Translation of academic medicinal products towards clinical practice

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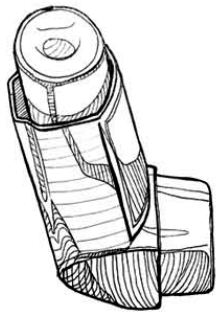
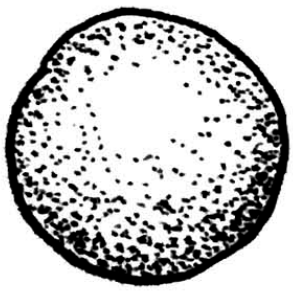
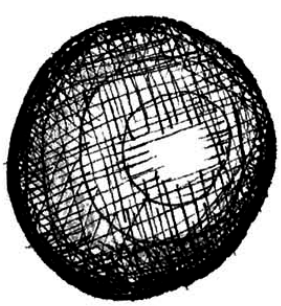




PART III - DISCUSSION, CONCLUDING REMARKS AND SUMMARIES



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 couch 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 ChrondoCelect®[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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