



Hurdles in gene therapy regulatory approval: a retrospective analysis of European Marketing Authorization Applications

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Gene therapy medicinal products (GTMPs) are innovative and promising treatment strategies. In Europe, the Committee for Advanced Therapies (CAT) is responsible for making marketing authorization recommendations to the Committee of Human Medicinal Products (CHMP). In the current study, we identified major objections, issues, or concerns raised during the Marketing Authorization Application (MAA) process for products resulting from the interaction of both committees between 2008 and 2017. During the first few years following CAT establishment, quality issues were often identified as major deficiencies, whereas issues at the nonclinical level appeared to be less frequent. Clinical efficacy and safety issues appeared to have a major role in unsuccessful MAA outcome for GTMPs. Most deficiencies were addressed through clarification during the MAA review or in postmarketing settings. The MAA procedure for GTMPs is complex and it is anticipated that continuous MAA submissions will further enhance the experience of both regulators and applicants, reducing the attrition rate for approval.

Introduction

Advanced therapy medicinal products (ATMPs) represent a major class of innovative therapies differing substantially from classic therapeutic agents. A specific regulatory framework was implemented in Europe for these products. The 'ATMP Regulation' [i.e., Regulation (EC) No. 1394/2007] together with Directive 2009/120, establishes definitions of ATMPs, as well as MA requirements. This regulation defines four different product types: GTMPs; somatic cell therapy medicinal products (sCTMPs); tissue-engineered products (TEPs); and combined ATMPs [1,2]. ATMP MAA follows the centralized procedure on a compulsory basis. This assessment is primarily performed by CAT. This independent specialized experts group was created following the implementation of the ATMP regulation. The CAT issues a draft opinion to enable CHMP to make a recommendation on the MAA to the European Commission (EC), which has the final authority to grant marketing authorization. In addition, CAT has a fundamental role in encouraging the development of new ATMPs through the implementation of regulatory strategies, such as the Innovative Task

Force, the ATMP Classification, the ATMP Certification, the Priority Medicines (PRIME) scheme, and Scientific Advice.

Several challenges represent important hurdles in the development of ATMPs, namely safety concerns, efficacy issues, or obstacles related to quality and/or scale-up [3]. The number of clinical trials using investigational ATMPs is almost two times higher in the period of 2010–2015 when comparing to 1999–2010, according to a recent study [4]. One might expect that the number of licensed ATMPs would follow this trend. Yet, 8 years after the adoption of the ATMP regulation, only a limited number of products have been granted marketing authorization in Europe [4,5]. During the initial years following the establishment of CAT, negative opinions or MAA withdrawals were often noted [6], although the approval rate of ATMPs in EU has increasing over the past few years. In fact, in 2018, three new GTMPs were recommended for marketing authorization [7,8], highlighting a positive learning curve for CAT as well as all the stakeholders involved.

ATMPs have the potential to become an important part of the therapeutic arsenal with high costs. By 2016, eight ATMPs had been approved in the EU: three GTMPs, three TEPs, and two sCTMPs [9]. The relevance of GTMPs is particularly significant

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when considering orphan ATMPs. According to Farkas *et al.*, ~50% of ATMPs designated orphan drugs were GTMPs [10]. Therefore, a significant impact of GTMPs on the healthcare system is expected and, thus, a broad understanding of these products is fundamental to manage properly their access and availability [3].

Here, we identify key aspects influencing regulatory GTMP approval in Europe. Publicly available data from the EMA from between 2008 and 2017 were analyzed. A comparative analysis of the major objections, issues, or concerns reported in the MAA assessment is presented (see supplemental information for details of the methodology used).

Quality data assessment

Deficiencies related to quality aspects were found in all products except one (Imlygic), regardless of whether the products were in the successful or the unsuccessful MAA group (Table 1). Importantly, during the review of quality data, the most frequently discussed objections related to drug product and substance manufacture and/or specification at the level of: (i) issues with production process; (ii) issues with drug specification; or (iii) issues regarding release assay data. Changes in the production process of the drug substance were common, raising comparability issues. This was observed in two out of four unsuccessful MAAs (both Cerepro MAAs) and two out of three successful MAAs (Glybera and Strimvelis). Regulators were aware that these changes occurred not only during the development process, but also during the post-authorization setting. We hypothesize that, because GTMP drug development is often initiated at the academic level, where resources are limited, optimization of the manufacturing process before clinical drug test is not a priority. Ideally, any changes in the manufacturing process should take place as early as possible during product development to reduce the impact of potential comparability issues during regulatory approval [11]. Positive comparability data should indicate that, regardless of manufacturing process, the resulting drug product or drug substance is equivalent for clinical use in terms of product safety, identity, purity, and potency [12]. However, this might not always be possible for applicants, especially for GTMPs, where more understanding of the product features is obtained during development.

Issues in the specification of the drug substance and/or drug product were often encountered. As per EMA Guidance, the applicant should provide adequate criteria for the acceptance or rejection of a production batch. The specifications should cover, among others, identity, purity, content, and activity [13]. Given that ATMPs are generally considered more complex entities compared with small molecules or other biologic agents, variability between batches is acknowledged [14].

Inadequate release assay validation (Advexin, CLG, and Glybera) or insufficient and/or unacceptable release criteria (Cerepro and Glybera) were the most common issues found regarding specification. There are no validated assays with associated reference standards available for many of these parameters. Additionally, regulators have not established a complete set of release criteria [15], although a nonexhaustive list is available as guidance [13]. An additional guideline regarding the validation of analytical methods is also available [16]. Therefore, at the time of MAA, each applicant is required to define a suitable validation assay with a cut-off value for release criteria. It became clear that this was a

massive challenge, given the scarce experience with these innovative products. Importantly, variability in the product manufacturing process makes this task even more difficult [17]. Issues with release criteria were noted at the drug substance level (unacceptable specification of potency) and drug product level [unacceptable process-related impurities and replication competent adenovirus (RCA)].

The EMA quality data certification is part of a set of initiatives promoted by CAT to foster the development of ATMPs. The quality data certification procedure involves the scientific evaluation of these data and intends to identify any potential issues early on so that these can be addressed before the submission of a MAA. This is a well-recognized incentive that could be instrumental in the development of GTMPs and is considered a powerful tool for early-phase GTMP developers. This procedure is viewed as leverage regarding future partnerships with commercial stakeholders. However, quality data certification is available exclusively to those applicants who have the micro-, small-, or medium-sized enterprise (SME) status according to the SME Regulation [1]. This is a limitation given that nonprofit organizations (i.e., academia, hospitals, and charities) are, in general, the majority of ATMP sponsors [5]. Many of these might not hold SME status and, therefore, would not benefit from the certification procedure [10].

Quality data assessment via scientific advice or protocol assistance (for orphan drugs) is also an important instrument, whereby quality deficiencies could be identified before the request for MAA [18]. In general, there has been a clear trend regarding quality data acceptability by CAT/CHMP. This could either be a result of the increased experience of regulators with GTMP assessment or the submission of more robust quality data by the applicants. This could be verified, for instance, by considering the overall difference between the assessments of Cerepro in 2007 compared with 2010. Here, there was a clear improvement, to the point where there were no deficiencies precluding GTMP approval in the 2010 MAA submission for Cerepro as far as quality data were concerned.

Nonclinical data assessment

At least one deficiency related to nonclinical aspects was found in each of the GTMP assessments examined except for Cerepro and Imlygic (Table 1). Here, we describe the main deficiencies noted at the level of pharmacodynamics, pharmacokinetics, and toxicology.

Regarding pharmacodynamics, finding the adequate animal model(s) to demonstrate the mode of action is a recurrent issue in GTMP nonclinical development [14,17,19]. Our analysis showed that there were no deficiencies noted regarding animal model suitability. Conversely, issues were raised on secondary pharmacodynamics. Two out of four unsuccessful MAAs (Advexin and CLG) were reported to exhibit unresolved objections related to the unclear role of RCA. The presence of RCA in adenoviral batches to be used in humans is undesirable, because these can replicate in an uncontrolled manner in the patient, resulting in potential safety risks [20].

With regards to the assessment of pharmacokinetics, two out of four unsuccessful MAAs (Advexin and CLG) presented major objections. Methodological deficiencies were noted, especially regarding the use of unqualified and unvalidated assays, as well as lack of a GLP compliance, as described elsewhere [14]. For two

TABLE 1

Major objections, issues or concerns noted in the assessment of GTMPs at the level of quality, and nonclinical and clinical data^a

	Unsuccessful MAA				Successful MAA		
	Advexin	CLG	Cerepro	Cerepro	Glybera	Imlygic	Strimvelis
Commercial name	Advexin	CLG	Cerepro	Cerepro	Glybera	Imlygic	Strimvelis
Year of opinion	2008	2009	2007	2010	2012	2015	2016
Clinical Indication	Li-Fraumeni cancer	Squamous cell carcinoma of head and neck	High-grade glioma	High-grade glioma	Lipoprotein lipase deficiency	Unresectable melanoma	Severe combined immunodeficiency because of adenosine deaminase deficiency
Orphan designation	Orphan	Non-orphan	Orphan	Orphan	Orphan	Non-orphan	Orphan
MAA approval mechanism	Withdrew MAA	Withdrew MAA	Negative opinion	Negative opinion	Approved under exceptional circumstances	Standard approval	Standard approval
QUALITY							
Drug substance							
Manufacture	C	C	B	A	B	A	B
Characterization	C	C	A	A	B	A	A
Specification	C	C	B	B	B	A	B
Stability	F	C	A	A	A	A	A
Drug product							
Pharmaceutical development	A	A	A	A	A	A	A
Manufacture of the product	C	C	B	A	A	A	A
Product specification	C	C	C	A	B	A	A
Stability of the product	C	C	C	A	A	A	A
Adventitious agents	C	A	A	A	B	A	A
NONCLINICAL							
Pharmacology							
Primary pharmacodynamics	A	A	A	A	A	A	A
Secondary pharmacodynamics	C	C	A	A	A	A	A
Safety pharmacology programme	F	F	A	A	F	A	A
Pharmacodynamic drug interactions	A	A	A	A	A	A	A
Pharmacokinetics							
Biodistribution, persistence, clearance	C	C	A	A	A	A	A
Germline transmission	C	C	A	A	B	A	A
Shedding	F	F	F	F	F	A	A
Toxicology							
Single dose toxicity	A	A	A	A	A	A	B
Repeat dose toxicity with toxicokinetics	C	C	A	A	A	A	A
Genotoxicity	F	F	A	A	B	A	A
Carcinogenicity	F	F	A	A	B	A	A
Reproduction toxicity	F	F	A	A	B	A	A
Local tolerance	F	F	A	A	A	A	A
Other toxicity studies: immunogenicity/toxicity	F	F	A	A	A	A	F
CLINICAL							
GCP	F	C	C	B	A	A	B
Clinical pharmacology							
Pharmacokinetics	C	C	C	B	B	B	A
Pharmacodynamics	C	C	C	C	B	A	A
Clinical efficacy							
Dose selection and schedule	C	C	A	A	B	A	A
Clinical efficacy data	C	C	C	C	B	B	B
Clinical safety							
Clinical safety data	C	C	C	C	B	B	B
Pharmacovigilance system	C	C	C	A	A	A	A
Risk management plan	C	C	C	C	B	B	B
Environmental risk assessment	C	C	A	A	A	A	A

CLG (Contusugene Ladenovec Gendux).

^a A, immediate satisfactory assessment; B, satisfactory assessment after resolution of objection, issue, or concern; C, objections, issues, or concerns were found, resulting in unsatisfactory assessment; F, not mentioned in EPAR/withdrawal report.

out of four unsuccessful MAAs (Advexin and CLG), as well as for one out of three successful MAAs (Glybera), objections were raised regarding the pharmacokinetics of germline transmission, where the data submitted were considered insufficient. The possibility of

the vertical germline transmission of expression and/or transfer vector DNA raises ethical and safety concerns [13,21]. For Advexin and CLG, these concerns were unresolved at the time of opinion. For Glybera, submission of an additional breeding study in mice

resolved this concern, indicating that there was no paternal germline transmission of the drug. This study was also able to resolve the issue on reproduction toxicity.

For the assessment of toxicology, deficiencies were noted regarding repeat-dose toxicity studies in two out of four unsuccessful MAAs (Advexin and CLG). Safety data limitations as well as study design not adequately reflecting the intended clinical use resulted in an unsatisfactory regulatory opinion. Assessment of insertional mutagenesis risk was not applicable to products using non-integrating vectors, such as Advexin, CLG, and Cerepro (adenoviral vector) as well as Imlygic (herpes simplex vector). The risk was higher in products using integrating vectors, such as Glybera (AAV vector) and Strimvelis (retroviral vector). The tumorigenic risk of Glybera was associated with two elements: (i) potential for insertional mutagenesis; and (ii) inclusion of woodchuck post-transcriptional elements. The applicant highlighted that there were no further practical methods to assess the risk of tumorigenicity and the available evidence suggested that the risk was low. Theoretically, the product could integrate and cause a tumor. However, both CAT and CHMP agreed with the applicant that no further animal testing or experiments could usefully address these concerns. For Strimvelis, even though it theoretically exhibited a higher insertional mutagenic potential of all the GTMPs included in this analysis, because of the nature of the vector used, carcinogenicity studies have not been conducted because no adequate animal model was available to evaluate the tumorigenic potential. The main reason was the inability to achieve long-term engraftment of transduced cells in mice.

Similarly to quality assessment, applicants are able to use the certification procedure for a regulatory and scientific evaluation of nonclinical data already collected before MAA, along with a request for scientific advice or protocol assistance. The ATMP nonclinical data certification can only be used by SMEs [1]. Although not legally binding, these allow the identification of concerns from a nonclinical perspective before the request for MAA [18].

Nonclinical data appear to be generally satisfactorily accepted considering the low number of deficiencies identified. Given its unique nature, the nonclinical development of GTMPs could be supported by a risk-based approach (RBA), a strategy to determine the extent of data to be included in the MAA.

Clinical efficacy data assessment

Regarding GCP aspects, major objections, issues, or concerns were found in three out of four unsuccessful MAAs (CLG and both Cerepro submissions) and one out of three successful MAAs (Strimvelis) (Table 1), especially during the academic phase of the trials. This supports that prior experience and the resources of the applicant are key factors in regulatory approval. Importantly, the GCP findings noted for the 2007 assessment of Cerepro appeared to have an impact on the overall regulatory assessment, considering not only the nature of the findings, but also the fact that this was a pivotal single-site trial [22].

Concerning the analysis of clinical pharmacokinetics and pharmacodynamics, three main issues were identified during MAA, namely regarding data collection methods, data analysis, and study design. Submission of additional data generally addressed these concerns.

In terms of clinical efficacy, dose identification is not a recurrent objection. Instead, the administration frequency, treatment dura-

tion, and concomitant therapeutic regimens were highlighted as concerns in two out of four unsuccessful MAAs (Advexin and CLG) and one out of three successful MAAs (Glybera).

The most frequent objections in clinical efficacy assessment were: (i) lack or insufficient efficacy demonstration in three out of four unsuccessful MAAs (CLG and both Cerepro assessments) and two out of three successful MAAs (Glybera and Imlygic); (ii) change or use of a nonvalidated primary endpoint (pEP) in two of four unsuccessful MAAs (both Cerepro assessments) and all three successful MAAs (Glybera, Imlygic, and Strimvelis); and (iii) application of post-hoc and subgroup analysis in two out of three unsuccessful MAAs (Advexin and the 2010 Cerepro assessment) and one of three successful MAAs (Imlygic).

Efficacy demonstration has been persistently identified as a key challenge in gene therapy development [18,23,24]. We found this to be one of the most frequent objections in MAA assessments. One GTMP was found to be more harmful than its comparator (CLG had a more negative effect on survival versus standard treatment). For both Cerepro MAAs, no statistically significant difference was seen compared with the standard of care. For Glybera, the long-term beneficial effects were not clear. Analysis of pancreatitis events as surrogate markers of efficacy was proposed to support the positive efficacy profile of the product, but methodological issues hampered the conclusions. Independent adjudication of pancreatitis events by an expert panel according to defined criteria was reviewed and accepted by CAT and CHMP in a restricted patient population. For Imlygic, concerns were noted over the potential delay in next-line treatment for nonresponders. Additional studies submitted as part of a risk management plan (RMP) addressed this objection.

The change or use of novel and nonvalidated pEP was reported as one of the most common objections to GTMP assessments [15,17,23]. For gene therapy, particularly in terms of rare diseases, the use of standard validated endpoints might not be as informative as for traditional medicinal products. Application of more innovative endpoints might be an option, although demonstration of validity might ultimately have an important role in the assessment. From the GTMPs analyzed, most (five out of seven MAAs) were intended to be used as anticancer treatments. The selection of the pEP in clinical trials in oncology has typically been the subject of strong discussion. In this context, the EMA guideline on the evaluation of anticancer medicinal products recommends cure rate, overall survival (OS), progression-free survival (PFS), or disease-free survival (DFS) as acceptable pEPs [25,26].

For both Cerepro MAAs, the survival pEP was updated from patient's lifetime after surgery to time to death or time to reoperation, which was considered by CAT and CHMP as a significant methodological deficiency. Even though the updated pEP was assessed by an independent re-intervention committee, this did not compensate the potential bias resulting from the open-label nature of the study. For Strimvelis, the survival endpoint was initially defined as time to death related to disease and all-cause mortality, upon CAT and CHMP recommendation. It is well acknowledged that the accuracy of disease-specific mortality depends on correctly identifying the cause of death [27], and the updated endpoint was considered acceptable. For Glybera, the change in pEP was based on the evolution of knowledge around the disease. Initially, triglyceride reduction was used as the pEP, which was later updated to postpran-

dial chylomicron (ppCM) reduction. Given the rarity of the disease, CAT and CHMP recognized that the pEP update is common. An additional problem with this change was that ppCM was a novel and nonvalidated endpoint. To address this concern, the applicant proposed to conduct a postauthorization study to assess ppCM metabolism in patients previously treated with Glybera. The applicant supporting Imlygic applied the durable response rate (DRR) as the pEP. CAT and CHMP acknowledged that DRR captured a relevant clinical effect of the treatment and, thus, this issue was considered resolved.

Efficacy claims based on non-prespecified post-hoc analysis were reported for two out of four unsuccessful GTMPs (Advexin and Cerepro 2010) as well as for one out of three successful GTMP (Imlygic). These analyses are useful especially if the trial population is heterogeneous. However, interpretation should be carefully conducted because there are several commonly known disadvantages [28,29]. Methodological issues resulted in data being regarded as hypothesis generating rather than confirmatory. The intended patient population for treatment with Imlygic was based on a post-hoc analysis. Here, even though CAT expressed concerns over the post-hoc nature, the regulator acknowledged that these were conducted in compliance with the appropriate EMA guideline [30].

Of the seven GTMP MAAs analysed, five were intended to be used as orphan drugs. Challenges to generating efficacy and safety data are known. Often the trials are limited by low patient numbers because of recruitment difficulties, inadequate follow-up, and trial design issues (i.e., open-label nature) [31–33]. Expedited regulatory approval pathways, such as conditional approval or approval under exceptional circumstances, might be useful tools to bring orphan drugs to the market. Glybera was intended to be used in an ultra-rare indication and the data and the follow-up period presented at submission were limited, which resulted in an approval only in a small subset of patients (i.e., approval under exceptional circumstances). By contrast, for Strimvelis, despite the recruitment issues as a pediatric study in an orphan disease, the data as a whole were more compelling and the follow-up period was more extensive, which resulted in a standard approval.

Clinical safety data assessment

All MAAs reported at least one deficiency regarding safety assessment, and unsurprisingly similar results were obtained for RMP, taking into account that most safety concerns were addressed through this tool (Table 1). The most common observations were limited or incomplete safety database (three out of four unsuccessful GTMPs and in two out of three successful GTMPs), as well as specific safety concerns over immunogenicity (two out of four unsuccessful GTMPs and all three successful GTMPs). The risk of immunogenicity was previously reported as an important hurdle in GTMP development [24].

Immunogenicity safety concerns regarding Advexin and CLG were noted because the local immune response risk described in the literature was not adequately assessed by the applicant. For Glybera, delayed humoral and cellular immunogenicity were identified across all studies. The 3-month immunosuppressive regimen was intended to address this risk, although data showed no reduction in unwanted humoral and cellular immunogenicity. CAT and CHMP raised concerns over the need for an immunosup-

pressive regimen, although, after extensive discussion, the regulator concluded that removing the immunosuppressant treatment would represent a major change in therapeutic protocol, potentially affecting patient outcome. Additionally, considering the short-term regimen, the immunogenicity concerns were addressed. For Strimvelis, CAT and CHMP reported that the applicant assumed a low immunogenicity risk and, therefore, the evaluation of anti-adenosine deaminase (ADA) antibodies was not conducted. This issue was addressed because the applicant agreed to assess ADA antibodies in a postmarketing setting.

Deficiencies regarding RMP were identified in all MAAs. For Advexin and the 2007 Cerepro assessment, the risk minimization measures were not enough to assess important safety risks. CAT and CHMP required a more robust RMP to be proposed before positive Marketing Authorization could be granted. By contrast, for CLG and the 2010 Cerepro assessment, the RMP was not sufficient based on the inability to establish the efficacy and safety of the products. For the successful MAA products, the applicants accepted updates to the RMP requested by CAT and CHMP. Measures included the collection of additional long-term safety data via a patient registry and/or implementation of educational programs for healthcare professionals (e.g., Glybera).

Concerning environmental risk assessments, deficiencies were noted for Advexin and CLG. For all other MAAs, the data presented were considered satisfactory to support the claim that the risks to human health (other than patients) and the environment were negligible. The main issues concerned immunocompromised individuals who were at high risk because of the presence of RCA in the medicinal product (which can be transferred, in a potentially sustained fashion, if immunocompromised individuals came into contact with treated patients), shedding of the Ad5-p53 vector, and possible horizontal transmission. Risk management strategies were considered insufficient to address this concern in both MAAs.

Concluding remarks

Here, we have provided valuable insights for use in future GTMP MAAs. Clearly, the benefit–risk assessment with subsequent issuing of a successful MAA is a complex and multifactorial exercise. Strimvelis is the only gene therapy included in this analysis administered as *ex vivo* gene therapy, as opposed to the other GTMPs, which are intended to be used *in vivo*. This feature represents an added complexity regarding the review of quality, non-clinical, and clinical data upon MAA request. Each individual GTMP component might impact the efficacy and safety profile of a product, including the vector, inserted sequence(s), target cells modified by the vector, or the encoded protein [18].

Although at the initiation of CAT, quality data were noted as a significant deficiency, over the years there have been substantial improvements. Manufacture changes and issues regarding drug product and/or drug substance specification were highlighted as particular objections. GTMP development is often initiated in academic facilities, where resources are limited and manufacturing process optimization before clinical drug testing might not be a priority. For Advexin and CLG, a necessary consequence of being the first to be assessed for MAA was that there was none or limited past experience as to how the products should be evaluated. It is hypothesized that the submission dossiers were either deficient or that the regulatory assessment was overly strict.

Nonclinical data appear to be the section with the fewest deficiencies. Nonclinical pharmacokinetic and pharmacodynamic data as well as toxicology are the most frequent concerns, although the importance of using a RBA for the assessment of nonclinical data is highlighted [34].

Clinical assessment is undoubtedly where the regulator tends to encounter unacceptable issues. In particular, clinical efficacy demonstration and safety have a key role in GTMP approval. Our analysis suggests that lack or insufficient efficacy demonstration, change or use of a nonvalidated pEP, and application of post-hoc and subgroup analysis constitute the most predominant objections. Safety wise, limited databases and inadequately addressing immunogenicity concerns are highlighted as the most frequently raised objections.

In the case of successful GTMPs, most deficiencies were addressed through oral explanation or written answers or by the submission of additional data (either during a MAA review or post marketing). In this context, RMP updates were noted in almost all GTMPs.

Although quantitative data on the request or use of EMA initiatives to support ATMP development, particularly for ATMP certification and classification, were not analyzed here, these are acknowledged to be an advantage. By contrast, regarding the request

for protocol assistance and/or scientific advice, Farkas and colleagues previously described how, in orphan-designated GTMPs, applicants did not use these as frequently as desired. An analysis of 185 ATMPs that had submitted requests for orphan drug designation between 2001 and April 2016 noted that only 29.8% requested protocol assistance [10]. The data from our analysis suggest a more optimistic outlook and, from the analyzed GTMPs, all except CLG requested scientific advice and/or protocol assistance, highlighting the importance of this strategy in MAA outcome.

Experience in the evaluation of these products has accumulated over the years, and the expectation is that these products will continue to be at the forefront of innovation as important treatment strategies, while subsequent MAAs will further enhance the experience of both regulators and applicants.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.drudis.2018.12.007>.

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