Influence of Scientific Advice on Marketing Authorisation and post-authorisation withdrawal of ATMPs

Study: Drug Innovation (Writing assignment)

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Abstract

Background: Regulators from the European Medicines Agency (EMA) provide comprehensive guidelines and expert guidance before Market Authorisation Application (MAA) to enhance the chance of Market Authorisation (MA). The primary objective of this study is to ascertain the influence of Scientific Advice (SA) on Advanced Therapeutic Medicinal Products (ATMPs) at different stages of development on the MA and to investigate its potential impact on withdrawal decisions.

Methods: In-depth analysis of scientific literature was used to gain valuable insights into the impact of SA on various pharmaceuticals. Based on this, regulatory research was conducted to gain further insight into ATMPs. Articles were retrieved from PubMed. The Medicines Evaluation Board (MEB) database was used to collect SAs from ATMPs, while the EMA website, ClinicalTrials.gov, and AdisInsight were used to gather data on the ATMPs. The results from the scientific literature were compared to the results of the regulatory research.

Results: SA is offered by regulatory authorities to generate robust and reliable data by minimizing Major Objections (MOs) and thus effectively facilitate MAA. Pharmaceuticals which asked for MAA can be approved, rejected or pre- or post-authorisation withdrawn. From all SAs found between 2009 and 2022, 437 SAs were found according to 263 ATMP products, of which 35 ATMP products were asking for MAA. Scientific literature revealed that 23 (68%) ATMPs that underwent MAAs were initially developed by small- and medium-sized enterprises (SMEs) and 20 (59%) were applied by SMEs. However, the MAA outcome was more often positive for non-SMEs, with 12 out of 14 (86%) receiving approval compared to 12 out of 20 (60%) for SMEs. After MA, post-authorisation withdrawal was observed for both 4 (25%) SMEs and non-SMEs. The number of sought SAs differed among ATMPs, but the ATMPs which obtained MA asked for advice an average of four times. In contrast, pre-authorisation withdrawals asked for advice an average of two times. Early SA was strongly recommended based on the scientific literature. Regulatory research showed that five (29%) marketed ATMPs sought advice before the trial start, while twelve (71%) marketed ATMPs sought advice during the trial. The ATMPs that were post-authorisation withdrawn all sought advice during the trial, while none asked before the trial. Furthermore, compliance with SA before and during the trial was researched. The ATMP SAs which were compliant with the study had more influence on MAA success rate when given during the main study. On the other hand, ATMP SAs which were given before the main study had no post-authorisation withdrawals at all, independent of compliance.

Conclusions: SA should be actively sought by enterprises multiple times in order to facilitate the MAA. Adherence to SA raises the suspicion of a positive relationship with MA, but it was not proven. Moreover, early (before trial start) SA decreases the chance of post-authorisation withdrawal.

Plain language summary

To bring medicines from development to the market, they must be approved by the European Medicines Agency. Regulators from the European Medicines Agency offer guidelines before pharmaceutical companies apply for authorisation to bring their medicines to the market. One crucial aspect is seeking scientific advice from regulators. Regulators provide advice to manufacturers of medicines to ensure the collection of reliable data, making sure the process goes smoothly and addressing issues. The aim of this study is to see how scientific advice affects the approvals of advanced biologics and if the advice has any impact on how long a medicine is marketed.

To conduct this research, scientific literature was studied to understand the impact of scientific advice on the development and approval of medicines. The regulatory research is specifically focused on one type of medicine, advanced biologics. Articles were found using the website PubMed. Information about the advanced biologics was collected from the Medicines Evaluation Board's database, and even more information was found on ClinicalTrials.gov and AdisInsight.

The study found that regulatory authorities offer scientific advice to help pharmaceutical companies generate robust and reliable data, reducing the likelihood of facing issues during the approval process. Medicines applying for approval can either be approved, rejected, or withdrawn from the market, either before or after authorisation.

Between 2009 and 2022, a total of 437 pieces of scientific advice were provided for 263 advanced biologics, out of which 35 advanced biologics were applying for approval. Notably, 68% of the advanced biologics that asked for approval were initially developed by small companies, and 59% were applied by small companies. Surprisingly, the outcome of the approval application was more positive for large companies, with 86% (12 out of 14) receiving approval, compared to 60% (12 out of 20) for small companies. After receiving approval, both small and large companies faced withdrawal after approval, each at a rate of 25%.

The number of advices sought varied among advanced biologics; those obtaining approval asked for advice an average of four times. In contrast, advanced biologics experiencing withdrawals before approval sought advice an average of two times. The study strongly recommended seeking early scientific advice based on insights from scientific literature. Regulatory research revealed that 29% (five) of the marketed advanced biologics sought advice before starting their clinical trials, while 71% (twelve) sought advice during the trial. Interestingly, all advanced biologics that were withdrawn after approval sought advice during the trial, and none of them requested advice before the trial began.

Furthermore, compliance with advice before and during the trial was analysed. Advanced biologics that followed the advice recommendations during the main study had a more significant influence on the success rate of approval. On the other hand, advanced biologics that received advice before the main study had no withdrawals after approval, regardless of compliance with the advice.

In conclusion, this research emphasizes the importance of seeking scientific advice multiple times during the development of medicines to improve the chances of getting approval. While adhering to scientific advice seems to be associated with a higher likelihood of being approved, more research is needed to confirm the connection. Additionally, seeking scientific advice before starting the main study can reduce the risk of withdrawal after approval.

Introduction

Before medicines become available on the European market, they have to go through complete development, research, and testing. The European Medicines Agency (EMA) is a European regulator that ensures scientific evaluation, supervision, and safety of pharmaceuticals available on the European market [1]. Enterprises have to develop a dossier with details about the development to get a pharmaceutical product marketed.

The dossier has to contain information about the quality, efficacy, and safety of the pharmaceutical. To support enterprises in formulating a high-quality dossier, the EMA provides Scientific Advice (SA) services [1–3]. SA is guidance and direction from the EMA about all subjects of the dossier, for example, the development of the pharmaceutical and the study design of clinical trials, and other questions to generate robust data and share regulator's experiences/knowledge [3]. Furthermore, SA can be asked by the applicant at any time during the development and is voluntary [4]. Before an enterprise can request SA, the EMA has to be notified, and a briefing document should be available [4]. After that, the applicant can send a list of questions and proposals which are being evaluated by EMA on scientific relevance for SA. All enterprises can apply for SA; only administrative fees are asked for the provision of SA, which might be reduced up to 90% for small- and medium-sized companies (SMEs) and up to 75% for orphan medicines [4,5]. It is expected that SMEs have reduced financial resources, availability, and knowledge than larger enterprises, so it is important to ask for SA more often. However, SA does not guarantee MA and is not evaluating benefit-risk balances.

SA can be given anytime during the development, Market Authorisation Application (MAA), and after Market Approval (MA) [4]. For some pharmaceutical products, it is important to provide SA early on in the development. Based on the nature of the pharmaceuticals, enterprises can apply for a special status such as orphan in case of rare disease pharmaceuticals and PRIME in the case of pharmaceuticals developed for patients with an unmet medical need [6,7]. In the case of a pharmaceutical that gained orphan status, this advice can either be protocol assistance (PA) or SA. If orphan status is not applicable, SA can be asked and will be given. PA and SA slightly differ in content, but in this research, both will be referred to as SA. SA is provided by the Scientific Advice Working Party (SAWP).

From 2009 to 2023, 25 advanced therapeutic medicinal products (ATMPs) received Market Authorisation (MA). ATMPs are medicinal products including gene therapy, cell therapy, and tissue engineering that contain similar characteristics (containing biologicals) [8]. These pharmaceuticals are relatively new and require new techniques and analysing methods, which can result in a burden for enterprises because it increases uncertainty about the expectations of regulators. The EMA acknowledged that ATMPs are more complex than small molecule pharmaceuticals and admitted that ATMPs require specific expertise, so the Committee for Advanced Therapeutics (CAT) was set up in 2009 [9]. The CAT is cooperating with SAWP to give input for SA, participates in discussions with enterprises, and shares expertise about ATMP development.

When the product has side-effects and/or adverse events, the product can be withdrawn from the market. SA gives recommendations to adapt in order to prove the efficacy, safety, and/or quality aspects in the dossier. Since the effect of efficacy, safety, and quality have an influence on the MA, it also may have an effect on the post-authorisation withdrawal.

However, it is not clear whether ATMPS similarly benefit from early SA and whether SA has any effect on the duration of the MA and possible withdrawal of ATMPs. Therefore, the aim of this study is to

find out what the influence of SA at different moments in the development has on the MA of ATMPs and if this affects possible post-authorisation withdrawal. The following research question was drawn up:

"What is the impact of Scientific Advice (SA) at various stages of development during the Market Authorisation Application (MAA) of Advanced Therapeutic Medicinal Products (ATMPs), and does it influence the likelihood of post-authorisation withdrawal?"

Scientific literature was used to gain information about SA's influence on all sorts of pharmaceuticals, while based on this, regulatory literature was used to further investigate the role of SA for ATMPs specifically.

Methods

Scientific literature

A two-step approach was taken to investigate the role of SA on MA and (lack of) post-authorisation withdrawal. First, a scientific literature review about SA and the factors of possible influencers on MA was performed. A search query, which can be found in the supplementary, was set up in order to find relevant literature. This search query was used in PubMed and scanned for relevant titles and abstracts. Subsequently, the relevant articles were scanned for relevant articles via forward and backward snowballing. These articles were also scanned for relevant titles and abstracts.

From literature, information about the contents of a pharmaceutical dossier, SA regulation, PRIME and Orphan designations, specific timing of SA, the relation of SA and MOs, compliance with SA, post-authorisation withdrawals, and parallel SA was found. Drawing upon these findings, data from regulatory literature with a specific focus on ATMPs were obtained.

Regulatory literature

All SA from 2009 till 2022 were collected from the CBG database. After that, R-studio was used (with a code provided in attachments) to search files which contained the following terms: Committee for Advanced Therapeutics, CAT, ATMP, gene therapy and cell therapy. After that, each file was looked into and qualified by either ATMP or non-ATMP.

The ATMPs had different names, codes and synonyms. In order to subdivide all SA into SA per product, ADISinsight was used to track different names, codes, synonyms and original developer[10]. This information was used to link different SA/PA to one ATMP product. From these products, the date of when a SA/PA was given and the amount of found SA/PA was tracked down by using the EPARs. This was only performed from the MAA products, because non-MAA products did not have an EPAR. The information about which ATMP had applied for MAA was from the European Union Register as well as from the EMA [11]. The MAA ATMPs were gathered and information, such as SAs, companies, MA data, refusal data, pivotal trials, pre- and post-authorisation withdrawal data was collected. Furthermore, from literature, the size of enterprises seemed to have a major impact at MA, so the sizes of enterprises was researched with help of the EMA SME database as well as the websites of the enterprises [12]. Furthermore, the EPARs consisted information about the main study which was used to search the start data on ClinicalTrials.gov [13]. The data of the main study was only reported in case of an existing EPAR or withdrawal assessment. EPARs were scanned for a positive or negative advice of the CAT which indicates whether an enterprise adhered to SA or not.

Lastly, the SAs were compared to the EPARs in order to draw conclusions about compliance. The relevant SA(s) associated with the main study or studies was/were compared to the main study or studies. The three subjects which the SA(s) and EPARs were scanned for were about clinical trials: the primary endpoint, the comparator and the robustness of statistical methodology. In case the three subjects were compliant or did not show data (at least one had to be compliant), the ATMP was qualified as “compliant”. On the other hand, in case one or more of three subjects were non-compliant, the ATMP was qualified as “non-compliant”. The last qualification was “unknown”, in case the SAs were absent or the compliance was doubtful.

Results

Scientific literature

A total of 15 publications were identified initially, and from this set, 24 articles were related to this research (see figure 1). By the forward and backward snowballing technique, an additional 34 relevant articles were retrieved, expanding the dataset to a total of 58 articles. These selected articles were the primary foundation for our research.

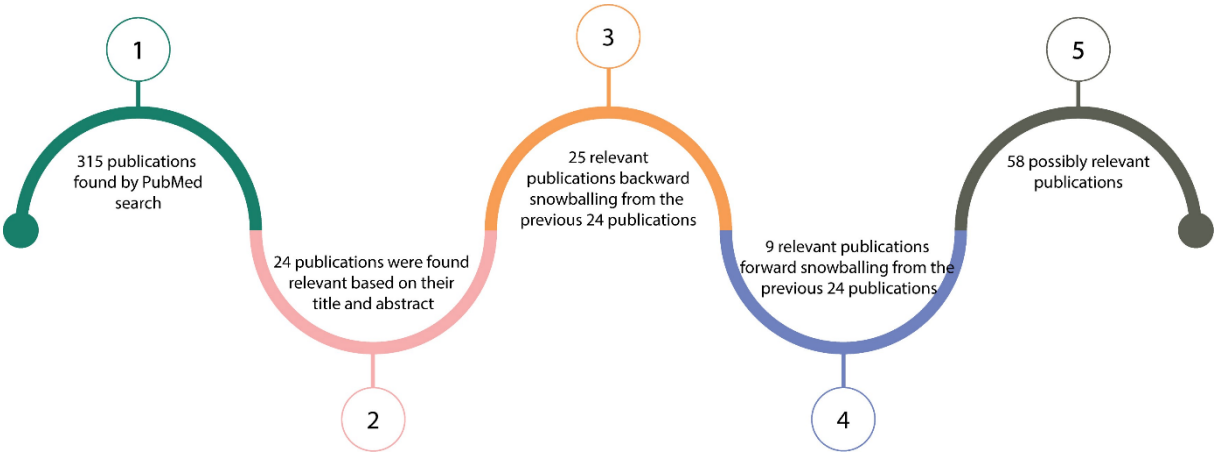

Figure 1: PubMed was used to search interesting publications for this research. First, a search query was set-up which resulted into 315 publications. After that, the titles and abstracts were scanned at relevance and led to 24 publications. These 24 publications had 25 interesting publications cited and referred to another 9 interesting ones. This led to a total of 58 possibly interesting publications which might be included in the literature review.

Different contents

The regulatory dossier consists of multiple sections, of which quality, efficacy, and safety are the main components. During the SA, enterprises are able to ask questions about, for example, the subsections of quality, efficacy, and safety [14]. Below, the importance of the main parts and the effects of SA are explained. Quality comprises non-clinical aspects, while efficacy and safety encompass both non-clinical and clinical aspects.

The quality part of the dossier consists of information about the substance as well as the product to ensure its quality. It includes details about the manufacturer, characterization, control tests, reference standards, packaging, and stability [15]. The importance of this subsection lies in enterprises having to demonstrate that the substances and the product are free from significant impurities, stable, and reproducible.

In the efficacy part of the dossier, enterprises have to prove the effectiveness of their developed pharmaceutical [16]. This section describes the non-clinical studies, in vitro experiments to demonstrate efficacy, as well as the clinical studies, including study design.

The safety section is crucial to ensure a positive benefit-risk balance for the successful approval of the pharmaceutical [6,17]. Enterprises must describe and monitor the side-effects and adverse events, as well as provide long-term data on their pharmaceutical to ensure its safety during clinical trials. Additionally, they need to describe non-clinical studies, such as toxicity evaluations. Pharmacovigilance is another essential aspect of the dossier, as enterprises must demonstrate how they will ensure the safety profile, minimize risks, develop plans to gain more knowledge, and measure the effectiveness of risk-minimisation measures [17,18].

Small- and medium enterprises

According to the EMA, approximately 45% of novel methodologies are proposed by small- and medium-sized enterprises (SMEs) each year [19].

A variety of companies, including small ones (less than 50 employees), medium ones (less than 250 employees), and large ones, attempt to market pharmaceuticals. SMEs often lack the knowledge that larger companies possess, but they are responsible for developing a significant portion of ATMPs. To facilitate the entry of these pharmaceuticals into the market, SMEs can seek SA to leverage the professional knowledge of regulators during the process [20]. SA involves a fee which could resist SMEs to ask for SA [21]. However, the involvement of SA incurs a fee, which may deter some SMEs from requesting SA. Nevertheless, Carr et al. (2010) demonstrated that SMEs have a lower success rate compared to larger companies [21]. This could be attributed to SMEs having fewer SA meetings compared to other companies, as shown by Garsen et al. (2021) [6].

Special programs like PRIME and Orphan may play a role in the process of obtaining SA, and therefore, these programs should be considered, particularly by SMEs. Orphan designations can be granted to enterprises that develop pharmaceuticals for rare diseases (prevalence less than 5 per 10,000 people) [20,22,23]. To obtain Orphan Designation (OD), enterprises must also comply with the following criteria: the disease must be life-threatening or chronically debilitating, and the pharmaceutical should offer significant benefits.

PRIME designation provides early and active support from the EMA to generate and optimize robust data, aiming to facilitate accelerated assessment (AA) for MA [6,7,17,24]. The objective of this designation is to expedite the availability of medicines for patients. Enterprises applying for PRIME designation must meet the requirement of addressing an unmet medical need where no treatment currently exists.

Timing of scientific advice

SA is provided to enterprises to offer advice on any aspect of their development dossier, including quality, efficacy, safety, pharmacovigilance, or any other subject. Consultations with the EMA can enhance knowledge and understanding of dissimilarities and perspectives [25]. Furthermore, SA has the potential to avoid unnecessary studies and stimulate further research [26]. According to the EMA, enterprises can request SA during the initial development or later in the post-authorisation phase [27]. Research papers by Carr et al. (2010), Dintsios et al. (2018), and Tafuri et al. (2016) suggest that early timing of SA has a more significant influence than later in the development [21,25,28]. A possible explanation for this finding is that during the early development stage, more adjustments can be made compared to later stages in the study [29,30]. Early SA is often referred to as SA given before or during non-clinical studies. According to Dintsios et al. (2018), early advice is SA provided before pivotal trials have been initiated[28]. However, Hofer et al. (2018) argues that there is a need for support at the proof-of-principle stage [22]. Moreover, Rosenberg et al. (2023) advise academia to seek SA as early as possible [26]. In conclusion, the literature is not clear on the specific stage of pharmaceutical development at which SA should be sought, but it emphasizes the importance of obtaining it early in the process.

“Scientific advice should be sought early, proactively and comprehensively” (Carr et al, 2010) [21]. One major advantage of requesting early SA is that it enhances knowledge and awareness of variations and perspectives [25]. Enterprises can benefit from the information provided by the EU commission, which may deal with comparative studies and possess inside knowledge about the regulatory benefit-risk assessment. This information can be advantageous in refining study designs and endpoints and also in avoiding unnecessary studies [26]. From an industry perspective, SA can necessitate modifications that should be implemented before studies commence [28]. However, it is possible that implementing the given SA advice may be challenging [31]. Additionally, seeking SA too early might disrupt the development process if it leads to advice that steers the pharmaceutical towards a different direction. Furthermore, there is a fee for SA, which might make enterprises reluctant to apply for it. However, for SMEs, the fee can be reduced by 90% [21].

SA can be sought at any stage during the development of a pharmaceutical. The advice is directed towards the most effective way of generating appropriate data for the evaluation of possible benefits and risks [4]. Additionally, EMA SA also recommends the type of authorisation that should be applied for, whether it's standard market authorisation (SMA), conditional market authorisation (CMA), or authorisation under exceptional circumstances (AEC), depending on the purpose and background of the pharmaceutical. The purpose of SA is to prevent Major Objections (MOs) during MAA and to avoid unnecessary trials."

Major objections

The advice provided in SAs aims to prevent difficulties and uncertainties during the development of pharmaceuticals. During the MAA process, the Committee for Medicinal Products for Human Use (CHMP) evaluates whether the benefit-risk balance is positive [2,18,32]. If the CHMP identifies difficulties and uncertainties, it may raise MOs that require attention from the applicant. Failure to address these MOs could result in the pharmaceutical either being withdrawn by the applicant (pre-authorisation withdrawal) or being refused by the CHMP.

Effect on MAA outcome

After requesting and receiving SA, enterprises have the option to either implement the advice, propose an alternative strategy, or ignore the SA. Following up on SA can be challenging; however, adhering to SA offers advantages [33]. Garsen et al. (2021) conducted a study on the procedural timelines of anticancer drugs MAAs by analysing European Public Assessment Reports (EPARs). They concluded that adhering to SA is crucial [6]. Additionally, Breckenridge et al. (2010) mentioned that implementing SA increases the likelihood of obtaining a positive opinion from the CHMP and, consequently, gaining MA [34,35].

However, no studies were found that specifically examine the relationship between SA and post-authorisation withdrawal after MA.

ATMP scientific advice

In 2009, the first ATMP, ChondroCelect, obtained MA in Europe. ChondroCelect is a tissue engineering product (TEP) characterized by viable autologous cartilage cells expanded ex vivo expressing specific marker proteins. Subsequently, other ATMPs, including cell therapy medicinal products (CTMPs) and gene therapy medicinal products (GTMPs), also gained MA. ATMPs are required to undergo a centralised procedure by the EMA to be brought to the market [36]. To evaluate and elaborate on the processes of ATMPs, the EMA established the CAT [8]. The development and evaluation of ATMPs present challenges due to their complexity, utilizing biological products such as cells and genes. These products bring new risks to light, including infections, rejections, and tumorigenicity [37]. Additionally, ATMPs are mainly developed against orphan diseases and in case of high unmet medical needs, according to Iglasias-Lopes, et al (2021) [24,38]. Therefore adaptive designs are being used and more uncertainties exist during the MA. Rousseau et al, 2018 addressed the challenge of finding an animal model that fits into the study and determines proof-of-concept is a persistent issue for gene and cell therapy developments [30]. Missing fitting models can hamper the evaluation of regulators and thus the MA. Furthermore, remarkable is that mostly academia, hospitals and small- and medium enterprises (SMEs) are developing ATMPs. These organisations have minimal knowledge of regulatory requirements and have less capacity than larger enterprises. In conclusion, there are challenges for the process towards MA for ATMPs, but by asking SA of the CAT can facilitate the process. Therefore this research will focus on the SAs given during the development of ATMPs. Tavridou et al, 2021 also found that during the pivotal development of ATMPs more SA about advice domains were asked than during the exploratory development [36]. Reasons were that during the early development, the pharmaceutical was not fully understood and interrelations between advice domains could be reflected more finer when remaining uncertainties were more researched.

Parallel scientific advice

EMA is not the only organization that provides SA; the NCAs and HTAB also offer SA to enterprises. It might be interesting to request parallel SA from, for example, the EMA and a few HTABs. The advantages and disadvantages of this approach will be discussed.

Seeking parallel SA can have the advantage of gaining perspectives from different parties [25]. Simultaneously, the different parties can engage in discussions to narrow the gap between them [17,39]. This is important because it is more efficient to conduct one study that addresses the concerns of all parties rather than conducting separate studies [40]. From the industry's perspective, obtaining information from both regulatory and HTAB sources can lead to a higher quality study setup [28]. Furthermore, during these sessions, discussions can resolve issues, relieving enterprises from having to make these choices independently.

On the other hand, parallel SA can also have disadvantages. Regulators might feel undermined due to significant interaction with HTAB [31]. Moreover, from the industry's perspective, inconsistencies and friction between parties may arise during these sessions [28]. Friction could be caused by a lack of knowledge about the specialties of regulators and HTAs. However, these disadvantages can be addressed and resolved through compromise.

Regulatory literature: Scientific advices and European public assessment reports

In the period 2009-2022, there were 8,292 files found by the R-studio search, as seen in figure 2. Out of these, 437 were related to ATMPs. Since enterprises can request multiple SAs for one product, different SAs were found for a single product. After organising SAs by product, 263 ATMP products were identified.

Out of these 263 products, 35 applied for MAA. However, not all of them eventually obtained MA. In the end, 24 ATMPs were granted MA, and one is currently in the process of MAA. On the other hand, one MAA was refused, and nine ATMPs were withdrawn pre-authorisation, while seven were withdrawn post-authorisation. As a result, there are currently seventeen ATMPs marketed.

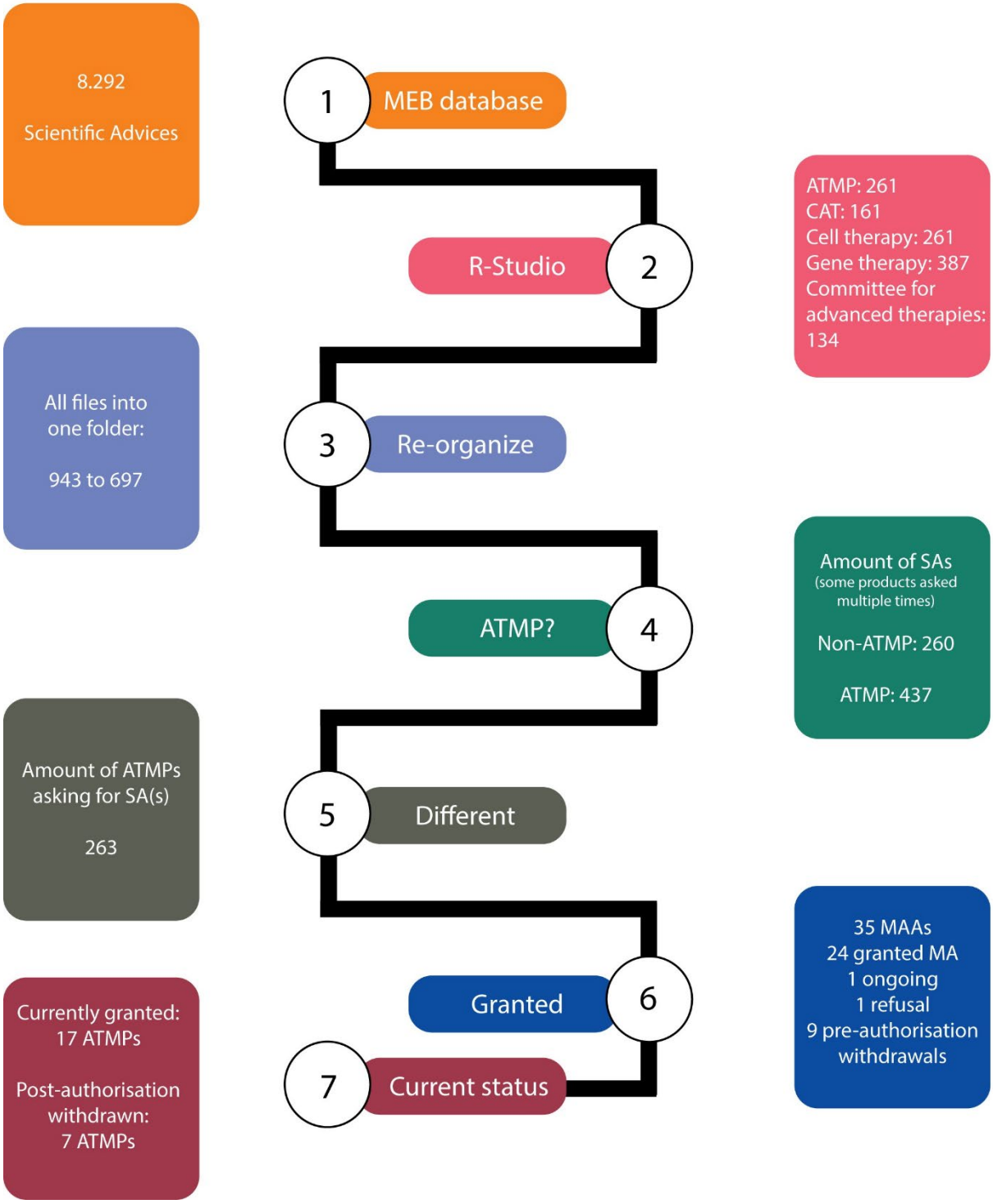

Figure 2: A flowchart of the search for SAs of ATMPs from the MEB database. First, a search was performed with help of R-Studio in order to collect only SAs including the terms "ATMP", "CAT", "Cell therapy", "Gene therapy" and "Committee for advanced therapies" which led to 943. Of the 943 results, 246 were double files which were found by two or more terms. Of the 697 SAs, 437 appeared to be ATMPs. Some ATMPs asked multiple times for SAs, these were linked to one ATMP and led to 263 different ATMPs. From these 263 ATMPs, only 35 applied for MAA and only 24 granted MA (while one was ongoing). Others got refused (one), withdrawn before authorisation (nine) or after authorisation (seven).

In Table 1, it is shown how many SAs are asked, divided over marketed, refused, and withdrawn ATMPs. The number of asked SAs for refused ATMPs is one, and for the pre-authorisation withdrawals, it is two, while for the marketed and post-authorisation withdrawal ATMPs, the number is four.

Tabel 1: The amount of SAs asked during the development divided over MA, refusal, pre- and post-authorisation withdrawals. The average number of asked SA is shown in the last row. Remarkable is that the pre-authorisation withdrawal products asked about two times for advice, while the post-authorisation withdrawals asked four times for advice.

	MA	Refusal	Pre-authorisation withdrawal	Post-authorisation withdrawal
Total numbers of ATMPs	24	1	9	7
Number of ATMPs without SA	0	0	3	0
Number of ATMPs with SA	21	1	6	7
Average number of SA	4	1	2	4

During the development of a medicinal product, not only SA could be gained, but orphan designations and PRIME designations were also granted. The development of the ATMPs differed in the amount of asked advices (ranging from zero to eight), the type of application (SMA, CMA and AEC) and the reason for finishing MAA/MA (pre-authorisation withdrawal, refusal or post-authorisation withdrawal).

For some products, the main study occurred before SA was requested, while for others, it was after the requested SA. Only one ATMP (Glybera) received a negative draft opinion from the CAT. Glybera also received a negative opinion from the CHMP for an AEC but obtained the AEC during a re-examination. Later on, Glybera was withdrawn from the market post-authorisation (data not shown).

Influence of SMEs

Another researched factor was the involvement of enterprises, whether they were SMEs or not. Table 2 provides an overview of MAAs, MAs, pre-authorisation withdrawals, rejections, and post-authorisation withdrawals of ATMPs originating from SMEs and non-SMEs. There were 23 ATMPs that originated from SMEs, while only eleven originated from non-SMEs. Out of the 20 SME

applicants' ATMPs, 60% were marketed, and 35% were pre-authorisation withdrawn. For non-SME applicants originating ATMPs, 86% were marketed, and 14% were pre-authorisation withdrawn.

Tabel 2: ATMPs that are marketed could have different enterprises from the original developer to the market developer. From the 35 ATMPs, 23 had a SME as original developer while eleven had a non-SME enterprise. During the MA, twenty products had a SME, while fourteen had a non-SME. There is a major difference between SME and non-SME in the pre- and post-authorisation category of the developer as well as of the applicant.

	MAAs	MAs	Pre-authorisation withdrawn	Rejected	Post-authorisation withdrawn
Developer					
SME	23	15 (65%)	7 (30%)	1 (4%)	6 (40% of MAs)
Non-SME	11	9 (82%)	2 (18%)	0 (0%)	2 (22% of MAs)
Applicant					
SME	20	12 (60%)	7 (35%)	1 (5%)	4 (20% of MAs)
Non-SME	14	12 (86%)	2 (14%)	0 (0%)	4 (29% of MAs)

The flow of the ATMPs from originating SMEs or originating non-SMEs to approval, withdrawal, or refusal is shown in Figure 4. This figure indicates that five ATMPs were originated by SMEs but taken over by non-SMEs during development, while two were originated by non-SMEs and taken over by an SME.

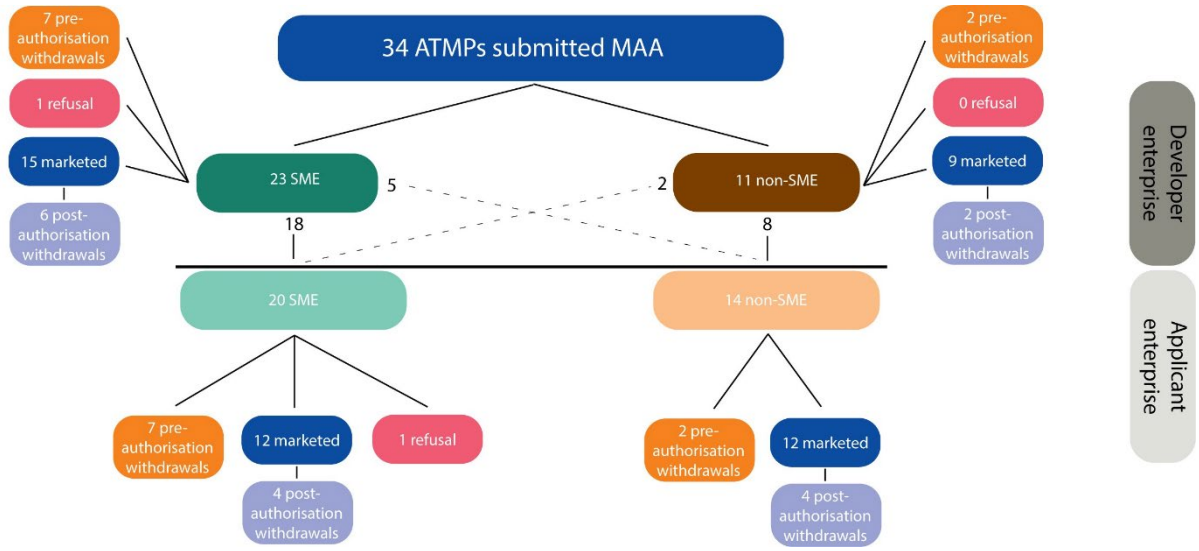

Figure 3: A flowchart of 34 ATMPs (one was left out due to the ongoing MAA). This flowchart shows how many ATMPs became available onto the market. 23 ATMPs were originated by SMEs and 11 by non-SMEs. From the 24 ATMPs originating from SMEs, five were adopted by non-SMEs during the development. From the 11 non-SMEs, two products were adopted by a SME.

Influence of timing and compliance

For a total of 31 ATMPs, SA was requested during the development and pivotal trials, of which 22 were available and their timing of SA request (before or during the main trial) was known (see figure 5). Among these ATMPs, only eleven pivotal trials were compliant with SA, and nine obtained MA

(figure 5a). Seven products were non-compliant, and only five of them gained MA. For four products, it was not clear whether they complied with SA.

Early SA was only given to eight of the ATMP products from which five got MA, see figure 5c. Three of the five products were compliant with SA and got MA, while only two products which were not compliant with SA was asked but both got MA.

During the pivotal trials, 14 products requested SA, and 12 of them obtained MA. All six products that were compliant with SA were granted MA (figure 5d). Figures 5e and 5f displayed the post-authorisation withdrawal rate of the ATMPs in comparison to the adherence to SA. Figure 5d revealed that five out of the seventeen approved ATMPs were post-authorisation withdrawn, with most of them being compliant with SA. The timing of SA for the other two post-authorisation withdrawn ATMPs was unclear. A similar trend was observed for SA given during the trials (figure 5e), while ATMPs that received SA before the trials were not post-authorisation withdrawn at all (Figure 5f).

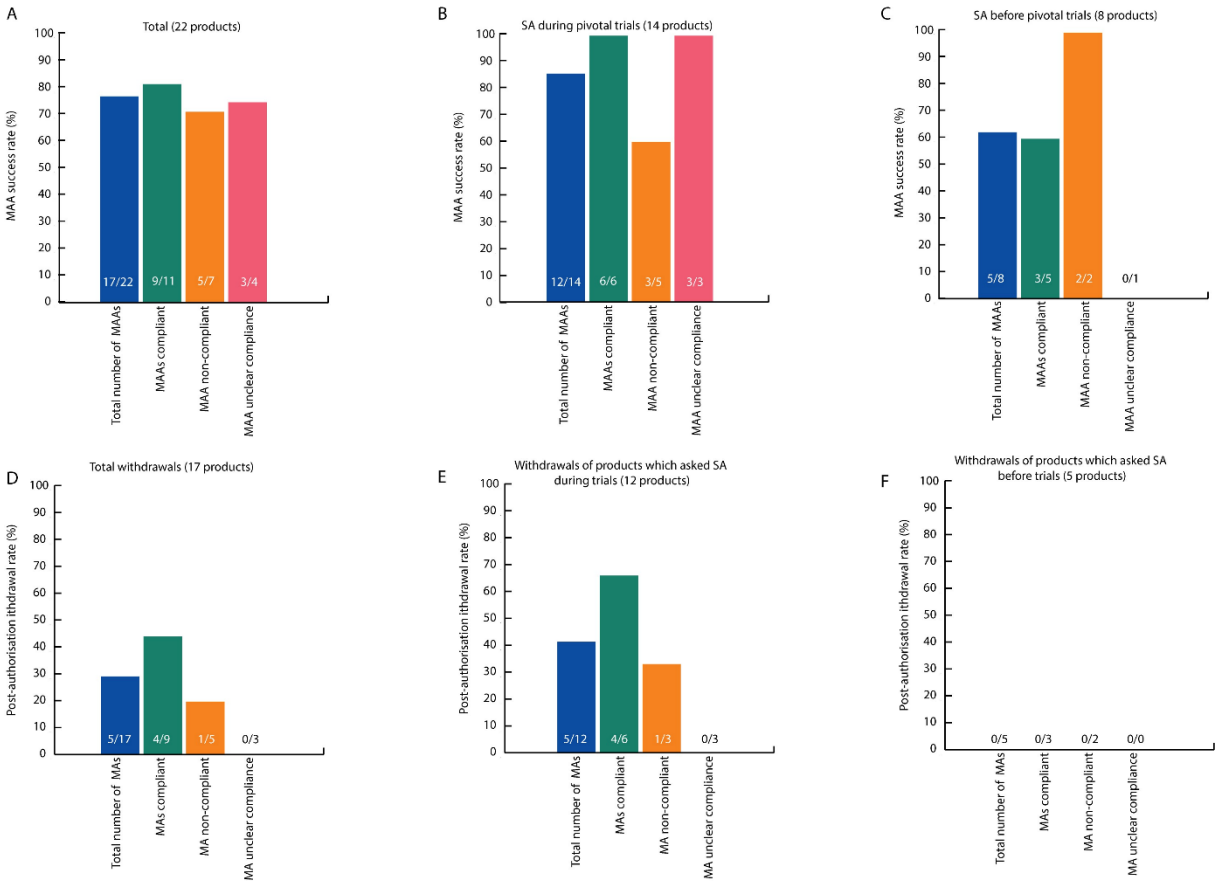

Figure 4: Influence of SA on MAA and withdrawal/rejections. For a total of 31 ATMP products SA was asked during the period of 2009 to 2022, but from nine products the SA was unavailable or uncertain about when the SA was given (before or during the main trail. Part of these SAs was asked during the pivotal trials (B and E) while others were asked before the pivotal trials (C and F). Figure A, B and C showed the influence on MAA success rate, while figure D, E and F showed the influence on post-authorisation withdrawal.

The overview in figure 6 shows the flow of 32 ATMPs, of which twelve were compliant and seven were not compliant. In contrast to figure 5, the ATMPs for which it was unclear when they asked for advice were not excluded from this analysis. 83% gained MA after being compliant with SA, while only 71% gained MA while they were non-compliant to SA. Among the compliant ATMPs, 40% were post-authorisation withdrawn, and 14% was refused, while the products were not compliant with SA. For twelve products, it was unclear whether they complied with SA, but 75% obtained MA, 25% received pre-authorisation withdrawal, and 22% experienced post-authorisation withdrawal.

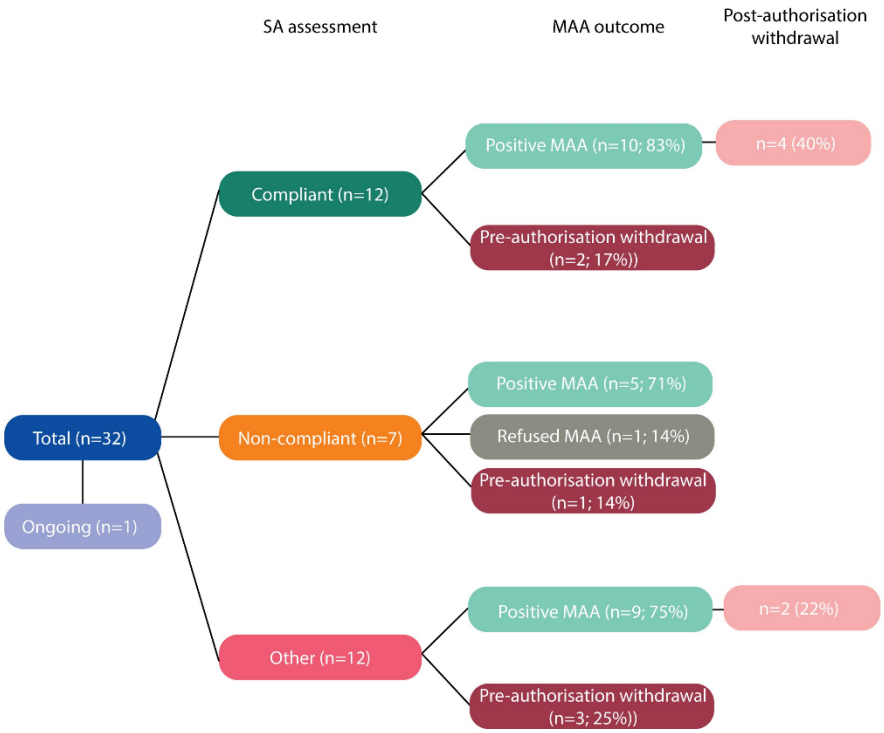

Figure 5: Overview of the total of ATMP products to MAA outcome and withdrawal. Advices from SA were compared to the pivotal trials in the EPARs of the products for compliance.

Discussion

This study aimed to investigate the influence of SA at different stages of development on MA and its potential impact on withdrawal decisions. Various factors were considered, including company size, designations obtained (Orphan and PRIME), timing of SA requests, and compliance with SA. These are explained in the following paragraphs.

The number of SAs requested could significantly impact the likelihood of an ATMP obtaining marketing authorisation (MA). Existing Orphan and PRIME designations are associated with providing SA, which allows for more opportunities to receive feedback on development and studies. Literature suggests that products with Orphan or PRIME designation had even more options to receive feedback on development and studies [40,41]. The results of this research showed that ATMPs which had MA or were post-authorisation withdrawn both received an average of four SAs in contrast to rejected ATMPs which received only one SAs. On top of that, the pre-authorisation withdrawal ATMPs only received SA twice on average. Furthermore, all of the marketed ATMPs asked for SA at least once. Tenhunen et al, 2020 as well as Bloem L et at, 2023 also showed that 77% of all cancer products MAs did sought for SA with an average of two SAs [42,43]. However, this study was about cancer products and not about ATMPs but both groups have to be evaluated through the centralised procedure. Moreover, cancer products as well as ATMPs struggle with a high unmet medical need and minimal patient groups and are therefore comparable groups for the influence of SA [7,42]. To conclude, there is a strong suspect that asking for more SA contributes to the chance of granting a MA.

From the research, fifteen (of the 23) of the ATMPs originating from SMEs granted MA against nine (of the eleven) ATMPs originating from larger enterprises. Thus, SMEs have more ATMPs developed than larger companies. This is in line with literature which also found that SMEs had more effort with granting ATMPs [6,21]. On the other hand, there is no difference between SME and non-SME applicants of ATMPs which both had twelve products marketed. Remarkable is that SME applicants asked more often for pre-authorisation withdrawal (seven times in comparison to two times for non-SME applicants. Pre-authorisation withdrawal could be due to negative effects from clinical trials or due to MOs of the CHMP during the MAA. This is in line with Carr et al, 2010 which found that the amount of MOs is often higher in development plans of SMEs [21]. SMEs do develop more ATMPs, but do not have more ATMPs marketed than non-SMEs.

The timing of SAs could have influence on the possibility of adapting the study and flexibility of enterprises for the development. There are no ATMPs currently marketed which did not receive SA, five which received SA before the main study start and twelve during the main study which indicates that the timing of SA should be during the study instead of before. To conclude, the timing of SAs seems to have a positive effect on MA when SA is given during the start of the main study. This is not in line with literature which is also recommending to seek for SA early on in the process [28,31,44,45].

The study found that success of MAA was not related to the compliance of SA given before the main study start. Compliant SA given during the trials, was more successful than non-compliant SAs. Compliant SAs before trial was not more successful, but this could be influenced due to the fewer SAs requested before trial. Glybera, received a negative opinion initially, but received AEC after re-examination before it got post-authorisation withdrawn. Other products which received a positive opinion granted MA and are still on the market. So, in this research compliance with SA seemed to have a positive effect on MA. This complies to results found in literature [6,34,46].

Furthermore, Hofer et al, 2015 also performed analysis for all MAA submissions between 2008 and 2012 [47]. This article also shows that compliance with SA seems to have a relation with MAA success rate. However, the method used in this article could be interpretable differently. The compliance of different SAs was based on the first SA or based on the first relevant SA. One way to address this is to perform a sensitivity analyse with the data based on timing from first SAs in comparison to compliance. Furthermore, this article compared the SA compliance with assessment reports within EMA instead of EPARs used in this research. The reports can slightly differ, but the outcomes should be the same.

The withdrawal rate was also researched. SAs given before the trials prevented ATMPs from post-authorisation withdrawal independently from compliance or non-compliance. However, SAs asked during the trials seemed to lead to more post-authorisation withdrawals when the SA were compliant in comparison to non-compliant. The small amount of post-authorisation withdrawn ATMPs from SAs gained during trials could misinterpret the effect of compliance in relation to post-authorisation withdrawal. From the withdrawn ATMPs, a few reasons were mentioned for the withdrawal. Some of these reasons were change of company strategy, failing to prove enough clinical evidence and issues regarding safety. Furthermore, some of the ATMP which applied a MAA were pre-authorisation withdrawn during the assessment with reasons as: extreme finance difficulties, negative opinion of the CAT on the benefit-risk balance for the CHMP and not performed enough clinical studies to come up with the evidence while no ongoing studies are being performed. No literature about studies researching withdrawals were found, so no comparisons could be made.

Based on the results of this literature review, it seems to be recommendable to search for SA multiple times. Furthermore, compliance with SA seems to have a positive effect on the MAA success rate, so recommended is to comply with SA. The CAT has set-up regulations in order to improve the ATMP marketing from development to MA and after MA, this should provide companies guidance8. If applicable, apply for PRIME or Orphan designation, because these offer programs specialised for these products [40,41].

Limitations were present in this research. This study was based on the database of the MEB which should have consisted out of all SA given from 2009 to 2022. However, not all SAs mentioned in the EPARs were found for each ATMP. The first reason could be that the SAs mentioned in the EPARs were given before 2009 and therefore were without the scope of this research. The second reason could be that the names and codes gathered for each ATMP was not complete, so a SA with a deviating name could be missed. The third reason could be that the MEB database missed a few ATMP SAs, because gathering of SAs from EMA database to MEB database was performed manually.

The qualification of ATMP or non-ATMP was based on finding information about the substances into the files and was sensitive for looking over information and wrongly qualifying files. Although, during this search, the SAs were scanned for the words “gene therapy”, “cell therapy” and “tissue” and should have given a good indication whether a product was an ATMP.

Another limitation of this study was the collection of information. Information gathered during this research was collected from databases such as AdisInsight and ClinicalTrials.gov [10,13]. These websites are not managed by the EMA and therefore might consist out of deviating information. The information about whether companies were SMEs was partly coming from the EMA SME database and partly from the enterprises websites [12]. The enterprises might have enlarged or reduced, while this information is not published so this can give a distorted perception of the enterprises sizes.

While this study was performed with all MAAs of ATMPs, the cohort was small due to data availability of only 35 ATMPs. A follow-up study should be performed with more ATMP products in the future to draw conclusions about the relation between SA and MA/post-authorisation withdrawal.

Conclusion

In conclusion, the study highlights that seeking SA is a valuable tool for enterprises to benefit from the expertise of regulators. Regulators are willing to share their knowledge to enhance the robustness and quality of pharmaceutical development. The research analysed ATMPs from 2009 to 2022 to understand their SA seeking behaviour during development.

The findings indicate that adhering to SA is positively related to obtaining a positive opinion from the CHMP for MA. Notably, 68% of the ATMPs undergoing MAAs were initially developed by SMEs, though the applicants were evenly divided between SMEs and non-SMEs, suggesting that SMEs face more challenges during MAA. The study found that approved ATMPs requested SA more frequently (an average of four times) compared to non-approved ATMPs (an average of two times). Thus, it is recommended to actively seek SA multiple times to facilitate the MAA process. Interestingly, the majority of marketed ATMPs sought SA during the main trial (71%). Notably, ATMPs that received SA before the main study had no post-authorisation withdrawals, regardless of compliance. Moreover, seeking SA before the main trial start was associated with a lower likelihood of post-authorisation withdrawal.

References

1. Who we are | European Medicines Agency. Accessed August 1, 2023. https://www.ema.europa.eu/en/about-us/who-we-are

2. What we do | European Medicines Agency. Accessed August 1, 2023. https://www.ema.europa.eu/en/about-us/what-we-do

3. Medicines Agency E. From laboratory to patient - the journey of a medicine assessed by EMA.

4. Scientific advice and protocol assistance | European Medicines Agency. Accessed July 23, 2023. https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance

5. Katsnelson A. FDA and EMEA pool scientific advice. *Nat Biotechnol*. 2004;22(12):1490-1491. doi:10.1038/NBT1204-1490

6. Garsen M, Steenhof M, Zwiers A. A Decade of Marketing Authorization Applications of Anticancer Drugs in the European Union: An Analysis of Procedural Timelines. *Ther Innov Regul Sci*. 2021;55(4):633-642. doi:10.1007/S43441-021-00260-5/TABLES/5

7. Hanaizi Z, Kweder S, Thor S, Ribeiro S, Marcal A. Considering Global Development? Insights from Applications for FDA Breakthrough Therapy and EMA PRIME Designations. *Ther Innov Regul Sci*. 2023;57(2):321-328. doi:10.1007/S43441-022-00475-0/TABLES/5

8. Celis P. CAT - The new committee for advanced therapies at the European Medicines Agency. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*. 2010;53(1):9-13. doi:10.1007/S00103-009-0998-Y/FIGURES/1

9. Committee for Advanced Therapies (CAT) | European Medicines Agency. Accessed August 1, 2023. https://www.ema.europa.eu/en/committees/committee-advanced-therapies-cat

10. Home - AdisInsight. Accessed July 23, 2023. https://adisinsight.springer.com/

11. Medicines Agency E. Advanced therapy medicinal products approvals for the following indication: treatment of severe and moderately severe Haemophilia B (congenital Factor IX deficiency) in adult patients without a history of Factor IX inhibitors. Based on the assessment of the CAT, the Committee for Medicinal Products for Human Use Extension of indication of authorised ATMPs Overview of product-related activities. Published online 2023. Accessed July 23, 2023. www.ema.europa.eu/contact

12. SME Search. Accessed July 23, 2023. https://fmapps.ema.europa.eu/SME/

13. Home | Beta ClinicalTrials.gov. Accessed July 23, 2023. https://www.clinicaltrials.gov/

14. Kaul S, May S, Lüttkopf D, Vieths S. Regulatory environment for allergen-specific immunotherapy. *Allergy*. 2011;66(6):753-764. doi:10.1111/J.1398-9995.2011.02552.X

15. Quality guidelines | European Medicines Agency. Accessed July 12, 2023. https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/quality-guidelines

16. Efficacy guidelines | European Medicines Agency. Accessed July 12, 2023. https://www.ema.europa.eu/en/veterinary-regulatory/research-development/scientific-guidelines/efficacy-guidelines

17. Enzmann H. New trends and challenges in the European regulation of innovative medicines. *Regulatory Toxicology and Pharmacology*. 2016;80:314-320. doi:10.1016/J.YRTPH.2016.05.033

18. Risk management plans | European Medicines Agency. Accessed July 12, 2023. https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pharmacovigilance/risk-management/risk-management-plans

19. oo. 2022 SME office annual report.

20. Elsäßer A, Regnstrom J, Vetter T, et al. Adaptive clinical trial designs for European marketing authorization: A survey of scientific advice letters from the European Medicines Agency. *Trials*. 2014;15(1):1-10. doi:10.1186/1745-6215-15-383/TABLES/2

21. Carr M. The small- and medium-sized enterprises office (SME office) at the European medicines agency. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*. 2010;53(1):20-23. doi:10.1007/S00103-009-0989-Z/FIGURES/2

22. Hofer MP, Hedman H, Mavris M, et al. Marketing authorisation of orphan medicines in Europe from 2000 to 2013. *Drug Discov Today*. 2018;23(2):424-433. doi:10.1016/J.DRUDIS.2017.10.012

23. Putzeist M, Heemstra HE, Garcia JL, et al. Determinants for successful marketing authorisation of orphan medicinal products in the EU. *Drug Discov Today*. 2012;17(7-8):352-358. doi:10.1016/J.DRUDIS.2011.10.027

24. Iglesias-Lopez C, Obach M, Vallano A, Agustí A. Comparison of regulatory pathways for the approval of advanced therapies in the European Union and the United States. *Cytotherapy*. 2021;23(3):261-274. doi:10.1016/j.jcyt.2020.11.008

25. Tafuri G, Pagnini M, Moseley J, et al. How aligned are the perspectives of EU regulators and HTA bodies? A comparative analysis of regulatory-HTA parallel scientific advice. *Br J Clin Pharmacol*. 2016;82(4):965-973. doi:10.1111/BCP.13023

26. Rosenberg N, van den Berg S, Stolwijk NN, et al. Access to medicines for rare diseases: A European regulatory roadmap for academia. *Front Pharmacol*. 2023;14:1142351. doi:10.3389/FPHAR.2023.1142351/BIBTEX

27. Scientific advice and protocol assistance | European Medicines Agency. Accessed July 12, 2023. https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance#when-scientific-advice-is-most-useful-section

28. Dintsios CM, Schlenkrich S. INDUSTRY'S EXPERIENCES WITH THE SCIENTIFIC ADVICE OFFERED BY THE FEDERAL JOINT COMMITTEE WITHIN THE EARLY BENEFIT ASSESSMENT OF PHARMACEUTICALS IN GERMANY. *Int J Technol Assess Health Care*. 2018;34(2):196-204. doi:10.1017/S0266462317004536

29. Collignon O, Koenig F, Koch A, et al. Adaptive designs in clinical trials: From scientific advice to marketing authorisation to the European Medicine Agency. *Trials*. 2018;19(1):1-14. doi:10.1186/S13063-018-3012-X/FIGURES/3

30. Rousseau CF, Maciulaitis R, Sladowski D, Narayanan G. Cell and gene therapies: European view on challenges in translation and how to address them. *Front Med (Lausanne)*. 2018;5(MAY):371205. doi:10.3389/FMED.2018.00158/BIBTEX

31. Wonder M. What can be gained from increased early-stage interaction between regulators, payers and the pharmaceutical industry? *http://dx.doi.org/101586/147371672014917966*. 2014;14(4):465-467. doi:10.1586/14737167.2014.917966

32. Authorisation of medicines | European Medicines Agency. Accessed July 23, 2023. https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines

33. Regnstrom J, Koenig F, Aronsson B, et al. Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency. *Eur J Clin Pharmacol*. 2010;66(1):39-48. doi:10.1007/S00228-009-0756-Y/TABLES/5

34. Breckenridge A, Woods K, Walley T. Medicines Regulation and Health Technology Assessment. *Clin Pharmacol Ther*. 2010;87(2):152-154. doi:10.1038/CLPT.2009.261

35. Butlen-Ducuing F, Zienowicz M, Pétavy F, et al. European regulatory experience with drugs for central nervous system disorders. *Nat Rev Drug Discov*. 2015;14(2):89-90. doi:10.1038/NRD4511

36. Tavridou A, Rogers D, Bonelli M, Schiel A, Hidalgo-Simon A. Towards a better use of scientific advice for developers of advanced therapies. *Br J Clin Pharmacol*. 2021;87(6):2459-2464. doi:10.1111/BCP.14672

37. Salmikangas P, Schuessler-Lenz M, Ruiz S, et al. Marketing regulatory oversight of advanced therapy medicinal products (ATMPs) in europe: The EMA/CAT perspective. *Adv Exp Med Biol*. 2015;871:103-130. doi:10.1007/978-3-319-18618-4_6/COVER

38. Iglesias-Lopez C, Agustí A, Vallano A, Obach M. Current landscape of clinical development and approval of advanced therapies. *Mol Ther Methods Clin Dev*. 2021;23:606. doi:10.1016/J.OMTM.2021.11.003

39. Liberti L, Breckenridge A, Eichler HG, Peterson R, McAuslane N, Walker S. Expediting Patients' Access to Medicines by Improving the Predictability of Drug Development and the Regulatory Approval Process. *Clin Pharmacol Ther*. 2010;87(1):27-31. doi:10.1038/CLPT.2009.179

40. PRIME: priority medicines | European Medicines Agency. Accessed July 23, 2023. https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines

41. Orphan designation: Overview | European Medicines Agency. Accessed July 23, 2023. https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview

42. Tenhunen O, Lasch F, Schiel A, Turpeinen M. Single-Arm Clinical Trials as Pivotal Evidence for Cancer Drug Approval: A Retrospective Cohort Study of Centralized European Marketing Authorizations Between 2010 and 2019. *Clin Pharmacol Ther*. 2020;108(3):653-660. doi:10.1002/CPT.1965

43. Bloem LT, Schelhaas J, López-Anglada L, Herberts C, van Hennik PB, Tenhunen O. European Conditional Marketing Authorization in a Rapidly Evolving Treatment Landscape: A Comprehensive Study of Anticancer Medicinal Products in 2006–2020. *Clin Pharmacol Ther*. 2023;114(1):148-160. doi:10.1002/CPT.2906

44. Backhouse ME, Wonder M, Hornby E, Kilburg A, Drummond M, Mayer FK. Early dialogue between the developers of new technologies and pricing and reimbursement agencies: A pilot study. *Value in Health*. 2011;14(4):608-615. doi:10.1016/j.jval.2010.11.011

45. Beinlich P, Müller-Berghaus J, Sudhop T, Vieths S, Broich K. Interplay between marketing authorization and early benefit assessment of drugs. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*. 2015;58(3):227-231. doi:10.1007/S00103-014-2108-Z/FIGURES/3

46. Liberti L, Breckenridge A, Hoekman J, McAuslane N, Stolk P, Leufkens H. Factors related to drug approvals: predictors of outcome? *Drug Discov Today*. 2017;22(6):937-946. doi:10.1016/J.DRUDIS.2017.03.003

47. Hofer MP, Jakobsson C, Zafiropoulos N, et al. Regulatory watch: Impact of scientific advice from the European Medicines Agency. *Nat Rev Drug Discov*. 2015;14(5):302-303. doi:10.1038/NRD4621

Supplementary

Search query PubMed

(("Scientific advice*"[tw] OR SA[tw] OR SAs[tw])

AND

("Drug Approval"[Mesh] OR "Marketing of Health Service*"[Mesh] OR MA[tw] OR MAs[tw] OR "market application*"[tw] OR "market approval*"[tw] OR "market authori*"[tw]))

AND

(((((("Time Factor*"[Mesh] OR late[tw] OR early[tw])

OR

("Research Design"[Mesh] OR "Endpoint Determination"[Mesh] OR "Drug Discovery"[Mesh] OR Proposal*[tw]))

OR

("Pharmaceutical preparation*"[Mesh] OR drug*[tw] OR medicin*[tw]))

OR

(EMA[tw] OR "European Medicines Agency"[tw]))

OR

("Post-authori*"[tw] OR "post authori*"[tw] OR "post-marketing" [tw] OR "post marketing" [tw] OR "withdrawn"[tw]))

R-studio search script

```
import os
from docx2python import docx2python
import fitz
import shutil

# define the directory path containing the Word and PDF documents
directory = "C:/Users/LotteH/Documents/Alle"

# define the keywords to search for and create a subdirectory for each keyword
keywords = {
   "keyword": "keyword"}
for keyword, subdirectory in keywords.items():
   if not os.path.exists(subdirectory):
      os.makedirs(subdirectory)

# loop through each file in the directory
for i, filename in enumerate(os.listdir(directory)):
   # check if the file is a Word document
   if filename.endswith(".docx"):
      print(i, filename)
      # open the Word document
      doc = docx2python(os.path.join(directory, filename))
      # loop through each paragraph in the document
      for paragraph in doc.body:
         # paragraph[0][0] is a list of strings -> ' '.join joins the items in the list to one string
         try:
            text = ' '.join(paragraph[0][0])
         except IndexError:
            continue
```

```
        # loop through each keyword
        for keyword, subdirectory in keywords.items():
            # if the keyword is found in the paragraph (case-insensitive), save the document in the corresponding subdirectory
            if keyword.lower() in text.lower():
                print(f'{keyword} = True')
                shutil.copy2(os.path.join(directory, filename), subdirectory)
            else:
                continue

    # check if the file is a PDF document
    elif filename.endswith(".pdf"):
        # open the PDF document
        with fitz.open(os.path.join(directory, filename)) as pdf_file:
            # loop through each page in the document
            for page_num in range(pdf_file.page_count):
                page = pdf_file[page_num]
                text = page.get_text()
                # loop through each keyword
                for keyword, subdirectory in keywords.items():
                    # if the keyword is found in the page (case-insensitive), save the document in the corresponding subdirectory
                    if keyword.lower() in text.lower():
                        shutil.copy2(os.path.join(directory, filename), subdirectory)
                        break  # stop searching for keywords if a match is found
```