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ORIGINAL ARTICLE

Towards a better use of scientific advice for developers of advanced therapies

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Scientific advice (SA) is an important tool offered by regulators to help developers generate robust evidence on a medicine's benefits and risks. Drawing on accumulated experience and looking at the SA provided by the European Medicines Agency in 2018 to advanced therapy medicinal products originally developed by public bodies, we discuss most commonly raised issues and the complexity and timings of the questions posed. Earlier and more frequent SA could help advanced therapy medicinal product developers to pre-empt delays at the marketing authorisation stage. Carefully addressing quality and nonclinical issues before entering the pivotal phase of development will clear the path for a smooth clinical development and successful marketing authorisation.

KEYWORDS
advanced therapy medicinal products, drug development, drug regulation, scientific advice

1 | INTRODUCTION

Public bodies (including academic institutions, research organisations, hospitals), public–private partnerships and small and medium-sized enterprises (SMEs) represent an important source of innovative therapeutics.[1] This holds particularly true for the area of advanced therapy medicinal products (ATMPs), as research on these products and their initial development is conducted to a great extent by public bodies and SMEs.[2] This is confirmed by a recent survey, which concluded that the European ATMP field is still in early phase of maturity with a high representation of SMEs (65%) and 72% of reported therapeutics in early clinical development (phases I–II).[3]

Public bodies and SMEs tend to have limited resources to conduct late-stage clinical trials and the majority of authorised ATMPs in the EU needed collaboration of SMEs or public partners with large pharmaceutical companies (e.g. Strimvelis, Imlygic, MACI, Holoclar, Zolgensma). Moreover, academic institutions and SMEs may encounter more challenges in navigating—and complying with—regulatory requirements on various aspects of development compared with large pharmaceutical companies.[4] These challenges could cause delays at different stages of development and even lead to abandonment of potentially promising projects.

The scientific advice (SA) service is provided by regulators around the globe and is a useful tool to support the timely and sound development of high-quality, effective and safe medicines, for the benefit of patients. At the European Medicines Agency (EMA), this service is provided by the Scientific Advice Working Party supported by the Committee of Advanced Therapies.[5] This is, however, a voluntary procedure in which developers can ask the regulators' opinion on the most appropriate way to generate robust

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evidence on a medicine's benefits and risks. The quantity, quality and breadth of questions asked by the applicants have an enormous impact on the benefits that this interaction can provide.

A lot of ideas originate from public institutions and make their way to companies (SMEs or large pharmaceutical companies), sometimes years after initial research. The aim of this study is to provide an overview and an insight into the characteristics of SA provided by the EMA for ATMPs originating in public institutions. We draw on our accumulated experience, and specifically looked at the SA reports for ATMPs submitted in 2018 that originated from public bodies. At the time of seeking SA, the products were still being developed either by SMEs/public bodies or were being further developed by large pharmaceutical companies. As the numbers were relatively small, we do not make comparisons between SMEs and large pharmaceutical companies, but instead concentrate on the characteristics of SA for ATMPs originally developed by public bodies. These findings could help optimise the content and timing of SA for ATMPs during their development, highlight the benefits of regulatory guidance, and ultimately help to meet regulatory requirements for the evidence package needed for approval.

What is already known about this subject

- Academic institutions and small and medium-sized enterprises, key early developers of advanced therapy medicinal products (ATMPs), may encounter more challenges in navigating and complying with regulatory requirements compared with large pharmaceutical companies.
- Regulatory challenges could cause delays at different stages of ATMP development and even lead to abandonment of potentially promising projects.
- Scientific advice is an important tool to help developers generate robust evidence on a medicine's benefits and risks, and a complete successful development.

What this study adds

- Earlier and more frequent scientific advice could help ATMP developers generate robust evidence and preempt delays at marketing authorisation stage.
- Carefully addressing quality and nonclinical issues before entering the pivotal phase of ATMP development will clear the path for a smooth and speedy marketing authorisation.
- Issues encountered in early development that frequently cause delays for ATMP developers are identified and discussed.

2 | METHODS

We identified 56 procedures of SA provided by the European Medicines Agency to developers of ATMPs during 2018. The origin of these ATMPs was queried either from the information provided by the applicant who requested SA or from information in the ADIS Insight database (https://adisinsight.springer.com/). Twenty-one of the identified SA procedures concerned ATMPs originally invented by academic institutions or other public bodies (hospital, research institute). Within those 21 products, we further categorised them in 2 groups, according to the type of developer at the stage of SA request: (i) those still in the hands of SME (according to the EU criteria) or a public body; and (ii) those that were being developed by a large pharmaceutical company.

Depending on the stage of clinical trials at the time of SA request, the development stage of each ATMP was categorised as exploratory (first-in-human, proof of concept studies) or pivotal.

Questions received from developers for these 21 SA requests were grouped in domains (quality, nonclinical, clinical) and such questions further analysed in the context of how useful they are to facilitate regulatory approval down the line.

For quality, the main areas relevant to ATMPs where developers asked for advice were comparability, process validation, control strategy, specifications, adventitious agents, stability, dose/posology, label claim/strength, container closure system, regulatory issues, characterisation, donation/donor issues, starting materials, formulation and potency testing.

Nonclinical areas of advice included pharmacodynamics, species selection, biodistribution/shedding, toxicity study design, developmental and reproductive toxicity, insertional mutagenesis/tumorigenicity, nonclinical development strategy, environmental risk assessment, mechanistic toxicity studies, bridging/comparability and juvenile animal studies.

Regarding advice on clinical development, the principal questions included: study design (duration, dose/regimen, endpoints, comparator), indication and population, statistical analysis (including sample size, extrapolation), efficacy/safety database, long-term follow-up, significant benefit for orphan designated ATMPs, and evidence package needed for conditional marketing authorisation or for approval under exceptional circumstances.

3 | RESULTS

ATMPs were a small proportion of the products that came to EMA for SA or protocol assistance (i.e. advice provided to orphan products) in 2018 (56 out of 635). The results presented here describe how developers of ATMPs that originated in public bodies (university, research organisation, hospital) use the SA process to develop these important and innovative medicines.

Of the total of 56 SA requests submitted for ATMPs in 2018, half (28) were brought to EMA by large pharmaceutical companies, the

TABLE 1 Areas of advice requested according to the type of developer

Area of advice	*n* SME/public bodies (*n* = 15)	% SME/public bodies (*n* = 15)	*n* Big pharma (*n* = 6)	% Big pharma (*n* = 6)
Quality	9	60.0	6	100.0
Nonclinical	5	33.3	5	83.3
Clinical	12	80.0	5	83.3

other half by public bodies and SMEs. We looked into their development, and for 21 we could trace their origins to a public body. For 15 of these, the current developer was an SME/public body (71%), while 6 were being further developed by a large pharmaceutical company (29%).

The most frequent domain of advice requested was clinical (*n* = 17, 81%), followed by quality (*n* = 15, 71.4%) and nonclinical (*n* = 10, 47.6%). Further analysis showed that advice on quality and nonclinical aspects of development was requested more frequently by large pharmaceutical companies (100% quality, 83% nonclinical) compared to SMEs/public bodies (60% quality, 33% nonclinical; Table 1). Fourteen SA procedures (67%) were initiated during the exploratory stage of ATMP development while 7 (33%) requested SA during the pivotal stage of development.

Each advice domain appeared more frequently in SA requested during the pivotal stage of development compared with the exploratory stage.

3.1 | Quality issues

A detailed analysis of the requests for quality development showed that both SMEs/public bodies and large pharmaceutical companies included many chemistry, manufacturing and control questions. The complex nature of ATMPs requires special attention to chemistry, manufacturing and control from early stages of development. Not surprisingly, the most sought-after advice was around the comparability and control strategy for the manufacturing. In 10 out of 15 procedures, developers asked about the comparability of the product before and after changes were introduced in the manufacturing process. Equally notably, 8/15 queries were received about the control strategy. The same number of requests (8/15) was received for issues related to quality regulatory matters, including topics such as definition of active substance/finished product, orphan similarity and batch release exemption. Also, a very common query related to the nature of ATMPs was related to potency testing (8/15). Less frequently raised issues were in relation to starting materials, mainly arising from the complex nature of these products that challenge established definitions.

3.2 | Nonclinical issues

Questions on nonclinical development covered a wide range of scientific areas. Only 10 out of 21 SA contained nonclinical questions. Most frequent were questions on design and adequacy of general toxicity studies (5/10), followed by consultations on the need/results of bridging/comparability studies as development progressed (4/10). Questions seeking feedback on the acceptability of the nonclinical development data package for a specific development milestone (be it a clinical trial application or a marketing authorisation), as well as queries on biodistribution/shedding studies and pharmacodynamics/proof of principle were also recurrent (3/10). Other less frequent topics for advice included strategies to investigate insertional mutagenesis (for gene therapy medicinal products) and tumorigenic potential (cell-based medicinal products), the choice of animal species and need for juvenile animal toxicology studies (all 2/10). Finally, regulatory consultation was sought on specific mechanistic toxicity associated to products and environmental risk assessment in one case.

3.3 | Clinical issues

For clinical development, questions on study endpoints and the proposed population/indication were asked in the majority of procedures (13/17 and 12/17, respectively). However, questions on study design and other elements of clinical trials (comparator, dose/dosing regimen, sample size/statistical analysis, study duration) were asked in less than half of requests.

The timing of the questions was also noted. Twelve out of 17 procedures with clinical questions included issues on pivotal/confirmatory trials, independently of the stage of development. SMEs/public bodies sought advice on pivotal trials during the exploratory stage of development in the majority of procedures.

4 | DISCUSSION

In this study, we focused on ATMP products invented by public bodies, because it is our experience that those products frequently arrive at EMA with dossiers that could have benefited from more guidance during the development process. Tracing back to initial sources, using the information provided within the SA dossier plus publicly available information, was not straightforward and may have resulted in misclassification of some products included in this dataset. The active role played by SMEs and public bodies in early development of ATMPs has been identified as an important source of innovation in 2014,[1] and that trend seems to continue in the cohort studied in this paper, with a significant proportion of the products having a traceable public body origin.

Experience in developing medicines over many years could be assumed to allow large companies to use the SA in a more comprehensive manner, with more questions asked, and wider coverage of areas in which questions were asked. In fact, we observed here that for products with a public body origin, for which SA was sought by a large pharmaceutical company, the issues covered in SA were more comprehensive compared with SA sought by SME/public bodies. The more comprehensive, pertinent and focused the questions, more

specific advice can be gathered to guide development in the future. We observed that each advice domain appeared more frequently in SA requested during the pivotal stage of development compared with the exploratory stage of development. This finding may be due to the fact that developers gain further awareness of the interrelations between the various disciplines as they progress in development and could reflect a better understanding of remaining uncertainties in all domains at a later stage of development. There is evidence that following regulators' advice on pivotal studies has a positive impact on benefit–risk assessment,[6] although the numbers for ATMPs were small.

In our experience, the SA requests received for this study are aligned with the previous years and the advice received since. When a large part of the development is performed by an SME/public body, there are key questions and elements that regularly create delays, require additional lists of questions and generally are difficult to resolve when the dossier for MA is submitted.[7]

In the quality area, for example, recurrent issues during assessment have been observed as products used in clinical trials need comparability assessment in order to link them to the proposed commercial version of the product, and this is intrinsically linked to a strong potency assay that can compare the biological activity of products in the early stages with the final commercial product. The evaluation of potency plays a key role in defining the quality of ATMPs.[8,9] Having established robust testing tools and fully characterised material with a good understanding of its structural–functional relationship allows for a good comparability exercise. We have observed that the combination of poor comparability and lack of adequate potency testing raises doubts about the dose administered to patients across clinical trials. Robust potency testing together with adequate and timely planning for a comparability exercise also reduce the issues encountered, if the newly prepared product (different manufacture process, site or materials) has different stability. A drift on strength cannot be detected otherwise. Once the product has entered the pivotal clinical trial, it is challenging to retrospectively demonstrate comparability with the batches produced at early stages and developers usually have limited or no availability of earlier batches. Also, the stability of those could not be enough to establish comparability. These issues are usually raised as multidisciplinary major objections and frequently lead to serious delay of approval.[7] Scalability and site transfer are inevitable steps in the development of ATMPs before commercialisation and have been shown to be specially challenging for these products.[3] Recently, EMA has published a Q&A on comparability for ATMPs to help and guide applicants on these issues.[10] Being able to establish comparability during the early stages of development builds a solid dossier that will encounter fewer regulatory challenges for approval and faster evaluation time.

Quality regulatory issues that usually emerge from the innovative nature of these products are frequently raised by developers. Often developers find that new technologies do not clearly fit in the definitions or challenge established concepts. In these scenarios, it is especially useful to have early dialogue with regulators through ITF meetings and SA to inform future regulatory frameworks and plan accordingly the development of the product.

For nonclinical, it was interesting to see that even in a reduced dataset, SA questions cover a wide array of topics. Of note, a standard nonclinical package cannot be defined for ATMPs and case-by-case approaches are frequent. Probably, the most interesting differentiation can be made between cell-based medicinal product (CBMP) developments versus gene therapy medicinal product (GTMP) developments. This is especially true for assessment of tumorigenicity (a recurrent question mostly for CBMPs) and potential for insertional mutagenesis (solely applicable to GTMPs).

Questions on design of pivotal repeated-dose toxicology studies are common even for non-ATMPs. However this category ranked first in our dataset probably due to the fact that the design of the single pivotal toxicology study is highly dependent on type of product, its putative mechanism of action and inherently impacted by the availability of a (relevant) animal species (this latter especially for cell-based products). The need for Good Laboratory Practice compliance and nonclinical route of administration (mostly driven by feasibility) were often discussed as sub-questions and remain difficult to address in further detail in guidelines. The possibility of integrating tumorigenicity assessment/endpoints in repeated-dose toxicology studies is often requested as a possibility for cell-based products. While this holds potential benefits in number of animals included in these, in line with the 3Rs,[11] the risk of complicating the execution of the study should be carefully considered.

The second most frequent category of nonclinical questions in this dataset is bridging/comparability. This is probably the category with the largest difference in frequency as compared to non-ATMP developments and could be explained by the iterative process of product optimisation happening during ATMP development (e.g. viral vector design changes for GTMPs, cell selection/sorting systems for CBMPs) and its impact on product performance. Comparability and bridging can be supported largely by in vitro assays and characterisation efforts that normally form part of the quality development.

While receiving feedback on the overall nonclinical strategy is a frequent request from non-ATMP developers, general nonclinical strategy questions have been less frequent in this dataset. This might be linked to the fact that the majority of requests came from SMEs/public bodies with no routine experience in developing medicinal products and the timing of SA in relation to product development (i.e. mostly early phase).

Questions on biodistribution and shedding have also proven to be frequent (the latter mostly relevant to viral vector-based GTMPs). In this area, the ongoing development of the ICH S12 guideline should provide further clarity.[12] Regarding requests on the need for juvenile animal studies, the recently published ICH S11 guidance highlights that generally this type of study is not required for ATMPs.[13]

Finally, 1 category of requests that was not detected in this sample is queries on reproductive toxicity studies. In this field, flexibility is applied and scientifically valid (3Rs-compliant) testing strategies[14]

should mostly aim at identifying hazards. While recognising the limitations of animal studies for clinical risk assessment, it is still considered important that limitations, uncertainties and data gaps of the testing programme are addressed in clinical trials and marketing authorisation applications.

Regarding clinical development, although requirements for pivotal studies for ATMPs are similar to other medicinal products, ATMPs often target rare diseases where there are challenges in development associated with high morbidity/mortality and small patient populations, necessitating clinical studies which combine multiple objectives (proof-of-concept, dose-finding). In such cases, decisions on study design and choice of comparator are critical for benefit/risk assessment and developers should not miss the opportunity to raise these issues early when SA is sought.

Occasionally, feasibility issues preclude the conduct of randomised–controlled trials and in these cases the choice of alternative study designs such as single arm trials, appropriate primary/secondary endpoints, and methodology in constructing external controls to contextualise the results are crucial in generating evidence for efficacy and safety of ATMPs. Intrapatient comparisons can be considered when randomised–controlled trials are not possible and use of objective endpoints should be the norm where possible. Proposals to use surrogate endpoints are seen quite often and concerns on validity of such endpoints, in terms of predicting clinical outcomes, are frequently expressed by regulators.

Sample size considerations and statistical analysis of clinical results are not specific to ATMPs. However, when these products are developed for rare diseases, challenges can be related to establishing benefit based on a small and/or heterogenous population, as well as inability to demonstrate statistical significance of the primary endpoint. As regards the latter, demonstration of efficacy based on appropriate secondary endpoints could possibly support a positive benefit/risk.

Finding the right dose/dosing regimen for ATMPs is quite challenging due to their nature. Relevant knowledge from nonclinical studies is often limited and early clinical studies may play an important role in dose finding. Despite the hurdles often encountered, questions on dose/dosing regimen were not asked frequently in the procedures analysed. Developers should take the opportunity to discuss this issue with regulators as it is strongly related to both efficacy and safety of ATMPs.

Although the number of procedures analysed was too small to identify differences in clinical questions asked by different type of developer, the low frequency of questions on some key study elements (e.g. comparator, dose/dosing regimen, sample size/statistical analysis, study duration) indicates a potential for improvement in the scope of clinical advice sought. The fact that SMEs/public bodies frequently asked questions on pivotal trials during the exploratory stage of development could indicate less experience of these developers compared to large pharmaceutical companies on how to design pivotal trials and therefore could explain that they come early for advice. However, when there are obvious shortcomings in quality and nonclinical domains, questions on design and key elements of pivotal trials may be premature, resulting in more general regulatory feedback.

SA is not a free service for developers, and the associated cost could also have had an impact on the frequency and extent of consultations. The fees are strongly discounted for SMEs, but still present. Academic developers till recently did not benefit from reduced fees due to their status but have been granted free protocol assistance, if they develop orphan medicines, from 19 June 2020.[15] For SA applications, the charges are calculated by scientific domain, therefore it could be argued that a more comprehensive SA would be more expensive. This could probably explain the fact that advice on quality and nonclinical aspects of development was requested less frequently by SMEs/public bodies compared to large pharmaceutical companies. However, given that unresolved quality or nonclinical issues may adversely affect clinical development, SMEs/public bodies are advised to carefully consider such aspects when deciding the domains and timing of advice sought.

Moreover, developers can seek multistakeholder advice and the products for which parallel consultation with Health Technology Assessment bodies is most relevant are those that are innovative, offer a cure rather than chronic treatment, with potential pricing issues, or target a very restricted rare population.[16] Obviously, due to such characteristics, ATMPs would be appropriate for this type of advice during their development.

Although not part of the current analysis, there is a strong rationale for medicinal product developers to seek advice on Post-Licencing Evidence Generation. During initial assessment of a marketing authorisation application, there are often efficacy/safety gaps and having plans for Post-Licencing Evidence Generation timely might be instrumental in allowing approval in the presence of uncertainty once a positive benefit-risk balance is demonstrated. Product-specific proposals for postlaunch evidence generation advice early in the development are welcomed both by regulators and Health Technology Assessment bodies.[17]

Based on the above results and observations, some general reflections emerge. The scope of an advice is likely to be different depending on the time of taking over the ATMP development by an SME or large pharmaceutical company but this study could not answer this question. Cost constrains, lack of familiarity with the system and lack of custom to engage with regulators could be predisposing SMEs and academic developers to miss the opportunity for seeking adequate SA at the right time. Broader and early SA could help pre-empt problems at the planning stage for pivotal studies. In addition, the importance of clearing hurdles related to quality and nonclinical is paramount in smoothing the way for clinical trials. Leaving those unresolved and moving to the clinical phase underestimates the complexities and delays that could arise during pivotal studies, and eventually marketing authorisation.

Further studies comparing the SA approach and usage between SMEs and large pharmaceutical companies for ATMP procedures during a certain period, independently of the origin of the product, could provide more insights into the differences between small and large players in the development of ATMPs.

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COMPETING INTERESTS

The authors have no conflicts of interest to declare.

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DISCLAIMER

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or 1 of its committees or working parties.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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