kleine farmaceutische bedrijven) in Nederland zijn in **Hoofdstuk 3** geïnterviewd over hun ervaringen met de productontwikkeling van de geavanceerde therapieën. Meer dan de helft van de

hoofdonderzoekers (56% van de 45) van de academische centra wist dat het alleen mogelijk was om het geneesmiddel bij de patiënt te krijgen door het product te registreren, of door gebruik te maken van de '*hospital exemption*'. De *hospital exemption* maakt het mogelijk om geavanceerde therapieën niet geregistreerd en buiten studieverband onder restricties, welke gecontroleerd worden op nationaal niveau, bij de patiënt toe te passen. De overige hoofdonderzoekers wilden het geneesmiddel toepassen middels andere routes, zoals via de zogenaamde '*tissues and cells directive*' (n=12), die is opgesteld voor stamceltransplantaties. Een vijfde van de onderzoekers had nog geen toekomstplannen bedacht voor het geneesmiddel waarmee een klinische studie werd uitgevoerd. De belangrijkste knelpunten die werden ervaren door de stakeholders waren: financiële steun, het ontbreken van regulatoire kennis, het snelle ontwikkelingsveld, studie-gerelateerde problemen (zoals recruitment) en problemen in samenwerkingen met daarbij de verantwoordelijkheden van de verschillende betrokken partijen.

Om een beeld te krijgen van het ontwikkelingsveld met geavanceerde therapieën in Europa is in **Hoofdstuk 4** een overzicht gemaakt van de klinische studies die met deze geneesmiddelen tussen 2004 en 2014 zijn gedaan. In die tijd zijn 278 klinische studies uitgevoerd met 198 unieke geavanceerde therapie producten, waarvan de helft fase II studies waren. Meer dan de helft van de studies (56%) die werden uitgevoerd hadden een academische sponsor, alhoewel een lichte toename te zien was van het aantal studies met een commerciële sponsor in 2014 ten opzichte van 2010. Ook was er toenemende betrokkenheid van (grote) farmaceutische bedrijven als uitvoerders van de klinische studies (8% in 2014 tegenover 4% in 2010). Academische centra gebruikten meestal (78%) autoloog startmateriaal, vaak afkomstig uit beenmerg (29%). De commerciële bedrijven produceerden voornamelijk *in vivo* gentherapieën (46%) en zij voerden bijna alle fase III klinische studies uit. Ongeveer 10% van alle klinische studies werd opgevolgd door een klinische studie in de volgende fase.

In **Hoofdstuk 5** is ingezoomd op de klinische studies die werden uitgevoerd met een subtype van de geavanceerde therapieën, de *chimeric antigen receptor* (CAR) T-cel producten. Er is gekeken naar karakteristieken van de klinische studies die zouden kunnen dienen als voorspeller van succes in de klinische ontwikkeling. Succes werd gedefinieerd als 'wanneer een klinische studie is opgevolgd door een klinische studie in een opvolgende klinische studiefase of als dezelfde klinische studiefase wordt uitgevoerd voor bijv. een andere indicatie'. Van de 106 klinische studies met CAR T-cel producten gedaan in Amerika, Canada en Europa, waren de meeste studies (91%) uitgevoerd door een academische sponsor, was 68% een fase I studie en werd er voornamelijk autoloog startmateriaal gebruikt (89%). Bijna de helft van de studies (46%) werd opgevolgd door een volgende klinische studie. De karakteristieken die werden geassocieerd met een hogere kans op opvolging van een

klinische studie waren: commerciële sponsor, recruitment van een grotere groep patiënten ($n = >33$) en het uitvoeren van de studie in meerdere centra.

De regulatoire besluitvorming van de alle dossiers van geavanceerde therapieën die zijn ingediend voor registratie in Europa werd onderzocht in **Hoofdstuk 6**. Van de 14 onderzochte producten zijn er 5 producten standaard goedgekeurd, 3 'conditioneel' goedgekeurd (2 producten voorwaardelijk en 1 product onder uitzonderlijke voorwaarden) en 6 producten niet goedgekeurd voor registratie. Kwaliteitsissues kwamen voor bij alle ingediende dossiers voor registratie, wat laat zien dat dit een belangrijk knelpunt is in het veld van de geavanceerde therapieën. Waar voor de goedgekeurde producten deze bezwaren opgelost waren bij besluitvorming, bijv. door *post-marketing* eisen, waren echter de meeste van de kwaliteitsissues voor de afgewezen producten niet opgelost ten tijde van de uiteindelijke beslissing over registratie. Robuust ontworpen klinische studies en uitkomsten waren aangetoond voor de standaard goedgekeurde producten, wat echter niet het geval was voor de conditioneel goedgekeurde producten. Alle conditioneel goedgekeurde producten hadden het label van 'zeldzaam geneesmiddel'. Zodoende speelden argumenten omtrent hoge medische noodzaak een belangrijke rol in de afweging tot de uiteindelijke besluitvorming, met name wanneer er sprake was van onzekerheid in de effectiviteit en veiligheidsrisico's bij een product. Voor de afgekeurde producten waren het ontbreken van effectiviteit en de aangetoonde ernstige veiligheidsrisico's de voornaamste redenen voor afkeuring.

Deel II – Niet-geregistreerde farmaceutische bereidingen

In **Hoofdstuk 7** is een overzicht gemaakt van de verschillende soorten niet-geregistreerde farmaceutische bereidingen die worden geproduceerd voor kleine patiëntgroepen met daarbij de eisen voor kwaliteitsgarantie en het niveau van documentatie per type bereiding. Er kunnen drie typen farmaceutische bereidingen worden onderscheiden:

1. Voor toediening gereedmaken, op geleide van de bijsluiter
2. Aanpassing van een geregistreerd product (buiten het officiële label)
3. Geneesmiddel gemaakt vanuit een actief farmaceutische grondstof.

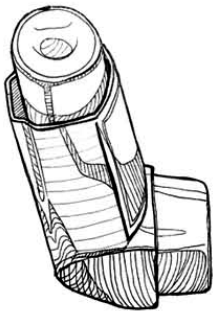
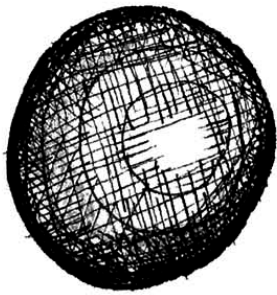
Om de kwaliteit te garanderen van deze niet-geregistreerde geneesmiddelen moet een risico bepaling worden gedaan aan de hand van een *benefit/risk* matrix, zoals beschreven wordt in de resolutie (CM/RES(2016)). Deze matrix kan bepalen welk niveau van risico is verbonden aan het product, wat op zijn beurt invloed heeft op de mate van documentatie. Een kanttekening van deze matrix is dat het slechts betrekking heeft op de kwaliteit van het product en dat het niet het therapeutisch belang meeneemt. In het geval dat er laag risico is kan de kwaliteit worden gegarandeerd conform de *Pharmaceutical Inspection Co-operation Scheme* (PIC/S) richtlijnen. Echter

wanneer het product een hoog risico heeft, moet er worden gehandeld volgens *Good Manufacturing Practices* (GMP). Naast de kwaliteitsrisicobepaling is het ook belangrijk om goede farmacovigilantie (geneesmiddelbewaking) uit te voeren met deze niet-geregistreerde producten. Door alle veiligheidsaspecten te documenteren, inclusief gegevens over de arts, de patiënt en bijwerkingen. Met name voor de geneesmiddelen die gemaakt worden uit een actief farmaceutische grondstof is een productdossier met een rationale en data over de effectiviteit en veiligheid van belang aangezien er geen beschikbare data hiervan zijn. De verantwoordelijkheid van deze documentatie ligt bij de maker van deze producten, in dit geval dus bij de (ziekenhuis)apotheek. De mate van documentatie is ook afhankelijk van de risicobepaling in de kwaliteit van het product, bijvoorbeeld bij schaalvergroting zullen meer kwaliteitscontroles nodig zijn dan voor de *ad hoc* producten.

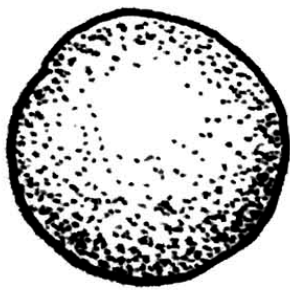
Niet-geregistreerde producten met een actief farmaceutische grondstof lopen het risico om door een firma te worden geregistreerd zonder dat oorspronkelijk onderzoek met die grondstof is gedaan door de firma, wat kan leiden tot extreme prijsverhogingen. **Hoofdstuk 8** beschrijft een casus van een farmaceutische bereiding (3,4-DAP) voor Lambert-Eaton myasteen syndroom (LEMS) die in 2009 werd geregistreerd, zonder oorspronkelijk onderzoek te hebben gedaan, door een commercieel bedrijf (Firdapse®) tegen een 50x hogere prijs. Na vergelijking van de data die zijn gebruikt in het registratiedossier van Firdapse® en de data die aanwezig zijn in het productdossier van de farmaceutische bereiding, bleek dat de meeste data die voor registratie zijn gebruikt niet zijn gebaseerd op onderzoeksresultaten van de firma zelf met die formulering. Slechts twee bio-equivalentie studies en één farmacologie studie zijn uitgevoerd met de Firdapse® formulering. De meeste data waren afkomstig van de 3,4-DAP direct afgifte formulering. Deze resultaten lieten zien dat de aanwezige data van Firdapse® niet substantieel verschilden van 3,4-DAP vertraagde afgifte. Wat betekent dat 3,4-DAP vertraagde afgifte zeker mogelijkheden had om geregistreerd te worden. Maar bovendien bevestigde het dat de extreme prijsstijging van Firdapse® in vergelijking met de 3,4-DAP farmaceutische bereiding formuleringen niet in verhouding zijn met de investeringen die in (pre)klinische studies zijn gedaan.

De rol van de ‘academische farma’

In **Hoofdstuk 9** zijn alle resultaten uit de verschillende hoofdstukken bediscussieerd en concluderende opmerkingen over de toekomst van de academische geneesmiddelen besproken. Academische centra zijn essentiële bereiders van geneesmiddelen voor het genereren van therapieën voor specifieke patiëntgroepen. De meeste van de academische geneesmiddelen zijn, tot nu toe, niet geregistreerd en commercialisatie gebeurt zelden, al is dit wellicht ook niet gewenst. Voor beide type academische geneesmiddelen, beschreven in dit proefschrift, is het belangrijk om veiligheid te garanderen en uitgebreide documentatie bij te houden. Via databases, zoals patiënt registers, kan documentatie op gestructureerde wijze plaatsvinden. Tevens zal een toename in (professionele) geneesmiddelbewaking bereikt kunnen worden door deze patiënt registers te koppelen aan centrale geneesmiddelbewaking databases. De academische instellingen zijn als ‘academische farma’ verantwoordelijk voor het opzetten en het handhaven van geneesmiddel product dossiers en voor het veilig gebruiken van deze academische geneesmiddelen in klinische patiënten zorg. De overheid en regulatoire autoriteiten moeten de ‘academische farma’ stimuleren in het blijven ontwikkelen en produceren van academische geneesmiddelen voor behandeling van speciale (ultra)zeldzame patiënten mogelijk te maken tegen een betaalbare prijs. De ‘academische farma’ worden aangemoedigd om zijn essentiële rol in geneesmiddel ontdekking en ontwikkeling in de huidige zorg te erkennen.



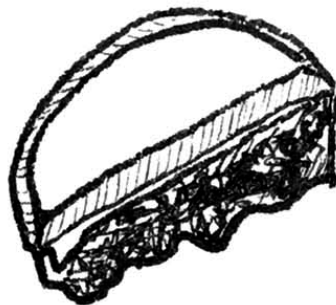
Part IV – LIST OF PUBLICATIONS, CURRICULUM VITAE



CHAPTER 12

List of Publications

Curriculum vitae auctoris



List of publications

This thesis

de Wilde S, Veltrop-Duits L, Hoozemans-Strik M, Ras T, Blom-Veenman J, Guchelaar HJ, Zandvliet M, Meij P. Hurdles in clinical implementation of academic advanced therapy medicinal products: A national evaluation. *Cytotherapy* 2016;18(6):797-805

de Wilde S, Guchelaar HJ, Herberts C, Lowdell M, Hildebrandt M, Zandvliet M, Meij P. Development of cell therapy medicinal products by academic institutes. *Drug Discovery Today* 2016;21(8):1206-12

de Wilde S, Guchelaar HJ, Zandvliet ML, Meij P. Clinical development of gene- and cell-based therapies: overview of the European landscape. *Mol Ther Methods Clin Dev.* 2016;3:16073

de Wilde S, Guchelaar HJ, Zandvliet ML, Meij P. Understanding clinical development of chimeric antigen receptor T cell therapies. *Cytotherapy* 2017;19(6):703-709

de Wilde S, de Jong M, Le Brun P, Guchelaar HJ, Schimmel K. Unlicensed pharmaceutical preparations for clinical patient care: ensuring safety. *Pharmacoepidemiology and Drug Safety.* 2017 October 19,

de Wilde S, de Jong M, Lipka A, Guchelaar HJ, Schimmel K. The possibility of obtaining marketing authorization of orphan pharmaceutical compounding preparations: 3,4-DAP for Lambert-Eaton Myasthenic Syndrome. *European Journal of Pharmaceutical Sciences.* 2017 November 27.

de Wilde S*, Coppens D*, Hoekman J, de Bruin M, Leufkens H, Guchelaar HJ, Meij P. Decision-making on marketing authorization of advanced therapy medicinal products in the European Union. *Submitted*

* These authors contributed equally to this work

Not related to this thesis

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Curriculum Vitae auctoris

Sofieke de Wilde was born in Kampen, The Netherlands, on 15 May 1988. After she finished secondary school at Gymnasium Ceeleum in Zwolle, she started in 2006 with the bachelor Pharmacy at the University of Groningen. After her Bachelor of Science, she continued with the Master Pharmacy at the University of Utrecht. During her Master studies, she performed a research internship on the influence of oxytocin on fear extinction in humans at the Mark Geyer lab at the University of California, San Diego (department of Psychiatry under supervision of V.B. Risbrough, Ph.D.). In 2013, Sofieke obtained her Master's Degree in Pharmacy and started working as a project pharmacist at the department Clinical Pharmacology and Pharmacy at the VU Medical Center in Amsterdam (supervisors P.M. Bet, Ph.D and M.W.J. den Brok, Ph.D.). One year later, she transferred to the department Clinical Pharmacy and Toxicology of the Leiden University Medical Center where she started her Ph.D. project on translation of academic medicinal products towards clinical practice (supervisor professor H.-J. Guchelaar, Ph.D.). From July 2017 Sofieke worked as a project pharmacist at the hospital pharmacy of the Zaanse Medical Center in Zaanstad and in November 2017 she started her residency Hospital Pharmacy at the Meander Medical Center in Amersfoort. Sofieke lives in Amsterdam together with Merijn.