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Declaro ter desenvolvido e elaborado o presente trabalho em consonância com o Código de Conduta e de Boas Práticas da Universidade de Lisboa. Mais concretamente, afirmo não ter incorrido em qualquer das variedades de fraude académica, que aqui declaro conhecer, e que atendi à exigida referenciação de frases, extratos, imagens e outras formas de trabalho intelectual, assumindo na íntegra as responsabilidades da autoria.

Resumo

Ao longo do tempo, tanto a Agência Europeia de Medicamentos (EMA) como a Food and Drug Administration (FDA) dos EUA estabeleceram quadros regulamentares que exigem a recolha de dados adicionais na fase pós-autorização, relativamente à segurança e, em certos casos, à eficácia, qualidade ou optimização terapêutica de medicamentos autorizados. Designadas por medidas pós-autorização (PAMs) pela EMA e por requisitos pós-comercialização (PMRs) e compromissos pós-comercialização (PMCs) pela FDA, estas medidas têm uma relevância acentuada no contexto de medicamentos de terapia avançada (ATMPs) ou de produtos de terapia celular e genética (CGTPs), tal como designados nos EUA, onde, frequentemente enfrenta-se o desafio duplo de equilibrar a aprovação ágil e conduzir avaliações exaustivas do risco-benefício. Esta dissertação descreve e contrasta as medidas pós-autorização impostas, exigidas e acordadas para uma coorte de 15 ATMPs aprovados tanto pela Comissão Europeia, na sequência de um parecer positivo da EMA, como pela FDA, no período de 2009 a 2023. Estende-se à identificação e discussão dos mecanismos regulamentares expeditos atribuídos aos mesmos ATMPs e a reflexão sobre o papel dos dados do mundo real no apoio aos objetivos destas medidas. Documentos regulamentares disponíveis nos websites da EMA e da FDA serviram de fonte para a extração sistemática de todas as medidas pós-autorização. As PAMs extraídas da EMA incluem condições do Anexo II, obrigações específicas, estudos pós-autorização de segurança de Categoria 3 no plano de gestão de risco, recomendações e pedidos de medidas juridicamente vinculativas. As PAMs da FDA incluem PMRs ao abrigo de quatro autoridades - secção 505(o)(3) do Food and Drug Administration Amendments Act, Aprovação Acelerada, Lei da Equidade da Investigação Pediátrica e Regra da Eficácia Animal, bem como PMCs acordados. Foram realizadas análises descritivas, contemplando variáveis como a categoria da medida, os seus objetivos, os desenhos de estudo, taxas de registo em repositórios eletrónicos e o estado relativo à data fixada para a conclusão da medida, tal como estabelecido pela EMA e pela FDA. Foram identificadas 53 PAMs impostas pela EMA e 44 estudos de Categoria 3. Em contrapartida, a FDA impôs 27 PAMs, tendo sido identificados 43 compromissos pós-comercialização acordados. Os resultados obtidos ressaltam diferenças na quantidade e na natureza das PAMs, entre a EMA e a FDA, tendo em conta a amostra do estudo. Variações observadas refletem principalmente diferenças nas estruturas organizacionais e nas abordagens para a recolha de dados pós-autorização, em vez de disparidades nas avaliações iniciais de benefício/risco.

Palavras-chave: Medicamentos de terapia avançada (ATMPs), Agência Europeia de Medicamentos (EMA), Food and Drug Administration (FDA), Requisito pós-comercialização (PMR), Medida pós-autorização (PAM).

Abstract

Over time, both the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) have established regulatory frameworks requiring the collection of additional data during the post-authorization phase, concerning the safety and, in certain cases, the efficacy, quality or optimal use of authorised medicinal products. Referred to as Post-Authorization Measures (PAMs) by the EMA and as Post-Marketing Requirements (PMRs) and Post-Marketing Commitments (PMCs) by the FDA, these measures have a pronounced relevance in the context of Advanced Therapy Medicinal Products (ATMPs) or Cell and Gene Therapy Products (CGTPs), as designated in the US, where the dual challenge of balancing the timely approval with thorough benefit-risk evaluations is often faced. This dissertation described and contrasted post-authorization measures imposed, required, and agreed upon for a cohort of 15 ATMPs approved both by the European Commission following a positive opinion from the EMA and by the FDA, from 2009 to 2023. It extends to the identification and discussion of expedited regulatory mechanisms allocated to the ATMPs, and a reflection on the role of real-world data in supporting measures objectives. Regulatory documents publicly available on the EMA and FDA websites served as sources for the systematic extraction of all post-authorization measures. The EMA extracted PAMs include Annex II conditions, Specific obligations, category 3 post-authorization safety studies in the risk management plan, Recommendations, and requests for Legally Binding Measures. FDA PAMs included PMRs under four authorities - Food and Drug Administration Amendments Act (FDAAA) section 505(o)(3), Accelerated Approval, Pediatric Research Equity Act, and the Animal Efficacy Rule, as well as agreed-upon PMCs. Descriptive analysis considered variables such as measure category, objectives, study designs, registration rates and status concerning the set date for completion, as set by regulatory agencies. Results evidenced that each selected ATMP received an expedited development program, with most benefiting from multiple FDA and EMA programs. 53 EMA-imposed PAMs and 44 category 3 studies were identified. In contrast, the FDA imposed 27 PAMs, while 43 agreed-upon post-marketing commitments were identified. The study highlights differences in the quantity and nature of PAMs between the EMA and FDA for ATMPs. These variations primarily reflect differences in organizational structures and post-authorization data collection approaches, rather than disparities in initial benefit/risk assessments.

Keywords: Advanced Therapy Medicinal Products (ATMPs), European Medicines Agency (EMA), Food and Drug Administration (FDA), Postmarketing requirement (PMR), Post-Authorization Measure (PAM).

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List of abbreviations

AA	Accelerated Assessment
ADR	Adverse Drug Reaction
ALL	Acute Lymphoblastic Leukaemia
ATMP	Advanced Therapy Medicinal Product
B-ALL	B-cell Acute Lymphoblastic Leukemia
BEST	Biologics Effectiveness & Safety Initiative
BLA	Biologic License Application
BTD	Breakthrough Therapy Designation
CAPA	Corrective Action Preventive Action
CAR-T	Chimeric Antigen Receptor T-Cells
CAT	Committee for Advanced Therapies
cATMP	Combined Advanced Therapy Medicinal Product
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulations
CGTP	Cellular and Gene Therapy Products
CHMP	Committee for Medicinal Products for Human Use
CIBMTR	Center for International Blood and Marrow Transplant Research
CMC	Chemistry Manufacturing and Control
COMP	Committee for Orphan Medicinal Products
CRFs	Electronic Registry Case Report Forms
CRS	Cytokine Release Syndrome
DLBCL	Diffuse Large B-cell Lymphoma
EBMT	European Society for Blood and Marrow Transplantation
EC	European Commission
EHR	Electronic Health Record
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EPAR	European Public Assessment Report
ETASU	Elements to Assure Safe Use
EU	European Union
FD&C	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FL	Follicular Lymphoma
FTD	Fast Track Designation
GTMP	Gene Therapy Medicinal Product
HCPs	Healthcare professionals
HCT/P	Human Cells, Tissues, and Cellular and Tissue-based Products

HPC	Hematopoietic Progenitor Cells
IND	Investigational New Drug
INN	International Non-proprietary Name
INTERACT	INitial Targeted Engagement for Regulatory Advice
LEG	Legally Binding Measure
LTFU	Long-Term Follow-Up
MA	Marketing Authorization
MAA	Marketing Authorization Application
MACI	Matrix-applied characterised autologous cultured chondrocytes
MAH	Marketing Authorization Holder
MCL	Mantle Cell Lymphoma
NCA	National Competent Authority
ODD	Orphan Drug Designation
OTAT	Office of Tissues and Advanced Therapies
PAES	Post-Authorization Efficacy Studies
PAMs	Post-Authorization Measures
PAS	Post-Authorization Studies
PASS	Post-Authorization Safety Studies
PHSA	Public Health Service Act
PMBCL	Primary Mediastinal Large B-cell Lymphoma
PMC	Postmarketing Commitment
PMR	Postmarketing Requirement
PRAC	Pharmacovigilance Risk Assessment Committee
PRIME	PRIority MEdicines scheme
PSUR	Periodic Safety Update Report
RMAT	Regenerative Medicine Advanced Therapy
RECs	Recommendations
REMS	Risk Evaluation and Mitigation Strategy
RMM	Risk Minimization Measures
RMP	Risk Management Plan
RWD	Real World Data
RWE	Real World Evidence
sCTMP	Somatic Cell Therapy Medicinal Product
SD	Standard Deviation
SME	Small and Medium Enterprise
SmPC	Summary of Product Characteristics
TEP	Tissue Engineered Product
US	United States

I. General introduction

Over the past decades, scientific advancements in cellular and molecular biotechnology have propelled the development of novel medicinal products, such as gene therapy, somatic cell therapy, and tissue engineered medicinal products [1]. These biological products present promising therapeutic effects by virtue of their innovative properties for treating or preventing diseases, offering the potential to address conditions with highly unmet medical needs [2].

According to Regulation (EC) No 1394/2007, in the European Union (EU), such therapies are classified as Advanced Therapy Medicinal Products (ATMPs) and comprise four heterogeneous categories, *i.e.*, Gene Therapy Medicinal Products (GTMPs), Somatic Cell Therapy Medicinal Products (sCTMPs), Tissue-Engineered Products (TEPs) and combined ATMPs (cATMPs) [3]. In the United States (US), on the other hand, another term is used to describe essentially the same categories of advanced products, namely, Cell and Gene Therapy (CGT) products [4].

In the latter jurisdiction, CGT products can cover human Hematopoietic Progenitor Cells (HPC) cord blood products when these are more than minimally manipulated or intended for use in unrelated donor hematopoietic progenitor cell transplantation procedures [5][6][7]. In this case, HPC cord blood products are regulated and subject to the requirements outlined in Title 21 of the Code of Federal Regulations (CFR) Part 601 and 351 of the Public Health Service Act (PHSA) [8][9]. Otherwise, If HPC cord blood products undergo minimal manipulation and are intended for homologous use, including autologous use, they are regulated as other category of products, namely, as Human Cells, Tissues, and Cellular and Tissue-based products (HCT/Ps), as specified in 21 CFR 1271.10 [10][11]. HCT/Ps are products containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples include hematopoietic stem cells derived from peripheral and cord blood, cornea, and skin grafts for treating burns.

In the EU, in contrast, hematopoietic progenitor cells are not considered to fit the definition of an ATMP, thus instead, considered as cell-based medical treatments/therapies, which are subject to distinct regulatory frameworks [12][13].

Notwithstanding variations in classification between the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), both regulatory bodies of the European Union and the United States, respectively, regulate ATMPs as biologic products within their regulatory landscape [14][15][16][17].

Moreover, both regulatory authorities have established mechanisms to expedite development and regulatory review of medicines targeting unmet medical needs and serious

conditions, as is often the focus in the development of ATMPs. These regulatory mechanisms, among other advantages, include more frequent interactions between developers and regulators to provide advice on the most appropriate way to generate robust evidence on the benefits and risks of products [18][19].

For instance, the European Medicines Agency introduced the PRIority Medicines (PRIME) scheme in 2016. The purpose of the scheme is to optimise development and enable Accelerated Assessment of medicines that offer a major therapeutic advantage over existing treatments or are expected to benefit patients with no current treatment options for their disease [20].

Similarly, in the US, pathways such as Breakthrough Therapy designation (BTD), Fast Track (FT), and Regenerative Medicine Advanced Therapy (RMAT) designation were implemented to speed up the development and review of medicines treating serious or life-threatening conditions [21].

While such regulatory mechanisms can help to expedite the development and approval processes of ATMPs and other innovative therapies, limited data may be present at the time of ATMPs marketing application, particularly in view of their commonly type of target diseases, i.e., orphan, and with unmet needs. Because of these distinctive attributes, their primary evidence often relies on single-arm pivotal trials involving a small number of patients, with limited follow-up time, and the verification of slow disease progression and treatment effects [22].

Overall, acknowledging the inherent complexities associated with ATMPs, their often targeted diseases, and an increased shift in data collection emphasis toward the post-marketing phase, prompted by expedited development mechanisms, regulatory agencies are likely to be confronted with considerable uncertainties, ultimately requiring further data collection in the post-marketing setting. In such scenarios, marketing authorization holders are frequently obliged to fulfil measures to further confirm clinical benefits and risks.

The European Medicines Agency addresses these remaining uncertainties by requiring in the post-authorization phase, the collection of additional data regarding the safety and, in certain cases, the efficacy or quality of authorised medicinal products through Post-Authorization Measures (PAMs) [23]. Post-Marketing Requirements (PMRs) and Post-Marketing Commitments (PMCs) are measures equivalent to EMA measures required by the US Food and Drug Administration or agreed to conduct by applicants [24]. These latter ones may represent observational studies and/or clinical trials that sponsors conduct after approval to gather additional information about the safety, efficacy, or optimal use of a medicinal product [24].

The implementation of these post-authorization measures plays a pivotal role in regulatory agencies' efforts to further characterize the overall safety, efficacy, and quality profile of medicines, in which for novel and complex medicines like ATMPs are imperative, bridging the knowledge gaps that frequently exist at the time of approval of these products. These measures not only crucially contribute to the ongoing assessment and monitoring of these innovative therapies but also serve to ensure their sustained safety and effectiveness in real-world settings.

II. Objectives, Rationale and Structure

The aim of the present research is to better understand how the EMA and FDA manage uncertainties surrounding the safety, efficacy, and quality of ATMPs at the time of authorization through requests on marketing authorization holders to further address on lingering concerns of these products. Hence a comparative analysis is conducted to evaluate post-authorization measures (EU) and post-marketing requirements and commitments (US) for approved ATMPs in both regions.

The primary objectives were to assess key characteristics, potential similarities and differences in safety, efficacy, and quality measures, and to attempt to understand and describe potential divergences in these, between the two regions. To achieve the latter, an assessment focusing on the nature, rationales, and objectives dictating both the EMA and FDA measure categories was carried out.

Moreover, existent literature approached post-authorization measures with a primary focus on one of the two agencies and were not necessarily aimed at advanced therapies [25][26][27][28]. For instance, some studies addressed comparisons of regulatory decisions in Europe and in the United States, through requested post-marketing studies, focusing, however, only on non-advanced therapy antineoplastic medicinal products [29][30].

Hence, providing a detailed description and contrasting the post-authorization measures* of ATMPs within the regulatory contexts of the European Union and the United States holds significant value and can offer a perspective into how the regulatory authorities address the uncertainties surrounding advanced therapies, while balancing the need for robust scientific evidence and assuring timely access for patients of these products. This research may contribute to an understanding of how the respective regulatory bodies navigate the

*Consistency in terminology is maintained throughout the dissertation text, where the terms "post-authorization measures" and "post-marketing requirements and commitments" are used interchangeably. Similarly, the terms "advanced therapy medicinal products" and "cellular and gene therapy products" are employed synonymously.

complexities of ATMPs, unveiling, through post-authorization measures, their regulatory post-marketing management of uncertainties for such products.

The body of dissertation is structured to provide, in the first part, a review of the regulatory framework for Advanced Therapy Medicinal Products in the EU and US. This part also explores the criteria for defining and classifying these products and provides an overview on the EU and US post-authorization activities and follow-up of safety and efficacy concerns. The second part describes the EMA and FDA expedited regulatory mechanisms and provides a summary of the different mechanisms used to accelerate the clinical development and application review of the advanced therapy medicinal products under study. These were explored for possible associations with the post-authorization measures identified, aiming to uncover potential influences of development and review expedited mechanisms on the requests for post-authorization measures.

The third part address the primary focus of this dissertation, detailing the measures imposed, required, and agreed to a cohort of fifteen ATMPs approved by both regulatory agencies. A comparative analysis of these post-authorization measures was performed, considering different variables, which consisted of the number and type/category of measures (according to each regulatory agency), objectives (e.g. addressing concerns related to safety, efficacy, and/or quality), studies designs, registration rates and status concerning the set date for each measure completion or final report submission, as required by the EMA and FDA.

The fourth part discusses the contribution of real-world data in supporting the objectives of ATMPs post-authorization measures. Lastly, an overall exposition of the findings is presented.

III. Methods

The methodologies employed to identify, extract, and assess data relevant to the study objectives are outlined as follows.

i. General data sources

Publicly available regulatory documents and information from the EMA and FDA websites served as primary data sources for this research. Detailed descriptions of the specific data sources used in which sections are provided hereafter.

ii. Eligibility criteria and ATMPs sample

Medicinal products classified as ATMPs according to the EMA criteria and those classified as Cellular and Gene Therapy products in the US were included. To identify and extract the latter, the EMA CAT quarterly highlights on ATMPs and the FDA page on Approved Cellular and Gene Therapy Products were last consulted last consulted in December 2023 [31][32].

The eligibility criteria used to create the research sample considered only the common ATMPs that were approved both in the EU (approved by the European Commission following a positive opinion from the EMA) and in the US (Approval granted by the FDA), over the period from the full implementation of the European Regulation 1394/2007/EC in 2009, commonly referred as to the ATMP regulation, up to December 2023. Consequently, the US approved hematopoietic progenitor cell cord blood products, classified as advanced cell therapies in the US were excluded from the present research sample, since in the EU, they are addressed by distinct regulatory frameworks [33].

The ATMPs sample, upon which all analyses were conducted, resulted in fifteen advanced therapy medicinal products approved by both the EU and the US regulatory agencies between the research period spanning from 2009 to 2023. Notably, the sample comprises the following ATMPs: MACI, Provenge, Imlygic, Yescarta, Kymriah, Luxturna, Zolgensma, Tecartus, Abecma, Breyanzi, Carvykti, Zynteglo, Skysona, Roctavian, and Hemgenix.

iii. Identification of expedited mechanisms granted to ATMPs

The expedited mechanisms granted to each ATMP in the research sample were identified and extracted from the *"Background information on the procedure"* section in the European public assessment reports and from the approval letters and "Regulatory History" section of the FDA summary basis of regulatory actions documents. These documents are accessible on the respective ATMPs EMA and FDA website pages.

Nevertheless, other related published documents in the FDA and EMA websites concerning the selected ATMPs were also consulted to clarify data questions and to provide missing information. For instance, the FDA BLA clinical and statistical reviews documents and pharmacovigilance memorandums presented in the respective hyperlinks “Approval History, Letters, Reviews, and Related Documents” from the FDA webpages of the respective ATMPs and occasionally EMA press releases concerning the selected ATMPs.

iv. Features extracted from expedited mechanisms

Mechanisms granted to each ATMP were categorized into two groups. One consisting of programs aimed at reducing the review time for marketing applications, such as Priority Review and Accelerated Assessment and another group comprising of programs which help to facilitate and accelerate clinical development, including PRIME (PRIority MEdicines), Fast Track, Breakthrough Therapy, and Regenerative Medicine Advanced Therapy designations.

The features identified and collected in conjunction with the expedited programmes for the ATMPs under study, included, the types of authorizations granted in each region, the programmes allocated to each advanced product and the approvals years by each regulatory agency. Additionally, orphan drug designation statuses attributions were also considered.

v. Identification and extraction of post-Authorizations measures

Data on the EMA PAMs were gathered from European Public Assessment Reports of ATMPs, including the *“EPAR – Procedural steps taken and scientific information after Authorization”* and the *“Summary of Product Characteristics”* (SmPC) in addition to publicly available meeting minutes from the EMA’s Committee for Advanced Therapies (CAT) and the Committee for Medicinal Products for Human Use (CHMP). Data were also retrieved from registries (ClinicalTrials.gov and EU PAS Register) and from ATMPs marketing authorization EMA variations assessment reports for extension of approved indications.

The EMA PAMs extracted include those listed as Annex II conditions to the marketing authorization, required additional pharmacovigilance activities in the risk management plan (category 3 studies), Specific Obligations under ATMPs granted with a CMA or a marketing authorization under exceptional circumstances, and recommendations [RECs] stated at products EPARs. Additionally, submission of final study results involving pediatric patients in fulfilment of Article 46 of the paediatric regulation, were also assessed as requests for directly Legally binding measures, evaluated as PAMs.

It should be noted that Specific Obligations associated with a conditional marketing authorization or a marketing Authorization under exceptional circumstances, may also constitute an additional pharmacovigilance activity. In such instances, if these obligations are related to identified safety concerns, these are included in the Risk Management Plan under

category 2 studies. Additionally, Annex II conditions, which are pivotal for the benefit-risk evaluation of the medicine and included in Annex II.D of the marketing authorization, may also serve as an Additional pharmacovigilance activity if linked to identified safety concerns. These conditions are also integrated into the RMP, although as category 1 studies [23].

Therefore, these measures when collected were thoroughly examined to ensure alignment. In cases where the same measure was adequately duplicated in the EPAR, namely in the pharmacovigilance plan sections of the risk management plan, and in the sections regarding post-authorization measures, the measure was documented and extracted as a single measure. Consequently, Annex II conditions that were already identified in the "obligation to conduct post-authorization measures" sections and in the RMP section as category 1 were only documented as Annex II conditions and similarly, category 2 studies in the RMP section were solely recorded as Specific Obligations. This unified classification facilitated rapid differentiation from category 3 studies outlined in the risk management plan.

Table 1 provides the measures categories adopted by the EMA, and presents the corresponding sources used to identify them and extract further respective information.

Table 1. Categories of EU post-authorization measures collected and respective sources. * The evaluation of the status of Recommendations was not conducted.

EU MEASURE CATEGORY	SOURCES USED TO IDENTIFY AND EXTRACT MEASURES	SOURCES USED TO IDENTIFY THE STATUS OF MEASURES
ANNEX II CONDITION (MEASURE CONSIDERED KEY FOR BENEFIT/RISK EVALUATION)	EPAR – Public Assessment Report – Section of "RMP" (category 1 studies);	EPAR - Summary of Product Characteristics;
	EPAR - Public Assessment Report – section of "Obligation to conduct post-Authorization measures";	EPAR - Procedural steps taken and scientific information after authorization (Opinion/ Notification issued date);
		EPAR – Public Assessment Report – Variation;
	EPAR – Summary of the risk management plan;	CAT and CHMP minutes;
	EPAR – Public Assessment Report – Variation.	EU PAS and Clinicaltrialsgov. status.
ADDITIONAL PHARMACOVIGILANCE ACTIVITY IN THE RISK MANAGEMENT PLAN (RMP), CATEGORY 3 STUDY (MEASURE LINKED TO A SAFETY CONCERN IDENTIFIED IN THE RMP)	EPAR - Public Assessment Report – Section of "RMP" (category 3 studies);	EPAR - Summary of Product Characteristics;
	EPAR – Summary of the risk management plan;	EPAR - Procedural steps taken and scientific information after authorization (Opinion/ Notification issued date);
		EPAR – Public Assessment Report – Variation;
	EPAR – Public Assessment Report – Variation.	CAT and CHMP minutes;
		EU PAS and Clinicaltrialsgov. status.
SPECIFIC OBLIGATION UNDER A CONDITIONAL MARKETING AUTHORIZATION OR MARKETING AUTHORIZATION UNDER EXCEPTIONAL CIRCUMSTANCES	EPAR - Public Assessment Report – Section of "RMP" (category 2 studies);	EPAR - Summary of Product Characteristics;
	EPAR – Public Assessment Report – Sections of "Conditions or restrictions with regard to the safe and effective use of the medicinal product - (RMP)", and "Specific obligation to complete post-Authorization measures for the conditional MA";	EPAR - Procedural steps taken and scientific information after authorization (Opinion/ Notification issued date);

	EPAR – Summary of the risk management plan;	EPAR – Public Assessment Report– Variation;
	EPAR – Assessment Report – Variation.	CAT and CHMP minutes;
		EU PAS and Clinicaltrialsgov. status;
LEGALLY BINDING MEASURE [LEG] (DATA REQUEST IS A STATUTORY OBLIGATION)	EPAR - Public Assessment Report – Section of "Information on Paediatric requirements";	EPAR - Summary of Product Characteristics;
		EPAR - Procedural steps taken and scientific information after authorization (Opinion/ Notification issued date);
	EPAR - Assessment Report – Variation -Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006;	EPAR – Public Assessment Report – Variation;
		CAT and CHMP minutes.
	EMA documents on agreed PIP, modifications, and deferrals (searchable list on the EMA of opinions and decisions on PIPs.	EudraCT and Clinicaltrialsgov. status
RECOMMENDATION [REC]	EPAR - Public Assessment Report	*

Regarding FDA, data on post-marketing requirements and post marketing commitments for the selected cellular and gene therapy products were retrieved from FDA Approval Letters, Summary Basis of Regulatory Actions documents, Clinical Reviews, the FDA online database on Postmarket Requirements and Commitments (PMR and PMC database), ClinicalTrials.gov., and from ATMPs FDA pharmacovigilance plans review memorandums.

The extracted categories of the FDA measures included all post-marketing requirements under four statutory or regulatory authorities, i.e. authorities falling under the purview of Accelerated Approval program, FDAAA (Food and Drug Administration Amendments Act) section 505(o)(3), under the Paediatric Research Equity Act (PREA), as deferred paediatrics studies, and under the Animal Efficacy Rule. Agreed-upon commitments (PMCs) were also duly extracted [24].

Table 2 provides a summary of the various categories of US post-marketing requirements (US measures) and their corresponding used sources for identification and extraction of information.

Table 2. Categories of US post-authorization measures and respective sources.

US MEASURE CATEGORIES	SOURCES USED TO IDENTIFY AND EXTRACT MEASURES	SOURCES USED TO IDENTIFY THE STATUS OF MEASURES
POSTMARKETING REQUIREMENTS (PMR) REQUIRED UNDER THE AUTORITIES OF: ACCELERATED APPROVAL, FDAAA SECTION 505(O)(3), PREA, AND UNDER THE ANIMAL EFFICACY RULE	**FDA Approval letters** - sections of "Postmarketing requirements under section 505(o)", "Paediatric requirements" and "Accelerated Approval Required Studies"	• FDA online database on PMRs and PMCs. • ClinicalTrials.gov. • Approval letter – supplemental approval for prescribing information updates based on data from required studies
	Summary Basis of Regulatory Actions documents - sections of "Postmarketing Requirements" and "Recommendation and risk/benefit assessment - Recommendation for Postmarketing Activities"	
	Pharmacovigilance plan review memorandum - section of "Post Marketing Requirement"	
	FDA online database on PMRs and PMCs	
	BLA clinical review – section of "Recommendations for Postmarketing Actions"	
	FDA Approval letters - sections of	

POSTMARKETING COMMITMENTS (PMCS)	"Postmarketing commitments not subject to the reporting requirements under section 506B"	
	Summary Basis of Regulatory Actions documents – sections of "CMC Postmarketing Commitment"	
	FDA online database on PMRs and PMCs	

vi. Analysis of post-authorization measures

The post-authorization measures were systematically characterized and compared based on several aspects, such as overall count, including the frequency of occurrence per medicinal product, objectives (addressing concerns related to safety/or and efficacy, or quality), status in relation to the set completion date or final report submission required by regulatory agencies, and as well by the study designs and characteristics associated with a post authorization measure (e.g., sample size, estimated population to be enrolled, comparators, allocation, and masking), if applicable.

Descriptive analyses were performed on collected data to characterize and assess similarities and differences. Means, standard deviation (SD), medians with their interquartile ranges (quartiles 25 and 75) and ranges (minimum and maximum) were used.

Excel spreadsheets were used as data collection instrument and relevant information cumulation.

vii. Post-authorization measures objectives

To determine the objectives, viz. the rationale for requesting the EU post-Authorization measures, the descriptions of measures were reviewed from the ATMPs public assessment reports, particularly from the sections "*discussion on clinical efficacy and clinical safety*" and from "*obligation to conduct post-authorization measures*". For example, statements such as "*In order to confirm the long-term efficacy and safety of...*" were used to define the intended objectives of measures. Nonetheless, information regarding FDA PMRs and PMCs with respect to their request rationale was obtained from the "*Recommendations on Postmarketing Actions*" and efficacy and safety conclusions sections of the BLAs clinical reviews as well as from FDA Approval letters sections of "*Postmarketing requirements under section 505(o)*", sections of "*Postmarketing commitments not subject to the reporting requirements under section 506B*" or *Postmarketing commitments subject to the reporting requirements under section 506B* and sections of "*Accelerated Approval Required Studies*", where applicable.

viii. Study design characteristics

For clinical studies associated with or comprising a PAM, the following data were extracted: (a) allocation; (b) masking; (c) comparator; (d) estimated population sample size. Allocation characterization involved classifying clinical trial arms as "randomized" or "non-randomized." Trials explicitly labelled as randomized were categorized as such, while others, including single-group assignments, were considered non-randomized. For masking, trials were classified based on the level of blinding into "Double blind," "Single blind," or "Open label". Comparators were categorized as "Active", "Placebo", or "None", where "None" referred to trials without a comparator. The estimated number of participants was extracted from EU PAS and ClinicalTrials.gov. Furthermore, trials without a comparator also included those with a single group assignment where the advanced therapy was administered to all participants and multi-arm trials where each arm received the therapeutic of interest at different doses or as part of various combination therapies. As for observational studies, information relevant to the study design (e.g., cohort studies, case-control studies, cross-sectional studies) was gathered.

ix. Post-authorization measures status

The determination of the status of the EU measures, whether planned, ongoing, fulfilled, delayed, or unclear, was performed by incorporating information from various sources. These sources included the EU PAS register, the ClinicalTrials.gov database (when applicable and registered), as well as a thorough review of evidence obtained from study result submissions, when the post-authorization measure related to the conduct or completion of a study. The EU PAS register, ClinicalTrials.gov, EPARs – Procedural steps taken and scientific information after authorization, the EMA committees' meetings minutes and public assessment reports of variations were reviewed.

Furthermore, the summary of the RMP and product information updates were also reviewed to verify the progress of the post-authorization measures. Specifically, the product information Annex II.D section which outlines the obligation to conduct post-Authorization measures, and the Annex II.E which specifies Specific Obligations to complete post-authorization measures within the conditional marketing Authorization. The objective was to identify reached milestones, including the removal of a measure previously identified in the initial public assessment report, indicating their fulfilment, as well as the possibility of new measures being added. For instance, due to a significant change in indication or adjustments to completion timeframes for existing measures.

The EU post-authorization measures fulfilment determination relied primarily on the dates of the “Opinion/ Notification issued” in the "Procedural steps taken and post-

Authorization scientific information" from EPARs, referring to final data submissions and if applicable to changes/updates on the Summary of Product Characteristics (SmPC) to add information, resulting from a previously identified post-authorization measure.

In cases where the fulfilment dates, defined as the issued opinion/notification dates, were not readily available in the EPARs "Procedural steps taken and scientific information after the authorization," or in the EMA committees' meetings minutes, alternative sources were used to verify the measure status. These sources included cross-referencing information with the ClinicalTrials.gov and EU PAS Register databases status. Therefore, by comparing the status information from these latter sources, PAMs were also classified as planned, ongoing, or withdrawn. Furthermore, measures statuses were also compared to the set due date stated in European public assessment reports and Products information, Annex II sections, in order to categorize them as possibly delayed, if the measure completion exceed the set date and no evidence of their fulfilment or submission for assessment was found. Additionally, there were considered possible delays in the publication of such evidence from the public data sources.

Moreover, the FDA Post-marketing Requirements and Commitments searchable database available at the FDA website was the primarily source used to determine the current status of each US study or trial required or agreed as PMR or PMC, for the selected ATMPs [34]. Therefore, the status criteria used in this dissertation to determine the status of PMRs and PMCs (FDA measures) was consistent with those employed by FDA in the PMRs and PMCs database.

The FDA assigns seven possible categories status to these studies or trials which are presented in the FDA database along with an explanation of status and description of the requirement or commitment.

These status categories include pending, indicating that the study or clinical trial has not yet been initiated (*i.e.,* no subjects have been enrolled or animals dosed); ongoing which denotes that the study or clinical trial is currently in progress and continuing until a final report is submitted and as long as the status is not delayed or terminated. In cases where the progression of the study or clinical trial lags behind the original schedule, the status is classified as delayed.

The terminated status is assigned when the sponsor prematurely ends the study or clinical trial and has not submitted a final report to the FDA. Also, when the sponsor concludes or terminates the study or clinical trial and submits a final report to the FDA, but the FDA has not yet provided notification regarding fulfilment, non-fulfilment, or release, the status is recorded as submitted. The fulfilled status is assigned when the sponsor submits the final report, and the FDA reviews the report, subsequently notifying the sponsor in writing that the terms of the post-marketing requirement or commitment have been satisfied. Conversely,

released status indicates that the FDA has formally informed the sponsor in writing of the release from the obligation to conduct the study or clinical trial.

Moreover the "fulfilled" and "released" status are only visible on the FDA database website for a maximum duration of one year from the date of fulfilment or release. To ensure comprehensive coverage, the ClinicalTrials.gov database was consulted to verify the status of trials and studies in cases where these were not identified in the requirements and commitments database, either because had been already fulfilled and released or in reason their absence in the FDA PMRs and PMCs database. Hence, the ClinicalTrials.gov database was additionally used to determine the US measures status in such situations.

x. Other EU PAMs: Legally binding measures and Recommendations

Recommendations were not evaluated for the frequency neither for their status, rather, their analysis focused on providing a descriptive overview of qualitative information. For this category of EU Post-authorization measure, all the subsections of the section *"2. Scientific discussion"* of the corresponding advanced medicinal products public assessment reports were reviewed in detail, including particularly the subsections of *" 2.2. Quality Aspects"* and *"2.3. Nonclinical aspects"*, to identify any applicant commitments relating to recommendations. Statements such as "The applicant accepted a recommendation to…", "Recommendations were made for the applicant to…" or "The applicant was therefore recommended to…" were assessed to extract the text related to recommendations. Overall, by conducting an assessment of statements mentioning recommendations, it was possible to present a detailed account of the measures advised to the applicant for further development of the medicinal product.

Moreover, the EPARs, serving as one of the primary sources of EU data in this dissertation, do not provide information regarding specific instances of Legally binding measures, such as requests for update of the product information, requests for supplementary information to evaluate a signal or for instance obligations to submit any data requested in relation to corrective action or preventive action in the context of performed inspections. Moreover, considering that these requests are directly addressed to MAHs and may not necessarily be publicly available, a few limitations have arisen in the analysis of the ATMPs post-authorization legally binding measures.

Therefore, given the limitations of the publicly available information, just the submission of final results of studies involving paediatric patients in fulfilment of the article 46 of the paediatric regulation on the ATMPs in study were ascertained for the analysis of Legally binding measures.

Consequently, the EMA public database, searchable list on the EMA opinions and decisions on PIPs was used to identify paediatric investigation plans of the advanced medicinal products. Also, the sections of "related content" on each ATMP EMA webpage were checked to verify published PIPs or evaluations of waivers to paediatric development requirements grant to the ATMPs. In conjunction the EPAR, sections of *"Information on Paediatric requirements"* were verified for waivers or decisions on the agreement of a paediatric investigation plan. From the identified PIPs, contained studies and their identification study number were extracted.

Considering that the paediatric regulation makes reference to the mandatory requirement to include and post results-related information on the European database (EU Clinical Trials Register) within 6 months of completion paediatric clinical trials, the EU Clinical Trials Register was used to verify registration and status of clinical trials included in PIPs, but also to extract information about trials with focus on a paediatric population un-associated with a PIP and sponsored by the MAH. When the study had published results, the "Global end of trial date" was defined as the date of study conclusion. Of the extracted PIPs studies, only clinical studies were analysed, mainly because these have to be registered at EU Clinical Trials Register and are subject to results submission requirements of the article 46 of the Paediatric Regulation.

To verify submission fulfilments and any possible delays from the six months stipulated in the Paediatric Regulation, the trial end date ("Global end of trial date") was compared to submissions dates of trials results stated at the published paediatric studies related assessment reports, when these were published at the EMA ATMP webpage. It was then attributed study status classifications based on the criteria of whether the study was completed and submitted on time, if the study was completed but experienced a delay in submission from the six months (considering potential delays in updated information), if the study was ongoing with interim results available, or if the study was still ongoing without any results reported yet.

xi. Real-world data (RWD) use analysis

The FDA Approval letters, Summary basis of regulatory actions documents, BLA Clinical reviews and the EMA EPARs, risk management plans summaries and variations assessment reports of the selected ATMPs/Cell and Gene Therapy Products were systematically analysed for post-authorization measures that indicated requests for/with real-world data utilization. In essence, it was sought instances where RWD was integrated to meet required, agreed-upon and imposed post-authorization measures for the ATMPs under study. Moreover, data from the EU PAS and ClinicalTrials.gov registries were included to support analysis.

The criterion for inclusion was the presence of descriptions outlining the use of RWD sources in study designs pertinent to the EU and US post-authorization measures previously identified in the third part of this dissertation. Descriptive analysis was used to characterize gathered information, estimating the count of post-authorization measures incorporating the use of real-world data, the objectives of associated studies, the sources of real-world data (e.g., electronic health records, claims data, hospital data, registries - including secondary data collection from existing registries), the study designs employed, and the associated categories of the post-authorization measures.

In an effort to further understand the role of real-world data in generating evidence based decisions related to post-authorization measures requests, a review was performed to the EU product information's (Annex I - SmPCs) and US prescribing information's updates, thus, it was explored potential implications for labelling changes.

PART I

Regulatory Framework for Advanced Therapy Medicinal Products in the EU and US

1. Regulatory Frameworks in the EU and US

1.1. European Regulatory Framework of Advanced Therapy Medicinal Products

In the Europe Union, the regulatory framework of all medicinal products for human use is primarily established by the European Commission (EC) Directive 2001/83/EC on the Community code relating to medicinal products for human use, and by the Regulation (EC) No 726/2004, on the authorization and supervision of medicinal products and establishment of the European Medicines Agency [35][36].

Concerning advanced therapy medicinal products, in late 2007, the Directive 2001/83/EC and Regulation (EC) No 726/2004 were amended by the Regulation (EC) No. 1394/2007, also known as the ATMP regulation [37]. ATMPs are defined in the preceding regulation as four specific types of medicinal products, *i.e.,* Gene Therapy Medicinal Products (GTMPs), Somatic Cell Therapy Medicinal Products (SCTMPs), Tissue-Engineered Products (TEPs) and combined ATMPs (cATMPs). The specific regulation – Lex specialis on ATMPs resulted from the necessity to determine harmonised rules in order to ensure the free movement of advanced therapy products within the Community and to introduce additional provisions to those laid down in Directive 2001/83/EC [37].

The principles and general provisions of the EU existing legislation on medicines apply to advanced therapies *i.e.* - quality, safety, and efficacy; marketing authorization and post-authorization vigilance. However, the presence of manipulated tissues and cells in advanced therapy products and associated risks, present significant hurdles for licensing these products and appropriate regulatory evaluation prior to clinical and commercial use in a consistent way across the European Community through a single integrated framework was needed.

Prior to the introduction of the ATMP regulation, the principle of a compulsory centralised authorization procedure had already been established for all other products resulting from biotechnological processes under the Regulation (EC) No 726/2004. Accordingly, with the introduction of the regulation, a single scientific evaluation was also made compulsory for advanced therapy medicinal products as these should be subject to the same fundamental regulatory principles as other types of biotechnology-derived medicines while also guaranteeing a high level of scientific evaluation.

Moreover, there was a pressing need for a tailored regulatory framework that addressed the distinct technical requirements associated with tissue engineered products. Contrarily to Gene and Somatic Cell Therapy Medicinal Products, which requisites had been formerly outlined in Part IV of the Annex I to Directive 2003/63/EC, the establishment of the main technical requirements that are specific to tissue engineered products were yet to be legally defined [38].

Further to laying down specific rules for the authorization, supervision, and pharmacovigilance of ATMPs, the integrated regulatory framework for advanced therapy products set up the Committee for Advanced Therapies (CAT) within the European Medicines Agency. The establishment of the committee guarantees that a multidisciplinary expertise is applied to evaluate the quality, safety, and efficacy of advanced medicinal therapy products, in addition to the committee responsibilities to stay abreast of scientific developments in the field and actively contribute to ATMP-specific activities within the EMA [39].

1.1.1. The centralised procedure and the Committee for Advanced Therapies

The central feature brought forth by the ATMP Regulation was the establishment of the scientific Committee for Advanced Therapies. The committee is composed of multidisciplinary members chosen solely for their specific scientific qualifications and different expertise's in areas relevant to advanced therapies, as tissue-engineering, cell therapy, gene therapy, including as well as biotechnology, medical devices, surgery, pharmacovigilance, risk management and ethic [40][41][42][43].

The Committee works in close collaboration with the Committee for Medicinal Products for Human Use (CHMP), which consults CAT on the assessment of data concerning advanced therapy medicinal products while maintaining the ultimate responsibility for the final scientific opinions. Consequently, the main CAT responsibility is to prepare a draft opinion on the quality, safety and efficacy of each ATMP serving as the basis for the CHMP final recommendation (adoption of the final scientific opinion) on the marketing authorization of a respective ATMP. After the adoption of a scientific opinion on whether the medicine should be authorised or not, this opinion is subsequently transmitted to the EC who has the ultimate authority of granting the marketing authorization [41][42].

The CAT draft opinion covers any scientific assessment of ATMPs necessary to draw up the scientific opinions by the CHMP and is not limited to the grant of a marketing authorization, its scope extends to variations, suspensions, or revocations of existing ATMPs marketing authorizations [42]. Additionally, the CAT is tasked with overseeing post-authorization activities of ATMPs.

Furthermore, the CAT is actively involved in other various areas, including but not limited to engaging in consultation for scientific advice requests pertaining to ATMPs, routinely participating in procedures regarding the provision of advice for undertakings on conducting efficacy follow-up, pharmacovigilance, and risk management systems of ATMPs, and assisting in the development of essential documents to meet the objectives set forth by the ATMP Regulation [43].

Moreover, with the implementation of the ATMP regulation several incentives to manufacturers of advanced therapies have been introduced, as outlined in Chapter 6 of the Regulation (EC) No 1394/2007. These incentives particularly target Small and Medium-sized Enterprises (SME) which in turn can facilitate and promote research on advanced therapies since this are commonly conducted by small companies and entities that operate on a non-for-profit basis [45][46]. Incentives include for instance, a substantial fee reduction of 90% for SMEs and 65% for other applicants on any scientific advice given with respect to ATMPs, scientific recommendation on advanced therapy classification as well as the certification of quality and non-clinical data [44][47]. Furthermore, ATMP developers can also benefit from existing schemes to support the development of medicinal products in the EU, such as the PRIority Medicines (PRIME) scheme, or initiatives properly designed to support SMEs and academia.

The certification of quality and non-clinical data refers to the process wherein small and medium-sized enterprises engaged in the development of an advanced therapy medicinal product can submit all pertinent quality and, where available, non-clinical data concerning their product to the EMA for scientific evaluation and certification by the CAT. The scope of the certification procedure is to verify and confirm that each submitted study displaying the quality and non-clinical safety of an advanced therapy medicinal product adheres to the applicable scientific and technical requirements outlined in Annex I of Directive 2001/83/EC, while also adequately follows to current state-of-the-art scientific standards and guidelines. Consequently, the evaluation of the submitted data for certification will be conducted considering the same scientific and technical requirements that apply to the evaluation of a marketing authorization application and provides an opportunity to identify early on potential issues [47].

Notably, the procedure allows the SME applicant to initiate an early dialogue with regulators and it could, nevertheless, facilitate the evaluation of any future application for a clinical trial authorization or a marketing authorization application, particularly if these applications are based on the same set of data already certified [47]. Also, the certification of quality and non-clinical data can enhance the attractiveness of the SME to potential venture capital investors, thereby providing them with additional resources to further develop their product [47].

Another important ATMP regulatory tool, is the optional procedure for scientific recommendation on an advanced therapy classification, also called ATMP classification procedure. It is recognized that questions of borderline may arise due to the complex nature of these products, the limited data package at an early stage of product development and the rapid evolution of science and technology [44]. In the past, there have been instances where

Member States reached different conclusions regarding the classification of innovative biological products. These divergences led to the same product being subject to different regulatory frameworks in various countries [44].

Accordingly, the ATMP classification procedure was introduced with the purpose to determine whether or not a given product based on genes, cells or tissues meets the scientific criteria that define an ATMPs and therefore to afford developers a clearer understanding of the regulatory framework applicable to their products and facilitate the adaptation of the development process to relevant requirements [44].

Many advantages are provided by the classification procedure, as addressing borderline cases as early as possible, between ATMPs versus non-ATMPs, clarifications of the applicable regulatory framework and on the development path and scientific regulatory guidance to be followed [44].

1.2. United States Regulatory Framework for Advanced Therapy Products

The regulatory framework pertaining to public health, food, drugs, and cosmetics in the United States is governed by two key statutes, namely the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the Public Health Services Act (PHSA). These statutes grant the United States Food and Drug Administration the legal authority to oversee and regulate human medicinal products, including drugs, biological products, and devices [48]. Within the field of biologics, various products are included such as blood products, vaccines, and cellular and gene therapy products which constitute the category of advanced therapies [48].

The regulation of advanced therapies is specifically addressed in section 351 of the PHSA, where is established the authority of the FDA to regulate the safety, effectiveness, and labelling of biological products [49]. Moreover, the title 21 of the Code of Federal Regulations (CFR) provides the specific and binding details on how the FDA carries out its regulatory responsibilities. The CFR serves as a codification of the regulations and requirements established under the FD&C Act and the PHSA, providing detailed guidance on how laws and related statutes are applied and enforced in practice. It establishes the procedures, requirements, and standards for the regulation of food, drugs, biologics, medical devices, and other products, serving as a key reference for understanding the regulatory framework and processes implemented by the FDA [50]. Briefly, the FDA regulations are documented in the CFR detailing how the FDA implements the activities that are defined in the FD&C Act and PHSA. Moreover, title 21, sections 600-680 of the CFR specifically cover the regulations pertaining to biologic products [51].

1.2.1. CBER - Office of Tissues and Advanced Therapies

The primary responsibility for the regulation of advanced therapies, including the review process for Biologics License Applications - BLAs, lies within the FDA Center for Biologics Evaluation and Research (CBER), specifically the Office of Tissues and Advanced Therapies (OTAT).

The main purpose of a biological license application is to demonstrate safety and efficacy of biological products and provide correct labelling based on CMC information, preclinical and clinical data, among other pertinent information and data of the biological product. By evaluating the data submitted to the FDA/CBER as part of a BLA and providing scientific evidence of the product safety and effectiveness for its intended use, the respective biologic product may receive approval for marketing [50].

The OTAT is one of three product offices within the CBER and is responsible for regulating a range of biological products, including purified and recombinant proteins for haematology, antivenins, gene therapies, cell therapies, therapeutic tissue engineered products, human tissue products, therapeutic vaccines, other antigen-specific active immunotherapies, certain devices, and xenotransplantation products [52].

Further to the review of initial BLAs or BLAs supplements submitted, several activities are develop by the office, such as, participate in informal and formal meetings with sponsors (OTAT interactions) which can be held in different critical phases of the drug development and marketing of products [52]. These for instance can comprise of an Initial Targeted Engagement for Regulatory Advice (INTERACT) and Pre-IND meetings, when in early stages of product development, sponsors want to obtain the OTAT advice on the data needed to support the submission of an Investigational New Drug application (IND) [52].

The office also engages with sponsors in other stages, including post-submission of an Investigational New Drug application, where in this case, these interactions can include end of phase meetings, pre-BLA meetings, Type A, B, C meetings. Additionally, after BLA approval, meetings also may take place to seek input from OTAT on planned BLA supplements, such as efficacy supplements or significant manufacturing changes [52].

Other spheres of the office include to participate in inspections of manufacturing facilities for compliance with applicable standards, develop policy and procedures governing the pre-market review and evaluation of cellular, and gene therapy to ensure compliance with the provisions outlined in the PHS Act and applicable provisions of the FD&C Act [53]. The OTAT also provides scientific and technical advice to other offices within the CBER, as well as other FDA Centers.

1.3. Classification criteria for ATMPs in the EU and US

In the EU, in order to classify a product as a gene therapy, it must meet the criterion of being a biological medicinal product in accordance with Directive 2003/63/CE. Additionally, the product should contain an active substance that holds or consists of a recombinant nucleic acid administered to human beings, in order to regulate, repair, replace, add, or delete a genetic sequence. Moreover, the therapeutic, prophylactic, or diagnostic effect of the product should relate directly to the recombinant nucleic acid sequence it contains, or the resulting genetic expression of this sequence. It is noteworthy that in the EU, products intended for the treatment or prophylaxis of infectious diseases are specifically excluded from being classified as a gene therapy [54].

In the US, the inclusion criteria for classifying a product as a gene therapy are equivalent to those in the EU, however, while the prevention and treatment of a human disease is explicitly stated as primary goals of these products in both regions, the aspect of diagnosis is not mentioned as a primary objective of a gene therapy in the US. Hence, the criteria in the US include that the product meets the definition of a biological product as outlined in the section 351 of the PHSA, and must be applicable to the prevention, treatment, or cure of a disease or condition in humans [55]. Moreover, gene therapies are defined in the US as therapeutic approaches that can employ a variety of mechanisms, such as replacing a disease-causing gene with a healthy copy gene, inactivating a disease-causing gene that is not functioning properly, or introducing a new or modified gene into the body. Additionally, in the context of gene therapy, recombinant DNA materials used for transferring genetic material are considered integral components of the therapy itself [55].

Somatic cell therapy medicinal products, in the EU are defined in Part IV of Annex I to Directive 2001/83/EC [54]. A straightforward definition for these products is the use of cells, regardless of their origin (whether human-autologous, allogeneic, or animal-derived), for the treatment of a disease. These biological medicinal products consist of cells or tissues that have been subject to substantial manipulation, resulting in alterations to their biological characteristics, physiological functions, or structural properties, all of which are relevant to their intended clinical use. Alternatively, somatic cell therapy medicinal products may include cells or tissues intended for use in the recipient that differ from the same essential function(s) in the donor, i.e., non-homologous use. The second attribute to consider when classifying a product as a somatic cell therapy medicinal product is that the product must be administered to human beings with a view for treating, preventing, or diagnosing a disease through the pharmacological, immunological, or metabolic action of its cells or tissues [54].

Moreover, in the EU, both tissue engineered products and somatic cell therapy medicinal products are subject to the same inclusion principles, where cells or tissues of the

product must be “engineered” meaning that they have undergone substantial manipulation to attain biological characteristics, physiological functions, or structural properties for their intended clinical use or the cells or the tissues are intended for a different essential function in the recipient compared to the donor. The primary distinction between somatic cell therapy medicinal products and tissue-engineered products lies in their intended functions as claimed by the applicant. sCTMPs are designed for the prevention, diagnosis, and/or treatment of diseases through pharmacological, immunological, or metabolic actions as aforementioned, whereas TEPs are designed to have properties that enable their use in, or administration to human beings with the purpose of regenerating, repairing, or replacing human tissues [54]. The classification of a product as either an sCTMP or a TEP is determined based on the claimed mode of action and its associated intended function, where the therapeutic action of the product, specifically its ability to regenerate, repair, or replace tissues, plays a crucial role in classifying it as a TEP.

In accordance with the ATMP regulation, Article 2(4) and 2(5), a product which may fall within the definition of a tissue engineered product and within the definition of a somatic cell therapy medicinal product shall be considered as a tissue engineered product [54].

In the US, within the group of Gene and Cell therapy products, there is no product class defined for tissue-based advanced therapies, where cell and tissue products that qualify as advanced therapies will fall under the categorization of somatic cell therapies. The definition and the inclusion criteria for human somatic cell therapy includes the administration to humans of autologous, allogeneic, or xenogeneic living cells which have been manipulated or processed ex vivo. The manufacturing process of these products involves ex vivo propagation, expansion, selection or pharmacologic treatment of cells, or other alteration of their biological characteristics, where the aim of this cellular products is the application in therapeutic, diagnostic, or preventive purposes [55].

Furthermore, exclusive to the European Union, a category known as combined advanced therapy medicinal product exists for products incorporating one or more medical devices as integral components of the product. These medical devices can fall into categories of general medical devices or active implantable medical devices [54]. To qualify as a combined advanced therapy medicinal product, the cellular or tissue component of the product must contain viable cells or tissues. Alternatively, if the cellular or tissue component contains non-viable cells or tissues, it must have a primary action on the human body that is considered independent of the devices, with a pharmacological action that can be considered as primary to that of the devices.

On the other hand, in the US there is no specific category for combined advanced therapy medicinal products as in the EU, although, similarly, a category of products know as

combination products is present, including drugs, biological, and medical devices. A combination product is defined under the title 21 of the CFR 3.2(e) as a product comprised of two or more different types of medical products i.e., a combination of a drug, device, and/or biological product with one another.

1.3.1. Manipulation and homologous use

Different definitions exist in both regions for the extent of manipulation e.g., minimal *vs*. more-than-minimal and intended use as homologous use or not. The consideration of the type of manipulation performed on the cells or tissues and the intended use is of utmost importance as these will determine the classification of products as either ATMPs or not. Specifically, in the European Union, cells or tissues that have undergone minimal manipulation and are employed for the same essential function are not regarded as advanced therapy medicinal products [54].

In the European Union, the term "substantial manipulation" refers to the intentional modification of cells and tissues during the manufacturing process to alter their biological characteristics, physiological functions, or structural properties to be suitable for their intended purpose [54]. Various techniques can be employed to achieve substantial manipulation, such as cell expansion through culture, genetic modification of cells, and differentiation or activation using growth factors. A list of manipulations that are not considered substantial for advanced therapy medicinal products, i.e., that do not significantly alter the cells and tissues biological characteristics, physiological functions, or structural properties is outlined in Annex I of Regulation EC (No). 1394/2007 [54]. Examples include for instance cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions and sterilization. Moreover, cell separation, concentration, or purification are not considered a substantial manipulation if the cells retain the same biological activity as they have in the human body.

In addition, in the EU, homologous use means that the cells, upon removal from their original environment in the human body are used to maintain the original function(s) within the same anatomical or histological environment. Similarly, transplantation of a nonmanipulated tissue to another location in the same anatomical or histological environment is also considered to achieve the same essential function, i.e., homologous use. Examples of cells falling into this category include bone marrow cells or peripheral blood cells used for hematopoietic or immune reconstitution. Another examples in the case of tissues is skin transplantation, where skin from one part of the body is transplanted to another part, the replacement of arteria by veins or the transplantation of pancreatic islets when these are not cultured before being transplanted [54].

On the other hand, in the United States, the definitions of manipulation and homologous use are specifically defined for human cells, tissues, and cellular and tissue-based products

(HCT/Ps). As per the guideline established by the FDA on Minimal Manipulation and Homologous Use for HCT/Ps, products that do not meet the criteria for HCT/Ps in terms of "minimal manipulation" and "homologous use" may be classified as biological products, and consequently, such products could fall under the category of an advanced therapy. Conversely, the criteria for HCT/Ps include “minimal manipulation” and “homologous use,” while “more-than-minimally manipulated” and “non-homologous use” are considered for cell and tissue-based products considered as biologic.

Moreover, minimal manipulation is defined in the US as processing of structural tissue that does not modify the tissue's essential characteristics necessary for its utility in reconstruction, repair, or replacement. For cells or non-structural tissues, minimal manipulation refers to processing that does not alter the relevant biological characteristics of the cells or tissues. On the other hand, homologous use signifies the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues using an HCT/P that serves the same basic function(s) in the recipient as in the donor.

Briefly, both in the European Union and in the United States, the classification of cell- and tissue-based products as advanced therapies is contingent upon the evaluation of whether the processing entails manipulation that results in the alteration of their characteristics. This concept is referred to as "substantial manipulation" in the EU and "more-than-minimally manipulated" in the US. Regarding the main differences, in the US, there is a subtle distinction between structural and non-structural tissues in terms of the definition of manipulation, which distinguishes it from the definitions outlined in the EU. Also, the European terminology uses the term "engineered" to designate cells or tissues that have undergone substantial manipulation or are used for a different essential function (non-homologous use), which ultimately comprise an EU mandatory criterion for classifying a product as an advanced therapy.

1.4. Post-authorization activities for ATMPs

The scientific and regulatory guidance provided by the EMA for post-Authorization activities concerning human medicinal products marketed in the European Union extends correspondingly to advanced therapy medicinal products [56]. These involve a wide variety of procedures that aim to ensure the continuous maintenance of an updated medicinal product marketing authorization dossier, with ongoing collection, evaluation, and reporting of data pertaining to the safety and effectiveness of the medicinal product, derived from both post-authorization studies and routine use in clinical practice. Ultimately, these procedures allow a robust benefit-risk assessment of the medicinal product.

The various EU regulatory post Authorization activities of advanced therapy and other medicinal products are defined by the EU legislation and may also stem from specific commitments related to the medicine, including for instance pharmacovigilance activities, such as, periodic safety update reports submission and assessment, post-authorization safety and efficacy studies protocols and study reports submission, signal management, updated RMP submission when new information with a significant impact on its content is received, marketing authorization variations applications, administrative changes and procedures (i.e., changing the invented name of a centrally authorised product; transfer of marketing Authorizations) and also but not limited to procedures and process related to post-Authorization measures, MA renewals and annual re-assessments [57].

On the other hand, several FDA post-approval activities are implemented to ensure the continued safety, efficacy, and quality of approved drugs and biologics, such pharmacovigilance activities as post-marketing adverse event monitoring and reporting, including monitoring systems like MedWatch and the Sentinel Initiative, revision of product labels to include new safety information, dosage adjustments, or updated indications based on new evidence; Lot release related activities, among others, also recalls procedures and post-marketing studies, including post-marketing requirements and commitments [58].

1.4.1. Pharmacovigilance activities - ATMPs postmarketing surveillance and risk management

All relevant legislation, and guidelines regarding pharmacovigilance in the European Union are deemed applicable to advanced therapy medicinal products, yet it is important to highlight that for ATMPs, additional pharmacovigilance activities can be often implemented to identify, characterize, or quantify the extent of a safety hazard, to evaluate the of effectiveness of risk management measures, or to investigate missing information [59][60].

Hence, when seeking marketing authorization for an ATMP, MAHs should consider, where applicable, for the pharmacovigilance system of the product, specific aspects of routine pharmacovigilance, as for example heightened requirements for spontaneous reports, follow-up reports, and specific methodology for signal detection. These in particular can involve follow up on adverse reaction reports that do not contain the batch number of the ATMP to ensure traceability of reports to the product [60]. In addition to, for instance, of signal detection and monitoring optimization, including detection of safety signals for any conditioning or pre-treatment, and also monitoring of adverse events related to administration procedures, surgical procedure, follow-up treatment, and transmissions and occupational exposures [60].

Furthermore, active surveillance should be frequently implemented, particularly in cases where the ATMP is intended for use in specialized centres that can act as sentinel sites [60]. Within additional considerations, for ATMPs containing tissues and/or cells, the use of

data traceability through databases or record systems is also recommended for effective surveillance purposes [60].

1.4.2. EMA

The implementation of the new European Union Pharmacovigilance legislation in 2012 (Regulation (EU) No. 1235/2010 and Directive 2010/84/EU, which amended the existing Regulation (EC) 726/2004, and Directive 2001/83/EC, respectively) heralded a significant advancement in pharmacovigilance activities across the EU member states. The legislation, for instance, introduced heightened procedures for Risk Management Plans - RMPs, such as enforcing the obligation to submit an RMP with all applications for new marketing authorizations, significant changes to existing Authorizations, or in response to new safety concerns [61][62].

The document provides a critical assessment of both the known (identified) and unknown safety profile of the medicinal product, along with strategies for identifying and mitigating risks, where the content and extent of the RMP should be commensurate with the risks of the medicinal product. The RMP is intended to be a dynamic document, continuously updated to reflect new knowledge about the risks and the benefits of the medicinal product gained from the post-marketing experience [62]. Furthermore, upon establishing the important identified/potential risks and missing information (safety concerns), the MAH needs to must assess whether additional pharmacovigilance activities are necessary to further detect and characterize these safety concerns.

In line with the possible need for additional pharmacovigilance activities, additional risk minimisation measures can be considered to reduce and manage some particular risks associated with the use or administration of ATMPs in the EU [62]. These are to be consistent with the specific product, notwithstanding, can include restricting the administration of the product to adequately trained and experienced clinicians by controlled access programs, and the development of educational programs based on targeted communication to physicians, pharmacists, patients, caregivers, and others, including specific risk communication materials as patient alert cards and brochures [60].

Moreover, the risk minimisation activities should be accompanied with specific tools to measure their effectiveness, via systems of measurement and assessment of such measurement, as for instance, testing the knowledge and skills of the target audience in educational programs in place, traceability data to evaluate the actual pathways of the product to patients within an implemented controlled distribution system and also for instance revision and update of training materials when there is a noticeable trend indicating a large number of adverse events potentially associated with medicine administration procedures [60].

1.4.3. FDA

In a similar vein to the EU context, pharmacovigilance activities pertaining to advanced therapies in the US are governed by general guidelines applicable to other biologic and drugs. However, beyond the implementation of routine pharmacovigilance practices, additional actions may be deemed necessary and are to be included as part of a pharmacovigilance plan submitted by applicants. For products for which no special concerns have arisen, routine pharmacovigilance should be sufficient for post approval safety monitoring, rendering the need for additional actions such as post marketing studies and the implementation of a Risk Evaluation and Mitigation Strategy (REMS) [63][64][65]. However, in the case of products presenting important identified risks, important potential risks, or important missing information, such additional actions should be considered within a pharmacovigilance plan designed to address these concerns [63].

Specifically, a US pharmacovigilance plan describes pharmacovigilance efforts beyond routine post-marketing spontaneous reporting to enhance the sponsor's acquisition of safety data, therefore the FDA believes that when safety risks are identified pre- or post-approval extra measures may be appropriate in addition to routine spontaneous reporting for post-marketing surveillance [63][64].

Therefore, in cases where a newly approved or previously approved drug or biologic raises significant safety concerns, the FDA may require the implementation of risk minimization strategies beyond standard labelling through the use of a REMS to ensure that the benefits of the medication outweigh its risks and to reinforce medication use behaviours and actions that support their safe use [65]. REMS are designed to address and mitigate a specific serious risk by providing information, education, and reinforcement of actions aimed at reducing the occurrence and severity of an adverse event [65].

A REMS includes a range of communications efforts and activities, such as the development of patient-oriented materials, e.g. medication guides and patient package inserts by the drug manufacturer, and direct communication to healthcare professionals to ensure they receive comprehensive information about medication specific serious risk and steps to take to reduce the risk accordingly [65]. In addition, a REMS may include other approaches such as training and certification for prescribers and dispensers, restrictions to limit the dispensing of the drug to specific health care settings, such as hospitals, and require evidence such as laboratory test results for drug dispensing and also close monitoring of each patient using the drug [65].

In certain REMS, patients that experience an adverse event of concern may be required to be enrolled in a patient registry with the purpose to follow patients during and in some cases after treatment with the drug.

All preceding activities are commonly known as Elements to Assure Safe Use (ETASU), and in numerous REMS, these are implemented in conjunction with communication strategies to accomplish the desired REMS objectives [65].

Further into US pharmacovigilance subject matters, the FDA initiated the Sentinel Initiative in May 2008 as a response to the FDA Amendments Act (FDAAA) of 2007 in which the FDA aims to develop new ways to assess the safety of approved medical products including drugs, vaccines, and medical devices [66]. The Sentinel Initiative is an active surveillance system consisting of two main components, the Sentinel System and FDA-Catalyst. Additionally, the CBER Biologics Effectiveness & Safety (BEST) System operates alongside the Sentinel Infrastructure to ensure the safety and effectiveness of biologic products [66].

Particularly, the CBER BEST system is an active surveillance program to conduct simple to complex queries and studies for biologic products. The system aims to create data, analytics capabilities, and infrastructure for an active, robust, efficient surveillance system for biologic products and develop innovative methods to utilize electronic health records effectively [67]. The system objectives also include automating adverse events reporting using natural language processing and artificial intelligence [67]. The vision for BEST is to become a leading resource for evaluating the safety and effectiveness of biologic products, utilizing high-quality data, analytics, and innovative approaches to enhance surveillance, generate real-world evidence, and improve clinical practice that benefits patients [67].

Furthermore, similar to the EMA pharmacovigilance reporting system EudraVigilance - central repository, and national schemes for the spontaneous reporting of Adverse Drug Reactions (ADRs), the FDA MedWatch program serves as a reporting system for healthcare professionals, patients, and consumers to submit safety reports concerning FDA-regulated medical products, including biologics, medical devices, combination products, and more. It for instance receives reports of adverse events and product quality issues from the public and, when appropriate, publishes safety alerts [68].

1.5. Safety and efficacy concerns of advanced therapies – post-authorization follow-up

The ATMP Regulation places significant emphasis on the post-authorization follow-up of efficacy and safety as a critical aspect for advanced therapies [60][69]. Precisely article 14 (4) of the regulation requests the EMA to draw up detailed guidelines referring to post-authorization follow-up of efficacy, adverse reactions, and risk management of ATMPs. to ensure compliance to this requirement the EMA has published specific guidance on pharmacovigilance for ATMPs which includes the Guideline on Safety and Efficacy Follow up and Risk Management of ATMPs [60].

The guideline provides a framework specific to ATMPs as far ongoing monitoring and post-authorization evaluation, complementing existing guidance, such as the EMA scientific guidance on Post-Authorization Efficacy Studies and GVP Module VIII - Post-authorization Safety Studies, applicable to medicinal products in general, and the guideline on the Follow-up of Patients Administered with Gene Therapy Medicinal Products [60].

The EMA guideline on Safety and Efficacy Follow up and Risk Management of ATMPs also provides an extensive list of potential safety and efficacy concerns that should be considered, including considerations for the objectives of long term follow up for each individual type of advanced product, where cell-based products, gene therapy and combined ATMPs are discriminated for considerations purposes for long term follow up of safety [60].

In the context of risks associated with ATMPs, the guideline highlights that special attention should be given to the potential risk of disease transmission to close contacts or healthcare professionals, the risk of tumorigenicity, as well as the risks related to the storage, transport, and distribution of the product. Additionally, it points out the importance to consider the possibility of unwanted immunogenicity, both intended and unintended genetic modifications of the patient's cells, risks associated with medical or surgical procedures and with the administration of the medicinal product, as also with the potential risks related to the persistence of the product within the patient's body [60].

Moreover, there is outlined that specific post-authorization studies included in the risk management system are expected to be requested for the majority of ATMPs. These can comprise of safety and efficacy studies for the follow up of data generated during the development phase, and may be extension phases of pre-Authorization trials, additional clinical trials and/or observational studies based on registry data [60].

The guideline also addresses methodological considerations for these studies. It acknowledges that safety and efficacy (S&E) follow-up may be necessary for all ATMP recipients, but also states the possibility of focusing the follow-up on a specific subset of patients that is relevant to the research objective or sufficient to gather the required data [60]. However, it emphasizes that in the case of ATMPs targeting orphan indications, the use of a subset of patients is generally not acceptable due to the limited number of exposed subjects. In such cases, the required scientific justification that should be provided when using a subset of exposed patients is waived [60].

As far the extent of follow-up for ATMPs, the guiding document provides detailed information stating that this can vary based on factors such as the epidemiology of the target population, objectives and endpoints chosen for the safety and efficacy follow-up, and the anticipated frequency of adverse reactions. Specifically in the case of gene therapy medicinal products that use integrating vectors or have the potential for latency and reactivation, it is

generally recommended to conduct patient follow-up in clinical trials and clinical trials extensions until marketing authorization and beyond for a duration of up to 15 years allowing for comprehensive evaluation of long-term safety and monitoring of potential delayed effects or reactivation of the therapy [60].

Furthermore, the FDA has equally developed several guidance documents pertaining to cellular and gene therapy products, including the Guidance document on Preclinical Assessment of Investigational Cellular and Gene Therapy Products, as well as the Guidance document on Human Gene Therapy for Rare Diseases [70]. These specific references, for instance, serve to address recommendations intended to assist sponsors in designing clinical development programs for human gene therapy products intended to treat rare diseases and recommendations on the substance and scope of preclinical information needed to support clinical trials for investigational cellular and gene therapies [70].

Nevertheless, to specifically address the risks and safety concerns of these products, in particular of gene therapy products, the FDA has published a guidance document on how to take possible delayed adverse effects into account in the design and duration of long-term follow up studies, titled Guidance for Industry - Long Term Follow-Up After Administration of Human Gene Therapy Products [71]. This FDA guideline aligns with the EMA guideline - Guideline on Follow-up of Patients Administered with Gene Therapy Medicinal Products, that details very similar key considerations and specific aspects of EU measures envisaged to ensure follow-up of efficacy and of adverse reactions for gene therapy medicinal products.

Frequently, gene therapy products are designed to induce therapeutic effect through permanent or prolonged changes in the human body and the resulting long-term exposure may place subjects on investigational studies at increased risk for delayed adverse effects requiring additional monitoring for an extended period of time, referred to as the long-term follow-up (LTFU) period [71].

The FDA guideline on the Long-Term Follow-Up After Administration of Human Gene Therapy Products provides a referential framework to assess the risk of gene therapy-related delayed adverse events, through key questions relating to unique characteristics of gene therapy products. These, for instance, include concerns revolving around the potential uses of genome-editing technology within the product, *ex vivo* vector modification of cells, results of a preclinical study showing persistence of the gene product, vector sequences integration and of the potential for latency and reactivation of the gene therapy product. Based on whether or not these gene therapy product considerations are confirmed, the FDA advice or not on the need for long-term follow-up observations to mitigate delayed risks to subjects [71].

Considerations for preclinical studies design to assess biodistribution and persistence of gene therapy products are also highlighted. As recommended to perform preclinical

biodistribution studies with methods shown to be sensitive and quantitative to detect product sequences and designed to determine the distribution of the product in non-target tissues and the persistence of the product in both non-target and target tissues following direct in vivo administration. Also, it describes that if possible and applicable studies should employ animal species that permit vector transduction and/or vector replication and also that the animal species should be biologically responsive to the specific transgene of interest or to therapeutic components in the product [71].

The FDA aligned with the EMA, recommends that sponsors monitor subjects for a duration of up to 15 years for delayed adverse events after exposure to the gene therapy product, suggesting that the maximum period would apply to the case of gene therapy products with integrating vectors. The guideline specifies that long-term follow-up (LTFU) in the US should involve a minimum of five years of annual examinations, followed by ten years of annual queries of study subjects, via in-person visits or questionnaires [71].

Significantly, the FDA guidance emphasizes the importance of conducting ongoing long-term follow-up during the post-marketing phase, as safety data from clinical trials may not capture all potential delayed adverse events, and also in view of the fact that the recommended long-term follow-up period may not be completed before product licensure [71]. Moreover, it states that the ongoing or the planned LTFU study under an investigational new drug could be a component of the pharmacovigilance plan (post-licensure), therefore it is advisable to submit the LTFU as an element of the pharmacovigilance plan along with the biologics license application submission [71]. The respective FDA guideline also asserts that the establishment of a registry or utilisation of an existing patient registry could be considered to systematically gather and monitor data from treated patients, including solicited sample collection. The registry can be incorporated as well as a part of the pharmacovigilance plan and undergo review during the licensure/approval process [71].

Overall, there are several guidelines designed to address advanced products in both jurisdictions. As part of compliance with the ATMP regulation requirements, the EMA has published a comprehensive guideline (Guideline on Safety and Efficacy Follow-up and Risk Management of ATMPs) that addresses safety, efficacy, and risk management aspects of ATMPs. The guideline has a scope on the pharmacovigilance system, including post authorization studies, identification of risks and risk minimization measures relevant to ATMPs.

In addition to offering numerous guidance documents related to Cellular and Gene Therapy Products, the FDA has developed the guideline (Guidance for Industry - Long Term Follow-Up After Administration of Human Gene Therapy Products) that outlines the unique considerations for long-term follow-up studies/observations specific to gene therapy products. This guideline not only focuses on tailoring LTFU strategies during the pre-marketing phase

but also provides valuable insights into post-marketing monitoring for this type of advanced therapy.

While these guidelines may not cover the exact same facets, serve as evidence of agencies commitment to providing guidance on pertinent aspects and considerations for advanced therapy products in the post-authorization/marketing phase. Nonetheless, these are to be considered in conjunction with others existing guidance and legislation covering all medicinal products/drugs and biologics in both regions.

Furthermore, one may also discern that both jurisdictions have provided guidelines to support the study design and other considerations for the follow-up of patients administered with a gene therapy product. While the EMA took in account relevant aspects to the pharmacovigilance of ATMPs and issued a single specific guideline, the FDA, in contrast, currently does not have a specific guideline for pharmacovigilance and risk management specifically addressing these products where requirements applicable are to be across the board.

In the post-authorization phase, a range of important activities are conducted as aforementioned summarized. Some of these activities are particularly essential from a public health perspective to supplement the available data on the safety, efficacy, and quality of authorised medicinal products. These activities include the mentioned post-authorization measures (EU), which involve obtaining additional data through different types of imposed, required, and statutory requests which are classified into their appropriate EU legal framework which dictates their enforcement [72].

Similarly, in the US, post marketing activities to further refine the safety, efficacy, or optimal use of a product or to ensure consistency and reliability of product quality may be necessary for drugs and biologics, typically involving the implementation of clinical and non-clinical studies – the mentioned FDA post-marketing requirements and commitments [72].

In the realm of post-authorization measures, post-marketing requirements, and commitments, neither the FDA nor the EMA has devised specific tailored standards for advanced therapies. Nonetheless, Part III of this dissertation further elucidates these central subjects [72][73].

PART II

EMA and FDA expedited regulatory mechanisms

2. Expedited regulatory mechanisms in the European Union and the United States

2.1. Programs for serious conditions and unmet medical needs: Accelerating Clinical Development

ATMPs are often developed to address diseases of rare nature, offering new treatments for currently unmet medical needs, or enhance existing treatments options. As a result, this class of medicinal products often qualify for expedited regulatory mechanisms launched by the EMA and the FDA. These established expedited mechanisms aim to swift patient access to ground-breaking therapies that target unmet medical needs or exhibit the potential to bring a significant therapeutic advantage to patients in the treatment of a serious or life-threatening conditions [20][74].

The FDA has implemented three pivotal mechanisms s intended to facilitate and accelerate review and approval of new medicinal products addressing serious or life-threatening conditions, namely the Fast Track, Breakthrough Therapy, and Regenerative Medicine Advanced Therapy, designations, while the EU launched the PRIority MEdicines designation Scheme – PRIME [20][74].

In regard to unmet medical needs definitions, in the European Union this is defined as a condition for which no satisfactory method of diagnosis, prevention or treatment exist. However, if such method exists, the medicinal product concerned should be of major therapeutic advantage over the existing method for individuals affected by the condition [75]. On the other hand, in the US, the FDA adopts a slightly different definition that excludes the aspect of prevention. Hence, an unmet medical need is defined by FDA as a condition whose treatment or diagnosis is not adequately addressed by available therapy [76]. Meaning that to fill an unmet medical need is to provide a therapy where none exists or provide a therapy which may be potentially better than available therapy.

The FDA, in addition, offers clear examples to consider when addressing an unmet medical need in cases where there is an available therapy in the industry's guiding document aimed at providing clarifications on expedited programs/mechanisms - *Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics* [74]. For instance, it is detailed that if a new treatment demonstrates an effect on a serious outcome of a condition that is not known to be influenced by existing therapies, or if it shows an improved effect on serious outcomes compared to available treatments, it would be considered as addressing an unmet medical need. Furthermore, if a treatment demonstrates an effect on a serious outcome of the condition in patients who are unable to tolerate or have failed to respond to available therapy, or if it can be effectively used with other crucial agents that cannot be combined with the available therapy, it would also be deemed to address an unmet medical need [74].

2.1.1. Fast Track, Breakthrough Therapy and Regenerative Medicine Advanced Therapy designations

The Fast Track designation (FTD) program was initially introduced in 1997 to expedite the development, evaluation, and marketing of novel therapies aimed at serious or life-threatening diseases [74]. The program includes the advantage of a rolling review and more frequent meetings with the FDA to discuss, among other topics, study design, extent of safety data and the structure and content of a New Drug Application - NDA or Biologic License Application - BLA [74]. To be eligible for Fast Track designation, sponsors must provide clinical or nonclinical data demonstrating the potential of the medicinal product to address an unmet medical need. This evidence should be submitted as early as the Investigational New Drug application and before BLA or NDA submission [74].

In 2012, mirroring the FTD, the Breakthrough Therapy designation (BTD) was introduced by the US Congress [74]. The BTD has focused even more FDA resources on investigational medicines for which sufficient preliminary clinical evidence suggests the potential for substantial improvement over available therapies on clinically significant endpoint(s) [74]. However, US legislation does not provide a specific definition for what constitutes "substantial improvement." In light of this, the FDA relies for the demonstration of substantial improvement on the magnitude of the medicinal product effect on a clinically significant endpoint, and on the relevance of the observed effect in the treatment of the serious condition or serious aspect of the condition [74].

The advantages of BTD incorporate all the benefits of a Fast-Track designation and also include intensive agency guidance, beginning as early as phase 1 to help the sponsor design and conduct a drug development program as efficiently as possible [74]. Other benefits include an organizational commitment to involve FDA senior managers and experienced review and regulatory health project management staff to facilitate an efficient review of the drug development program and also provides the possibility for sponsors to submit portions of an application for review (Rolling Review) [74].

Occasionally, not all products designated as breakthrough therapies ultimately will continue to show the BTD qualifying criteria during the course of drug development. Therefore, as a process to serve the opportunity to ensure that the designation remains valid and justified, the FDA may later rescind the BTD designation in the cases where the initial preliminary clinical evidence reveals to fail to conclusively demonstrate a substantial improvement over available therapies and once no subsequent data to support the designation is provided by the sponsor as an opportunity to justify the product continued designation [74].

As outlined in the FDA guiding document titled *“Guidance for Industry Expedited Programs for Serious Conditions - Drugs and Biologics”* [74], the preliminary clinical evidence

submitted should be based in a sufficient number of patients to be considered credible, where the FDA typically expects such evidence to be derived from phase 1 or 2 trials, allowing applicants to implement various approaches to demonstrate substantial improvement. Among potential approaches, it is feasible, for instance, to execute direct comparisons that demonstrate a significant or superior response compared to the available therapy. Alternatively, in instances where no therapy exists, it is conceivable to compare the new medicinal product against a placebo or a well-documented historical control, demonstrating a substantial and clinically meaningful effect on an important outcome.

Further into options to demonstrate substantial improvement over available therapies, one notable approach involves combining the available therapy with the new medicinal product to demonstrate a significantly greater or more significant response than available therapy alone, as evidenced by a controlled study or well-documented historical control. Or for example, a demonstration of substantial improvement may entail demonstrating how the new medicinal product reverses or inhibits disease progression, particularly in scenarios where available therapies solely offer symptomatic relief. Moreover, substantial improvement can also be exemplified in situations where the new medicinal product exhibits an important safety advantage concerning serious adverse reactions compared to available therapies, while maintaining a comparable efficacy profile [74].

Similar to the Fast Track designation, the request for BTD can be made when the IND is first submitted or at any subsequent point before receiving marketing approval of their BLA or NDA. For Both designations, i.e., FTD and BTD, the FDA will make a decision within 60 calendar days of receipt of the requests [74].

In essence, the primary disparity between the Breakthrough Therapy and Fast Track designations rests upon their qualifying criteria, notably with the Breakthrough Therapy designation necessitating a higher level of evidence in comparison to the Fast Track designation. As previously mentioned, the FTD requires the submission of nonclinical or clinical data to demonstrate the potential of the product to address an unmet medical need. In contrast, for BTD, preliminary clinical evidence must be submitted indicating that the product may demonstrate a substantial improvement over existing therapies in terms of a clinically significant endpoint(s).

Furthermore, in more recent times, the FDA, introduced the Regenerative Medicine Advanced Therapy (RMAT) designation in March 2017, acknowledging the potential of regenerative products to treat serious conditions, especially in patients with unmet medical needs, underscoring the necessity for efficient regulatory tools to expedite their development and availability to patients [76]. In contrast to the Fast Track and Breakthrough Therapy designation programs, in which apply to both small molecule-based medicines and biological

products, the RMAT designation program applies entirely to products that meet the definition of a regenerative medicine therapy.

In accordance with section 506(g)(8) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), regenerative medicine therapies include cell therapies (both allogeneic and autologous), therapeutic tissue engineering products, and human cell and tissue products. Additionally, this classification extends to combination products incorporating any of the aforementioned therapies or products, when the biological product constituent part provides the greatest contribution to the overall therapeutic effects [76]. Moreover, human gene therapies, including genetically modified cells that lead to a sustained effect on cells or tissues, as well as xenogeneic cell products, may also fall under the FDA's interpretation of regenerative medicine therapy as defined in section 506(g) [76].

To qualify for an RMAT designation, the investigational drug must aim to treat, modify, reverse, or cure a serious condition, supported by preliminary clinical evidence indicating its potential to address unmet medical needs for that condition. Products meeting the RMAT eligibility criteria receive all the benefits associated with fast track and breakthrough designations, including early and collaborative engagement agency/sponsor [76].

The FDA CBER assess the preliminary clinical evidence presented in each RMAT designation application tailoring its assessment decision to the specifics of each case. Additionally, the center takes into account several variables to determine the sufficiency of evidence supporting an RMAT designation. For instance, the rigor of data collection, the evaluation of outcomes, both in terms of their consistency and persuasiveness, the number of patients or subjects and the number of sites supporting the evidence, as well as but not limited to the severity, rarity, or prevalence of the condition [75]. Not limited to these points, CBER additionally intents to consider the potential bias in study designs, treatment assignments, or outcome assessments in the evidence provided supporting a RMAT designation application [76].

The RMAT designation follows to the same timeline as the Fast Track and Breakthrough Therapy designations, with a 60-calendar-day period from the receipt of the designation request to the granting of the designation. Briefly, in comparison, the RMAT designation unlike the breakthrough therapy designation, does not require evidence indicating substantial improvement over available therapies and applies exclusively to regenerative medicine therapies [76].

All the three aforementioned designations, namely Fast Track, Breakthrough Therapy, and RMAT present its distinct features and consequently different programmatic requirements, yet sponsors have the option to apply separately for and receive more than one designation for a given product.

2.1.2. PRIME

Comparable to the FDA expedited programs, a European scheme was established in March 2016 to reinforce scientific and regulatory support for optimizing the development and approval of medicinal products that stand to offer benefits to patients with unmet medical needs [77]. The PRIority MEdicines scheme - PRIME aims to maximise the potential of existing regulatory tools and procedures, providing proactive support to medicine developers through promoting early dialogue for efficient evidence generation and resource utilization.

PRIME offers tailored support based on the development stage of the product. This support includes Scientific Advice and the early appointment of a Rapporteur from EMA's Committees, CHMP or CAT. In addition, PRIME offers a range of other advantages, including but not limited to an initial kick-off meeting with the Rapporteur and a multidisciplinary group of experts, a dedicated PRIME Scientific Coordinator as a contact point throughout the scheme, iterative Scientific Advice at major development milestones and on key issues, access to expedited follow-up scientific advice with shortened timelines, and a submission readiness meeting approximately one year before the marketing authorization application filing date [77].

The PRIME scheme is exclusively available to medicines under development which are not yet authorised in the EU and for which applicants intend to apply for an initial MA through the centralised procedure [77]. Moreover, critical to obtaining PRIME is the ability to demonstrate that the medicinal product is specifically designed to target a condition where there is an unmet medical need, and that the particular medicinal product has a significant potential to address this unmet medical need, e.g., by introducing new methods of therapy or improving existing ones [77].

Furthermore, the data should provide evidence that substantiates the product's capacity to confer a major therapeutic advantage to patients within a particular indication. This can be demonstrated by evidence of a clinically meaningful improvement in outcomes, including effects on the prevention, onset, and duration of the condition, or in the morbidity or mortality associated with the disease.

Each PRIME request must justify the expectation that the medicinal product is of major public health interest particularly from the point of view of therapeutic innovation [77]. Moreover, it should be emphasized that the definition of what qualifies as a major public health interest is not fixed, i.e., there is no single definition, therefore the applicant must provide reasoning for their product assertion of major public health interest, and the CHMP will evaluate each case individually. Also, it is noted that the mere presence of a new mechanism of action or technical innovation per se may not necessarily constitute a sound basis for demonstrating major public health interest [77].

The overarching goals of the PRIME scheme entail granting eligibility as early as feasible, during the clinical development phase. Consequently, assessments regarding the potential therapeutic value of medicinal products rely on preliminary clinical data.

Other European tools supporting early access to medicines, such as conditional marketing authorization, and compassionate use are available to applicants, irrespective of their eligibility to PRIME scheme, offering also the scheme access for a shortened MA review process via the Accelerated Assessment.

Moreover, the CHMP aims to finalize the adoption of outcomes within a 40-day timeframe from the initiation of the procedure. For ATMPs, a CAT reviewer is additionally appointed, providing their recommendation to the CHMP [77].

2.2. Programs for serious conditions and unmet medical needs: reducing marketing applications review times - Accelerated Assessment and Priority Review

The regular evaluation procedure of a marketing authorization application, as per the conventional centralized procedure of the European Union, has a designated duration of 210 days, excluding clock stops, i.e., temporarily suspension of the review period until additional information is provided by the applicant. On the other hand, the FDA standard review times for a BLA or NDA typically span 10 months from the date of application receipt.

Notably, the FDA introduced the Priority Review designation in 1992 with the aim to reduce review times from 10 to 6 months [74]. Similarly, the EMA established the Accelerated Assessment (AA) in 2004, which minimizes conventional assessment time frames from 210 to 150 days [78].

Whitin the FDA procedures, an application or efficacy supplement[2] for a drug or biologic may receive a Priority Review designation if the respective drug or biologic is intended to treat serious conditions, that if approved, would provide significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions compared to other standard applications [74].

The FDA evaluate on a case-by-case basis the potential of a drug or biologic to be of significant improvement in the safety or effectiveness, at the time of NDA, BLA, or efficacy supplement filing [74]. A significant improvement can be demonstrated through various means, such as increased effectiveness in treating, preventing, or diagnosing a condition; the elimination or substantial reduction of adverse reactions that limit treatment options; improved

[2] Efficacy supplement refers to proposed changes in product labelling for an approved application, including adding or modifying indications, adjusting doses, introducing new administration routes, making comparative efficacy claims, or changing the intended patient population [79].

patient compliance leading to an improvement in serious outcomes or evidence of safety and effectiveness in a previously unexplored subpopulation.

Moreover, clinical trials can be used to generate such evidence of significant improvement. One approach is to conduct trials that compare the investigational drug with an already marketed product. Therefore, when an approved therapy is available, sponsors are encouraged to compare their investigational drug to it, aiming to demonstrate superiority in safety or/and efficacy. Alternatively, sponsors may demonstrate the investigational drug ability to effectively treat patients who are unable to tolerate or have not responded to the available therapy and can also investigate the drug compatibility with critical agents that cannot be combined with the existing therapy, presenting potential advantage in treatment options [76]. In addition, other valid scientific information of the produced from beyond randomized trials, such as historical controls, can be used to request a Priority Review designation [76].

The applicant may expressly request Priority Review with the original BLA, NDA, or efficacy supplement, however, the FDA decides regardless on the Priority Review designation for every application. The decision to grant the designation is made within 60 calendar days of receiving the BLA, NDA, or efficacy supplement [74].

On the other hand, in the EU as per Article 14 (9) of Regulation No 726/2004, a medicinal product of major public health interest may be reviewed under an Accelerated Assessment (AA) procedure by the EMA [80].

The Accelerated Assessment shares with PRIME identical eligibility criteria. Applicants should justify that the medicinal product is of major interest to public health, particularly in the context of therapeutic innovation, and should also justify their expectation that the product will, to a significant extent, fulfil an unmet medical need [78]. Based on the essential justifications of major public health interest, as well as the recommendations of Rapporteurs, the CHMP will formulate a decision regarding the request.

The submission of a request for Accelerated Assessment should precede the MA application, where is advisable to make this request at least two to three months prior to the submission of the MA application [78]**.**

In further detail about the procedure timelines, the reduced time frame of 150 days under the AA is divided into 3 phases of 90+30+30 days of assessment. A one-month clock-stop is allowed by default for preparation of responses after receiving the Day 90 List of Questions, however no clock stop is endorsed by default after Day 120 List of Outstanding Issues. The decision to allow a second pause (second clock stop) in the evaluation process will be at the discretion of the CHMP and will be based on a number of factors including the request itself, the arguments presented to support the request, and the recommendations provided by the rapporteurs [78]. In the case of ATMPs, the timetable is structured to

accommodate a CAT review prior to the endorsement of the outcome of the request for accelerated assessment by CHMP.

Moreover, if the CHMP, at any given time during the marketing authorization application evaluation, considers that it is no longer appropriate to continue with the procedure, e.g., if major issues arise, the assessment can reverse to standard centralized procedure timelines.

Figure 1 provides a schematic overview representation of the expedited mechanisms established by the European Medicines Agency and the U.S. Food and Drug Administration, along with suitable application timelines.

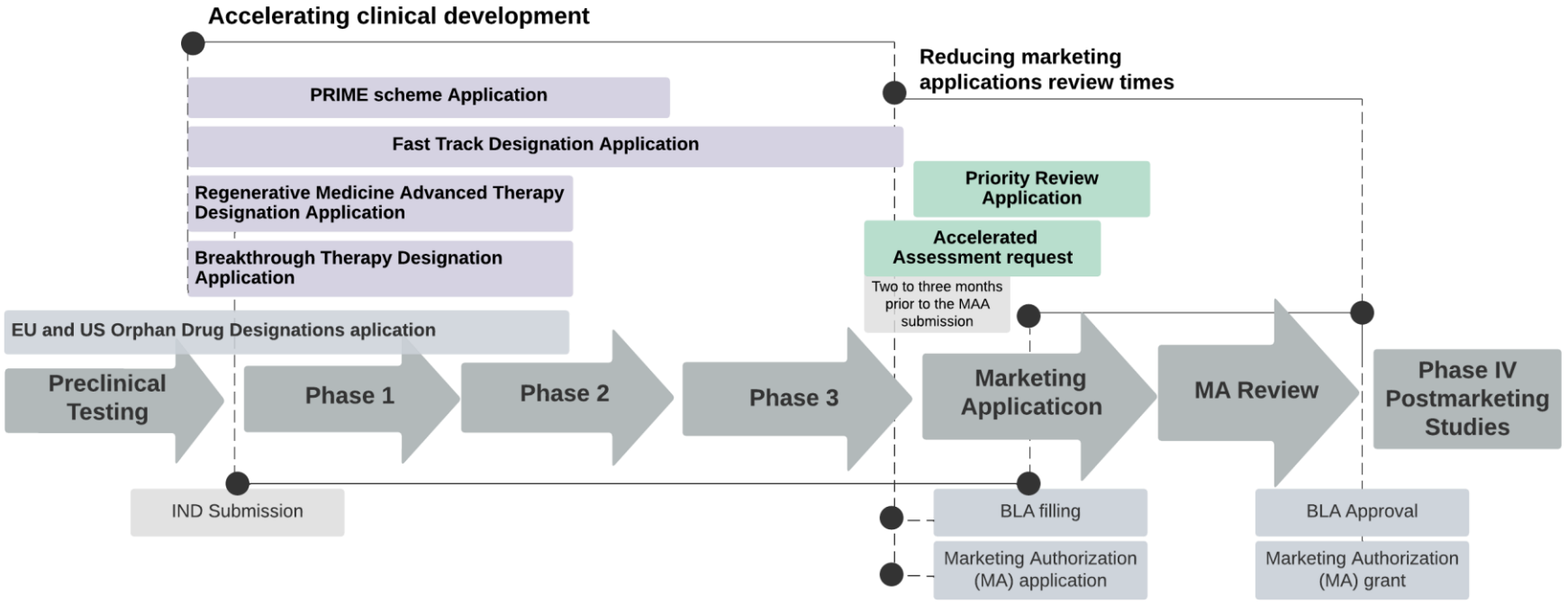

Figure 1. Schematic overview of the EMA and FDA expedited mechanisms and suitable applications times.

2.3. Expedited mechanisms: an analysis of selected ATMPs

The preceding sections outlined the specifies of the expedited mechanisms available in both the European Union and the United States. Subsequently, this discourse delves into the specific mechanisms that have been applied to the selected ATMPs under study.

Firstly, it is significant to highlight that in the EU, seven conditional marketing authorizations (47%) were granted, namely to the medicinal products Zolgensma, Tecartus, Abecma, Carvykti, Zynteglo, Roctavian, and Hemgenix. The remaining selected products (MACI, Provenge, Imlygic, Yescarta, Kymriah, Luxturna, Breyanzi, and Skysona) obtained standard "full" marketing authorizations (53%, n=8). MACI, Provenge, Zynteglo and Skysona, however, have their MA withdrawn from the European market, with companies primary citing commercial reasons for discontinuing their availability [81][82][83][84].

In the US, on the other hand, the majority of the advanced products received standard marketing approvals. Nonetheless, there were observed instances of approval through the Accelerated Approval pathway. Namely, two FDA Accelerated Approvals were granted based on initially submitted BLAs, for the medicinal products Tecartus and Skysona, in the treatment of adult patients with relapsed/refractory mantle cell lymphoma and for slowing the progression of neurologic dysfunction in boys with early active cerebral adrenoleukodystrophy, respectively. Moreover, the supplemental BLA submissions expanding the approved indications of Yescarta and Kymriah to include relapsed or refractory follicular lymphoma (FL) were also granted Accelerated Approval in the US.

Concerning orphan drug designations, in both regions most of the ATMPs are designated as orphan drugs, targeting at least one rare indication. Regarding the EMA-approved ATMPs, 12 have received orphan drug designation (ODD) indications, with the exceptions being MACI, Provenge, and Imlygic. Similarly, the majority of the 15 ATMPs in the US were granted orphan drug designation, in total 13 products. However, there is a notable contrast with the EU concerning Imlygic, which received in the US an orphan drug designation in March 2011.

Moreover, differences between orphan frameworks in the EU and US should be noted. Differently from the US context, in the EU, further from the need to demonstrate rare disease prevalence, there should be no satisfactory method of diagnosis, prevention, or treatment available, and if such methods exist, the given medicinal product must provide a significant benefit to those affected by the condition.

In the context of Imlygic, a possible rationale for the absence of orphan drug designation in the EU, can be attributed to the approved indication of the medicinal product, which specifically focuses on the treatment of regionally or distantly metastatic melanoma. This

condition might not have been classified as rare in Europe, or the product might not have been perceived/considered for as offering substantial benefit.

Moreover, all the orphan designations granted to the medicinal product Breyanzi indications, in the EU, namely for the treatment of diffuse large B-cell lymphoma, follicular lymphoma and primary mediastinal large-B-cell lymphoma were withdrew on request of the sponsor. It was, by the Committee for Orphan Medicinal Products (COMP), as described in the orphan designation withdrawal assessment report of May 2022, stated that the significant benefit required further discussion and justifications for all indications. Moreover, the sponsor was also asked to further elaborate on the indirect comparisons regarding better safety in relation to other medicinal product, particularly to Yescarta, given that a plausible clinically relevant advantage claim on safety was expressed. The withdraw of the designations for Breyanzi occurred prior to COMP final opinion [85][86].

This fact may suggest that the MAH may have decided against pursuing the orphan drug designation due to the inability to provide sufficient justification for significant benefit. Additionally, methodological challenges regarding demonstrating significant benefit can arise when the population size, as applied for, does not allow for randomized active controlled trials, which is often the case for many ATMPs, including Breyanzi. In such circumstances, the exploration of real-world evidence may emerge as a viable option. Furthermore, it is essential to note that higher levels of evidence are typically required at the time of marketing authorization compared to the time of designation, in alignment with the stage of development, where these differences might also influence in arising ODD maintenance assessments issues.

Concerning the mechanisms for reducing marketing applications review times, the marketing authorization applications of Yescarta, Kymriah, Zolgensma, Tecartus, Abecma, Breyanzi, Carvykti, Zynteglo, Skysona, Hemgenix, and Roctavian were reviewed under Accelerated Assessment, (73%, n=11), table 3. However, all Accelerated Assessment procedures reverted to standard timetables, except for Zynteglo, which the MA application was assessed on a fully accelerated timetable.

In respect to the similar mechanism in the US, the following medicinal products BLAs - Provenge, Yescarta, Kymriah, Luxturna, Zolgensma, Tecartus, Abecma, Breyanzi, Carvykti, Zynteglo, Skysona, and Hemgenix, Roctavian – underwent review under Priority Review, 87%, (n=13). Furthermore, each of these products received a BTD, except for Provenge, which was granted just Fast Track designation, table 3. It is worth noting that at the time of Provenge development, the Breakthrough Therapy designation had not yet been introduced.

Among selected medicinal products, Yescarta, Kymriah, Zolgensma, Tecartus, Abecma, Breyanzi, Carvykti, Zynteglo, Skysona, Hemgenix, and Roctavian obtained PRIME

eligibility, 73% (n=11), table 3. Breyanzi, Kymriah, and Yescarta were granted PRIME eligibility in 2016, the same year the scheme was launched. Abecma and Zolgensma received PRIME eligibility one year later, in 2017, followed by Tecartus and Carvykti in subsequent years, 2018 and 2019, respectively. Approximately a year after obtaining PRIME eligibility, the MA applications for Kymriah and Yescarta were submitted to the EMA, while the MA applications for Zolgensma and Tecartus were submitted approximately two years later.

Table 3. Overview of the EMA and FDA expedited mechanisms for the selected ATMPs.

Product brand name	Year of Approval		Approval type and MA status		Expedited Regulatory Mechanisms		
	EMA	FDA	EMA	FDA	EMA	FDA	FDA Priority Review
Provenge	2013	2010	Regular Status: withdrawn	Regular Status: authorised	-	FTD	Yes
MACI	2013	2016	Regular Status: withdrawn	Accelerated Status: authorised	-	-	-
Imlygic	2015	2015	Regular Status: authorised	Regular Status: authorised	-	FTD	-
Yescarta	2018	2017	Regular Status: authorised	Accelerated Regular Status: authorised	PRIME AA	BTD	Yes
Kymriah	2018	2017	Regular Status: authorised	Accelerated Regular Status: authorised	PRIME AA	BTD RMAT	Yes
Luxturna	2018	2017	Regular Status: authorised	Regular Status: authorised	-	BTD	Yes
Zolgensma	2020	2019	CMA (Now regular/full) Status: authorised	Regular Status: authorised	PRIME AA	FTD BTD	Yes
Tecartus	2020	2020	CMA Status: authorised	Accelerated Regular Status: authorised	PRIME AA	BTD	Yes
Abecma	2021	2021	CMA Status: authorised	Regular Status: authorised	PRIME AA	BTD	Yes
Carvykti	2022	2022	CMA Status: authorised ed	Regular Status: authorised	PRIME AA	BTD	Yes
Breyanzi	2022	2021	Regular Status: authorised	Regular Status: authorised	PRIME AA	BTD RMAT	Yes
Zynteglo	2019	2022	CMA Status: withdrawn	Regular Status: authorised	PRIME AA	FTD BTD	Yes
Skysona	2021	2022	Regular Status: withdrawn	Accelerated Status: authorized	PRIME AA	BTD	Yes
Roctavian	2022	2023	CMA Status: authorised	Regular Status: authorised	PRIME AA	FTD BTD RMAT	Yes
Hemgenix	2023	2022	CMA Status: authorised	Regular Status: authorised	PRIME AA	BTD	Yes

ATMP, Advanced Therapy Medicinal Product; AA, accelerated approval; EMA, European Medicines Agency; FDA, Food and Drug Administration; PRIME, PRIority Medicines; BTD, Breakthrough Therapy designation; FT, Fast Track; RMAT, Regenerative Medicine Advanced Therapy; MA, Marketing Authorization.

In the US, 80% (n=12) of the selected medicinal products were granted a Breakthrough Therapy designation, including Yescarta, Luxturna, Kymriah, Zolgensma, Tecartus, Abecma, Breyanzi, Carvykti, Zynteglo, Skysona, Hemgenix, and Roctavian (Table 3). Additionally, 33%

(Provenge, Imlygic, Zolgensma, Zynteglo, Roctavian) received a Fast Track designation. It is noteworthy that Zolgensma, Zynteglo and Roctavian obtained consecutively a Fast Track and Breakthrough Therapy designation. The benefits offered by the BTD, FTD, and RMAT designations overlap in terms of regulatory advantages, albeit with distinct qualifying criteria, where sponsors stand to gain benefits maximization from leveraging multiple expedited mechanisms as they are not mutually exclusive.

Kymriah have received more than one BTD, each one for a different approved indication. In February 2016 for the treatment of patients up to 25 years of age with relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (ALL) indication, and in April 2017 for the indication for the treatment of adult patients with diffuse large-cell lymphoma (DLBCL), which was added through a submitted supplemental BLA.

Regarding RMAT designation, three medicinal products were granted with this program: Kymriah, Breyanzi, and Roctavian. Kymriah received RMAT designation in April 2020 for treating refractory or relapsed follicular lymphoma (supplemental BLA indication). Breyanzi obtained RMAT designation in October 2017 for treating subjects with R/R large B-cell lymphoma, including DLBCL, PMBCL, and grade 3B FL, while Roctavian received RMAT designation on March 4, 2021, for treating adults with severe hemophilia A. The same aforementioned medicinal products obtained a PRIME designation, however in the EU, Kymriah was eligible for PRIME scheme in the indication for the treatment of paediatric patients with relapsed or refractory B cell acute lymphoblastic leukaemia (ALL).

The RMAT designation notably distinguishes itself from the BTD by not necessitating preliminary evidence indicating substantial improvement on clinically significant endpoints over available therapies. Nevertheless, it combines all the advantages offered by both the Fast Track and Breakthrough Therapy programs. Taking into consideration both the qualifying criteria and the timeline of program inception it is noteworthy that the RMAT designation did not emerge as a preferred option for the advanced products under study. This observation suggests that sponsors may still prioritize other established programs, not specifically tailored for advanced therapies, over newer designations such as the RMAT.

Notably, every advanced product in the present dissertation sample has received an expedited development program, with most benefiting from multiple FDA and EMA programs/mechanisms. The medicinal product Luxturna was an exception, as it received BTD designation but not PRIME, and Imlygic and Provenge that were only granted one FDA program designation, namely Fast Track.

PART III

EMA and FDA Post-authorization measures

3. EMA and FDA Post-Authorization Measures

3.1. Characterization of the EMA PAMs

At the time of finalising a procedure or in follow-up of a signal evaluation, the European Medicines Agency may require the collection of additional post-authorization data, regarding safety, efficacy or quality of authorised medicinal products through Post-Authorization Measures - PAMs [87].

The EMA guiding document, titled: European Medicines Agency Post-authorization Procedural Advice for Users of the Centralised Procedure (EMEA-H-19984/03), provides answers to several inquiries that marketing authorization holders may have regarding post-authorization procedures. These responses clarify and cover various aspects of post-marketing procedures and activities, including but not limited to type IA, IB, and II variations, working sharing and grouping variations, extension of marketing authorization, imposed post-authorization safety and efficacy studies, updates to the risk management plan, renewals, annual re-assessment, annual renewal, and post-authorization measures. The document offers an in-depth overview of the Agency's stance on issues, which are typically discussed or deliberated during meetings or discussions between the EMA and MAHs in the post-authorization phase [87].

In accordance with the aforementioned EMA guidance document, post-authorization measures can be classified into five distinct categories based on the appropriate legal framework under which they will be enforced, as well as considering the nature and purpose of the measure. The guidance provides a schematic overview of a decision tree detailing how PAMs are categorised in the distinct categories by the agency [87].

Moreover, various criteria are considered by the EMA when categorizing a post-authorization measure, including assessing whether the additional data required during the post-Authorization phase is essential for the benefit and risk evaluation of the medicinal product. If the data is deemed key to the benefit-risk (B/R), the measure is therefore classified as an Annex II condition [87].

If the required additional data is specifically necessary in the context of a conditional or exceptional marketing authorization it is classified as a Specific obligation. Additionally, if the required additional data is associated with a safety concern identified in the risk management plan, the measure will be considered an additional pharmacovigilance activity in the RMP. Particularly, this latter category is not mutually exclusive with the beforementioned others, as measures classified as an Annex II condition or as a Specific obligation, if linked to a safety concern identified in the RMP are also categorised as additional pharmacovigilance activities, namely category 1 and 2 studies, respectively, included in the pharmacovigilance plan of the RMP [87].

Furthermore, if none of the aforementioned scenarios apply, the measures can be classified into other two possible categories: recommendations or legally binding measures [87].

In greater detail, for conditional marketing authorizations or marketing authorizations granted under exceptional circumstances, Specific obligations are binding to the marketing authorization and may include, for instance, conducting post-authorization studies. These obligations are imposed in addition to tools used to identify and characterize uncertainties in all EU marketing authorizations, including the risk management plan and Periodic Safety Update Reports (PSURs). MAHs are required to comply with the Specific obligations in order to renewal a conditional marketing authorization or continue with a marketing authorization under exceptional circumstances [87].

The data submitted to the agency pertaining to Specific obligations are evaluated on the annual re-assessment (MA under exceptional circumstances) or the annual renewal (conditional MA) procedures, where the benefit-risk balance of the medicinal product is re-assessed along with an assessment of the progress and potential available results of ongoing and completed obligations [87]. Interim results that do not present an impact on the product information (SmPC, Annex II, outer/ inner labelling, and Package Leaflet) can be submitted as a PAM, if they are not part of the annual reassessment or annual renewal. However, if interim results do impact the product information a variation should be submitted to the agency regardless of the timing of the annual reassessment or annual renewal process [87]. Moreover, final results that fulfil a Specific obligation should be submitted either within the annual re-assessment, the annual renewal, or a variation application, where it is deemed the most suitable appropriate procedure [86][87].

Moreover, Annex II conditions, namely post-Authorization measures regarded essential for the benefit-risk profile of the medicinal product, may consist post-authorization safety or efficacy studies (PASS or PAES) imposed at the time marketing authorization granting or at later stages, as binding conditions to the marketing authorization [87]. In the case of Annex II conditions, marketing authorization holders are required to submit a variation application once final results leading to their fulfilment are available, while interim results related to Annex II conditions can be submitted as a PAM, provided they do not present an impact on the product information, in which case a variation should be submitted instead. Final results leading to fulfilment of an Annex II condition should be submitted via a variation application [87].

Post authorization measures defined as additional pharmacovigilance activities in the RMP, specifically category 3 studies, are required to identify and characterize risks, or to assess the effectiveness of risk-minimisation activities. These measures can be set as non-clinical studies, clinical trials, or non-interventional studies in the pharmacovigilance plan of the

risk-management plan to investigate a safety concern of a medicinal product [87]. Any modifications to these measures, such as proposed adjustments to the due dates of agreed milestones, should be submitted through a variation procedure to amend the existing risk management plan version. Similarly, to the beforementioned measures, in the event of completing an additional pharmacovigilance activity - category 3 study - specified in the RMP, a variation application should be submitted for the final study report results. Similarly, interim results can be submitted as a PAM if no impact on the product information is verified [87].

As previously outlined, other post authorization safety studies might be included in the RMP section of additional pharmacovigilance activities, i.e., category 1 and 2 studies. However, category 3 studies in the RMP are voluntary but also considered required and legally enforceable as they are part of the pharmacovigilance plan agreed with the EMA [88]. In contrast, categories 1 and 2 PASS which while also investigate a safety concern of a medicinal product are mandatory, with specific regulatory requirements subject to penalties [88]. Additionally, certain legal requirements that are specifically mandatory for non-interventional PASS conducted under an obligation imposed by an EU competent authority are also recommended for non-interventional PASS conducted voluntarily, in order to ensure an equivalent level of transparency, scientific standards, and quality standards of both voluntary and imposed PASS [89]. For instance, this applies to aspects as the format and content of both the study protocol and the final study report, including its abstract.

Nevertheless, while non-interventional PASS (category 3) are subject to all general regulatory requirements for conducting post-Authorization safety studies, the requirements of non-interventional category 1 and 2 PASS, in contrast, comprise, for instance, additionally, of supervision and assessment by the Pharmacovigilance Risk Assessment Committee (PRAC). Such as the study draft protocol submission prior to the initiation of the study, as well as any subsequent protocol amendments after study start for endorsement/objection by the PRAC or National Competent Authority (NCA) [89].

Concerning the category of PAMs referred to as Legally Binding Measures (LEGs], these are already defined as statutory obligations in the pharmaceutical legislation, being directly binding measures that must be fulfilled by the MAH upon request from the EMA and its committees. The provision of Legally Binding Measures can be classified as a post authorization measure when this concern, for instance, of data requests related stand-alone submissions, requests for supplementary information to evaluate a signal, requests to update the product information, CAPA (Corrective and Preventive Actions) data requests in the context of inspections, as well as the submission of a final study results involving paediatric patients [87].

Furthermore, EMA Recommendations (RECs) are non-binding marketing authorization measures issued by the EMA committee(s) during the assessment of an application. These recommendations may entail pointers to further develop the medicinal product, such as optimizing certain quality aspects or yet considerations for extending the patient population [87]. These recommendations may also be pertinent for optimizing the benefit/risk ratio and may be of potential interest to prescribers or patients.

Recommendations can be submitted as a PAM, or also as self-standing data, within a variation or within a renewal. However, similar to other EU post Authorizations measures, if the data has an impact on the authorised medicinal product and its product information, the MAH is obligated to submit a variation application, as similarly to other PAMs.

Furthermore, the availability of new data or information pertaining to a medicinal product can lead relevant EMA committee(s) to review and potentially change the classification of a post-authorization measure. The process of reclassification will be performed within the procedure where the impact of the newly available information is assessed and discussed. The reclassification decision is subsequently justified in the assessment report, which specifies whether the measure has been upgraded or downgraded as a result [87].

3.2. Characterization of the FDA PAMs

The Food and Drug Administration may request the conduction of Post-Marketing Requirements (PMRs) or/and Post-Marketing Commitments (PMCs) to gather additional information about the safety, efficacy, or optimal use of approved drugs.

In the past, the FDA referred to studies or clinical trials conducted by the applicant after the approval or licensing of a product for marketing, that were intended to further refine the safety, efficacy, or optimal use of a product or to ensure consistency and reliability of product quality as “Postmarketing Commitments (PMCs)” [91]. These commitments were either agreed upon by the FDA and the applicant, or required by the FDA in circumstances of an accelerated approval where subsequent confirmatory studies are required to describe and verify clinical benefit under section 21 of the CFR part 314.510, Subpart H and part 601.41, Subpart E. These commitments were required including in the cases of deferred pediatric studies, where deferred studies are required under the Pediatric Research Equity Act (PREA) and as well as in the cases of medicines approved under the Animal Efficacy Rule, where studies to demonstrate clinical efficacy and safety could be agreed or required under the section 21 of the CFR part 314.610(b)(1), Subpart I and part 601.91(b)(1), Subpart H [91].

However, in 2007, the FDA Amendments Act – FDAAA, was signed into law, introducing a significant change in the rationale for requesting post-approval studies from sponsors [91]. This legislation, specifically Section 901 in Title IX of FDAAA, introduced Section

505(o) of the FD&C Act, which granted the FDA the authority to require postmarketing studies or clinical trials at the time of approval or after approval if the FDA becomes aware of new safety information [91]. These provisions clarified the rationale behind requesting post-marketing studies and provided the FDA to proactively address emerging safety concerns.

Moreover, the FDA Amendments Act, Section 505-1(b)(3) defines a “new safety information” to include data about a serious risk, or an unexpected serious risk associated with the use of a drug. In particular, there can be cases where the FDA may be concerned about a risk, considering it to be serious but may not have enough information to determine the appropriate actions to address the risk in labelling and provide relevant information. In such scenarios, with the new FDAAA authority, the FDA can require a postmarketing study or clinical trial to obtain more information [91]. These postmarketing studies and clinical trials under the FDAAA authority can be required under Section 505(o)(3) for one or all following three purposes, namely, to assess a known serious risk related to the use of the drug, to assess signals of serious risk related to the use of the drug and to identify an unexpected serious risk when available data indicates the potential for a serious risk [91].

Importantly, the FDA distinguishes between clinical trials and studies. Hence, clinical trials refer to prospective investigations where the assignment of drug product(s) or other interventions to human subjects is determined by the applicant or investigator. In contrast, studies cover a range of investigations that are not clinical trials, including for example observational epidemiologic studies, animal studies, and laboratory experiments [91].

Since FDAAA was signed into law, the term PMR was broadened and become applicable to describe all required postmarketing studies or clinical trials, including those required under FDAAA Section 505(o)(3) and those required under subpart H of 21 CFR part 314, subpart E of 21 CFR part 601 (Accelerated Approval requirements), the Pediatric Research Equity Act, and the Animal Efficacy Rule. In contrast, the term PMC evolved to describe studies and clinical trials that applicants have voluntarily agreed to conduct which typically do not meet the statutory requirements specified in 505(o)(3)(B). In short, PMCs ultimately do not meet the criteria for assessing or identifying a serious risk and therefore are not “required” neither their completion will be legally bound to medicine approval [91].

Furthermore, the FDA require applicants to conduct postmarketing studies or clinical trials when before requiring these, determines that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the FD&C Act will not be sufficient to identify a serious risk. In addition, the FDA must reach the conclusion that the pharmacovigilance system established under section 505(k)(3) of the FD&C Act, referred to as CBER Sentinel, will not be sufficient to assess the serious risk [91][92].

Specifically before requiring a postmarketing clinical trial, the FDA must find that a postmarketing study will not be sufficient to meet the capacity to assess a known serious risk, to assess signals of serious risk or to identify an unexpected serious risk [91][92].

In a broader perspective, PMRs required under subpart H of 21 CFR part 314 or subpart E of 21 CFR part 601 relate to postmarketing studies or clinical trials that FDA has the authority to require to confirm efficacy in the context of an Accelerated Approval. The relevant subparts of the Code of Federal Regulations, namely the Subpart H specifically addresses the Accelerated Approval of new drugs intended for the treatment of serious or life-threatening illnesses, and Subpart E addresses the Accelerated Approval of biological products for serious or life-threatening illnesses. The subparts apply to certain new drugs and biologics, respectively, that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments [93][94].

The Accelerated Approval pathway includes the condition that the applicant conducts further studies on the drug or biologic to confirm and describe its clinical benefit. This is particularly important when there is uncertainty regarding the relationship between the surrogate endpoint and clinical benefit, or when there is uncertainty about the observed clinical benefit's impact on the final outcome [93][94].

Importantly, these post-marketing studies, if required, are typically studies that are already ongoing. Furthermore, upon FDA's determination that the required postmarketing study or studies effectively verify and describe the clinical benefit of the drug or biologic product, the requirements will no longer apply and as a result, the drug or biologic product becomes eligible for approval under conventional procedures [93][94].

On the other hand, the Pediatric Research Equity Act, enacted in 2003, empowers the FDA to require pediatric studies for certain drugs and biological products. Each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration must include an assessment of safety and effectiveness for the proposed indication in all relevant pediatric subpopulations [92][95].

In accordance with CFR title 21, section 314.55(b) and section 601.27(b) the FDA may defer until after licensing of the product for use in adults, on its own initiative or at the request of an applicant the submission of some or all assessments of safety and effectiveness for a product proposed indications in relevant pediatric subpopulations [95]. Therefore, the FDA can include deferred pediatric studies or clinical trials as postmarketing requirements.

The deferral may be granted when, for example, the product is ready for approval in adults before pediatric studies are completed or when additional safety or effectiveness data need to be collected before conducting pediatric studies [95].

Nonetheless, section 505B(k) of the FD&C Act provides a statutory exemption from the obligation to carry out pediatric studies as required by PREA for drugs that have been granted orphan designation, commonly referred to as the PREA orphan exemption. The PREA orphan exemption relieves drug applications with orphan designation from complying with PREA requirements when they involve new active ingredients, indications, dosage forms, dosing regimens, or routes of administration. In essence, if an application falls within this exemption, it is not obligated to fulfil PREA obligations, even if it meets the usual criteria that would require PREA compliance [96].

The FDA also allows for waivers of certain requirements regarding pediatric studies based on specific justifications. Full waivers may be requested if the product offers no significant therapeutic benefit over existing therapies for pediatric patients, is unlikely to be used by a substantial number of pediatric patients, or if conducting necessary studies is impossible or highly impractical. Partial waivers may be requested for specific pediatric age groups under similar circumstances, such as lack of therapeutic benefit, impracticality of conducting studies, evidence of ineffectiveness or safety concerns, or unsuccessful attempts to develop a pediatric formulation [95].

Nevertheless, PMRs required under the Animal Efficacy Rule apply to drugs and biological products developed to reduce or prevent serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic chemical, biological, radiological, or nuclear substances. The Animal Rule allows approval of these drugs and biologics based on the use of data from adequate and well-controlled animal studies when the results of those animal studies establish that the drug or biologic is reasonably likely to produce clinical benefit in humans and when human efficacy studies are not ethical and field trials to study the effectiveness of drugs or biological products are not feasible [97][98]. The rule identifies the criteria that must be met for the FDA to evaluate the possibility of granting licensure based on efficacy studies conducted on animals. These include four essential elements, namely there must be a reasonably understanding of the pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product. Also, the effect should be demonstrated in more than one animal species that are expected to have a response similar to humans, unless the effect is shown in a single animal species that is a reliable predictor of human response. Likewise, the endpoint of the animal study should be directly linked to the intended benefit in humans and adequate data on the product's pharmacokinetics, pharmacodynamics, and other relevant information in both animals and humans should be available to determine an effective dosage for humans [97][98].

Approval under the Animal Efficacy Rule is subject to requirements, where human safety data is required and the applicant must commit to postmarketing studies as PMRs, to

verify the product clinical benefit and to assess its safety, such as field studies, when such studies are feasible and ethical [97][98].

If it is assessed that is not currently feasible or ethical to conduct such studies, they may be postponed until circumstances change. However, once it becomes feasible and ethical to conduct studies, the applicant is expected to proceed diligently with their implementation. Moreover, applicants must include as part of their application, a plan or approach to postmarketing studies in the event such studies become ethical and feasible [97][98].

Postmarketing commitments, on the other hand, can involve drug and biologic quality studies, including manufacturing, stability, and immunogenicity studies that do not have a primary safety endpoint. Nevertheless, other types of studies or clinical trials which may not meet the statutory purposes for a PMRs, might be considered for agreed-upon PMCs, such as pharmacoepidemiologic studies designed to examine the natural history of a disease, studies and clinical trials conducted with vaccines, such as surveillance and observational pharmacoepidemiologic studies, and clinical trials with a primary endpoint related to further defining efficacy [92].

Furthermore, after filling the marketing authorization application, the agency transmits to applicants the potential PMRs and PMCs with a brief rationale for necessity of requiring or suggesting these studies and clinical trials, proposing timelines for their completion [91].

For each PMR, Section 901 of FDAAA requires applicants to submit a milestone schedule for completion of each study/clinical trial and to periodically report on the status of the study or clinical trial required within 60 days of the anniversary of the respective drug or biologic approval. Section 506B of the FD&C Act stablishes the requirement to report study status. In the case of 506B-Reportable PMCs, reports are also required annually until notification of the fulfilment or released from the commitment [92].

Final study reports normally are submitted as a supplement to the NDA or BLA to modify product labelling and the FDA reviews the submission under established review times for supplements. However, If the study data do not provide any information that would impact the product labelling, the final study report can be submitted without a supplemental filing [99].

Untimely, the new amendments to the FDAAA also grant the FDA authority to enforce postmarketing studies and clinical trials requirements. Noncompliance with these requirements may result in charges under section 505 of the Act, misbranding charges, and civil monetary penalties [92].

3.3. Comparing the Post-authorization measures for ATMPs: EU vs. US

3.3.1. EU PAMs on selected ATMPs: General characteristics

Overall, ninety-seven (n=97) EMA post-authorization measures[3] were identified by reviewing the sections of the EPARs of the 15 sampled ATMPs, figure 2. A summarized overview of the EU data extracted on post-authorization measures are presented in table 6.

Among the 97 EMA post-Authorization measures, the most common category referred to additional pharmacovigilance activities in the RMP (category 3 studies), 46% (n=44), with a mean of 2.93 (SD: ± 2.63; IQR: 1.50-4.00; range: 0.00-9.00) required per ATMP. The second most prevalent category were those listed as Annex II conditions, 35% (n=34), mean of 2.27 (SD ± 1.39; IQR: 1.00-3.00; range: 0.00-5.00) and 20% (n=19) corresponded to specific obligations, imposed on conditional marketing authorizations, namely, to the medicinal products Zolgensma, Tecartus, Abecma, Carvykti, Zynteglo, Roctavian and Hemgenix. The mean number of specific obligations stood at 2.71 (SD ± 0.76; range: 2.00-4.00). Broadly across the European Union, the overall mean ± SD number of post-authorizations measures required or imposed per medical product was 6.47 ± 2.72 (IQR 5.00-7.50, range, 2.00-12.00).

Moreover, Imlygic and Roctavian had the most PAMs, with 12 and 11, respectively. Notably, these measures primarily comprised Category 3 studies outlined in the risk management plan. In contrast, Luxturna had only two (n=2) Annex II conditions, while MACI presented merely three (n=3) additional pharmacovigilance activities falling under Category 3 studies of the RMP. Consequently, Luxturna and MACI demonstrated the lowest number of post-authorization measures in the EU compared to the other advanced products under study.

Regarding the type of requests for additional data in the post-authorization phase, most of the EU measures (n=52) related to the submission of results (preliminary, interim, or final data) from ongoing studies (interventional and observational) or to the provision of follow-up data from subjects in ongoing clinical trials. The remaining measures (n=34) pertained to requests to conduct and submit results of newly studies (both clinical trials and observational studies) or to other measure requests (n=11), such as to implement assays or reassess specifications for drug substances or finished products, table 4. Hence, overall, an emphasis is noted towards addressing both, efficacy and safety concerns, through follow-ups from ongoing studies, rather than requests for the initiation of newly post-authorization studies.

[3] Recommendations [RECs] and Legally binding measures [LEGs] were considered in a separated analysis.

3.3.1.1. Overview of studies designs and characteristics

Overall, 45.4% (n=44) of the requests for post-authorization data collection or provision were associated with clinical trials, while 43.3% (n=42) were associated with observational studies, and 11.3% (n=11) were classified as other requests, table 4. The latter mainly referred to quality measures requests aimed at optimizing the medicinal product, for instance, to improve consistency of the batches and ensure optimal clinical outcomes or to perform assays.

Among the measures associated with clinical trials (n=44), the predominant trial phase observed was phase III, accounting for 39% (n=17), followed by phase II trials at 27% (n=12), and 20% (n=9) were related to phase I/II trials. Furthermore, 7% (n=3) concerned to phase I trials, and 5% (n=2) to II/III trials, table 4.

One study presented unclear information regarding their phase despite description of a randomized clinical trial. This latter related to an additional pharmacovigilance activity in the RMP (category 3 studies), of the medicinal products Imlygic. The study has no phase described and also an undetermined number/code identification in the medicine public assessment report which led to impossibility to identify the study and their phase in other data sources. It refers to a randomized, controlled trial to evaluate the safety and efficacy in children from birth to < 18 years of age with paediatric solid malignant tumour [100].

Furthermore, it is noteworthy that 75% (n=33) of the associated clinical trials had no comparators, while just 16% (n=7) were actively controlled or 4.5% (n=2) placebo controlled.

Moreover, out of the 44 associated clinical trials, only 2 (4.5%) were double blinding, consistent with the aforementioned placebo-controlled studies. In particular, these concerned the study P-11, a phase III placebo-controlled trial, associated with a requested for a follow up efficacy of the medicinal product Provenge and the study 20110265, also a phase III placebo-controlled trial associated with a request to provide preliminary efficacy results, aimed to address remaining efficacy issues of the medicinal product Imlygic.

Most of the clinical trials 91% (n=40) out of the 44 identified, had open-label designs, where a substantial portion were ongoing at MA application. Other two clinical trials, namely, the beforehand mentioned undetermined number/code identification Imlygic study and the additional pharmacovigilance activity (category 3 study, P13-2) of the medicinal product Provenge, lacked information regarding comparators, masking, and/or allocation [101]. The design characteristics of these trials, as comparators, masking, allocation, and primary endpoints were not possible to be assessed as this information was unavailable at products EPARs and also due to the impossibility to recognize/find the trials and access information in other data sources, i.e., EU PAS register and ClinicalTrials.gov database.

Overall, interventional studies commonly had a single arm design, 66% (n=29), while 32% (n=14) had at least 2 arms. Among the multiple arm studies, 8 are randomized clinical

trials (active or placebo controlled) and 5 are non-randomized trials with the same background advanced therapy in the different arms. Hence, a commonality among the trials associated with post-authorization measures for the advanced therapy products under study is their predominant design as open-label, non-randomized, single-arm studies without controls.

Among the identified observational studies (n=42), most followed a prospective registry-based design. Hence, observational studies typically relied on real-world data collected from registries (prospective observational registry-based studies) with frequently the Cell Therapy registries of the European Society for Blood and Marrow Transplantation (EBMT) and of the Center for International Blood and Marrow Transplantation Research (CIBMTR) identified to be used as established sources of patient data. Cross-sectional studies (surveys) accounted for 17% (n=7), while a single prospective case only design study was identified (study P12-1). The cross-sectional studies were requested as additional pharmacovigilance activities in the RMP (category 3 studies) and were mainly designed to assess health care professionals' knowledge of routine and additional risk minimization measures, e.g. to evaluate the knowledge levels of physicians regarding the key messages included in physician education materials.

Moreover, unlike to the measures associated with clinical trials, a pattern was observed wherein long-term safety data were frequently requested from associated observational studies. These requests often centered on assessing safety through the collection of long-term safety data or a combination of long-term safety and efficacy data.

This is in line with the fact that observational studies may be more feasible than a controlled clinical trial to investigate incidence of a rare adverse event or long-term clinical outcomes, considering trials limitations and orphan indications of the advanced products under study.

Overall, irrespective of measures requests type (submission of results from ongoing studies, conduct and submit results of newly studies or quality related) and study design associated with the post authorization measures (observational or interventional) the grounds for requesting measures was evenly distributed, with a focus in addressing the long-term safety and efficacy or long-term safety and safety/and or efficacy on a shorter term.

Table 4. Overview of the EMA post-authorization measures studies.

EU Post-authorization measures		
Total number of measures	n=97	n (%)
Additional PhV (category 3 study)	44	45%
Annex II condition	34	35%
Specific obligation	19	20%
Type of request		

Complete or submit results from ongoing studies	52	54%
Conduct and submit results of newly studies	34	35%
Other requests	11	11%
Design of study associated with EMA Post-authorization measures		
Clinical trial	44	45.4%
Observational study	42	43.3%
Other	11	11.3%
Focus		
On safety and efficacy	31	32%
On efficacy only	5	5.1%
On safety only	10	10.3%
Long term safety and efficacy	30	31%
Long term safety	7	7.2%
Effectiveness of RMM	7	7.2%
Other	7	7.2%
Post-authorization measures status		
Ongoing/Planned	59	61%
Fulfilled, on time	22	23%
Fulfilled, delayed by ≤1 year	0	0%
Delayed	0	0%
Status unclear	16	16%
Clinical trials associated with Post-authorization measures		
Phase		**n=44**
Phase 1	3	7%
Phase 1/2	9	20%
Phase 2	12	27%%
Phase 2/3	2	5%
Phase 3	17	39%
Unclear	1	2%
Allocation		
Single arm	29	66%
Randomized	10	23%
Non-randomized	5	11%
Blinding design		
Open label	40	91%
Single blind	0	0%
Double blind	2	4.5%
Unclear	2	4.5%
Control		
Placebo	2	4.5%
Active	7	16%
None	33	75%
Unclear	2	4.5%
Number of estimated subjects to be enrolled per total number of PAMs		

<100 subjects	40	41%
100-500 subjects	27	29%
501-1000 subjects	6	6%
>1000 subjects	5	5%
Unclear	9	9%
Not applicable	10	10%

Considering the sample size, the mean number of subjects expected to be enrolled in either observational studies or clinical trials associated with post authorization measures was of 298 subjects (SD ± 534; median: 89; IQR: 40.00-360.00; range: 3.00-3415).The mean estimated sample size of the clinical trials was of 84 subjects (SD ± 92; IQR 21.75-98.50) and ranged from 3 to 400 subjects, with most of the trials intending to enrol fewer than 100 patients. Whereas observational studies (here excluding cross sectional studies) had a mean estimated sample size of 577 subjects (SD ± 720; IQR 158.00-735.00; range 15.00-3415).

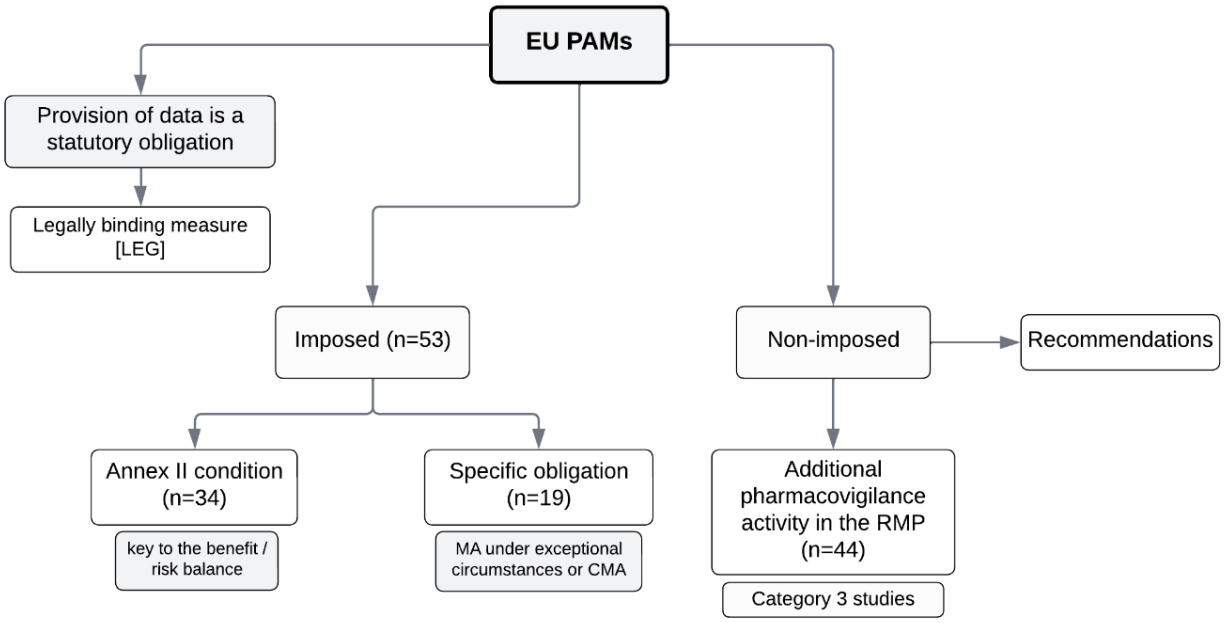

Figure 2. Schematic overview of the EMA PAMs abstracted.

3.3.2. Annex-II conditions: an in-depth analysis

All the marketing authorizations of the 15 advanced therapy medicinal products under study were subjected to Annex II conditions, except for the marketing Authorization of the tissue engineered product MACI (INN: matrix applied characterised autologous cultured chondrocytes) where only category 3 studies in the RMP of the respective medicine were verified. The medicinal product used to repair cartilage defects has no orphan status and was available in several European countries prior the introduction of the ATMP Regulation,

precisely since 1998 (i.e., Austria, Belgium, Denmark, Germany, Greece, Ireland, Italy, The Netherlands, Norway, Portugal, Spain, and the United Kingdom) in compliance with national legislations [101].

The efficacy of MACI compared to microfracture surgery was demonstrated in the pivotal SUMMIT study and was supported by data from the literature, without no major remaining efficacy concerns considered necessary to be further addressed [101]. Moreover, many of the risks associated with MACI were primarily related to the quality and accuracy of the surgical techniques employed during its administration, as well as to the quality of the rehabilitation of patients [101]. Following MACI implantation, patients should follow an appropriately controlled, phased rehabilitation programme based on the MACI rehabilitation manual in order to promote graft maturation and to reduce the risk of post-operative thromboembolic events and joint stiffness. The routine and additional pharmacovigilance and risk minimisation activities described in the RMP of the medicine were considered sufficient to manage risks, which included for instance the provision of additional long-term safety and efficacy data through the 5-year pivotal study (SUMMIT), extension study MACI00809 [101].

Yescarta, Tecartus, Abecma and Hemgenix had all just 1 Annex II condition binding to their marketing Authorization. Tecartus, Abecma and Hemgenix had conditional marketing authorizations and had at least 2 other MA binding conditions, i.e., Specific obligations.

A potential explanation for Yescarta having only a single MA Annex II condition could be attributed to its favourable effects as described in its EU-EMA clinical data assessment. However, some limitations and uncertainties concerning its unfavourable effects have been pointed out, partly due to the limited size and duration on the safety database [103]. Also, it is important to note that in addition to the one mentioned post-authorization measure, other 7 additional pharmacovigilance activities (category 3 studies) were included in the risk management plan of Yescarta, ranging from a HCPs survey (study KT-EU-471-0116) and ZUMA trials already ongoing at MA application, mainly considered with the purpose of additional characterization of Yescarta safety specification in the RMP. The identified risks comprise for example, serious neurologic adverse reactions including cerebral oedema, cytokine release syndrome reactions, infections, and further evaluation of potential risks, and also missing information (e.g., use in pregnancy and lactation, use in non-Caucasian patient populations, use in HIV positive patients) [103].

In general, the clinically relevant efficacy of treatment with Yescarta in the pivotal study (ZUMA-1) in patients with DLBCL and PMBCL with significant duration was demonstrated without the EMA committees recommending further post-authorization measures key to the benefit/risk balance of the product necessary to address issues related to efficacy. However, as regards to the EMA scientific assessment of clinical safety data, the treatment with Yescarta

was associated with a high incidence of ADR of a severity of ≥ grade 3 and/or serious [103]. Therefore, it was considered necessary to further address issues related to safety, with a non-interventional PASS (study KT-EU-471-0117/EUPAS32539), based on registries to assess the safety profile in patients with B-lymphocyte malignancies treated with Axicabtagene ciloleucel in the post marketing setting requested. In the proposed PASS, patient data is to be retrieved from established Registries conducted by the European Society for Blood and Marrow Transplantation - EBMT and Center for International Blood and Marrow Transplantation Research - CIBMTR [104].

Contrastingly, Kymriah represented the medicinal product with more Annex II conditions to their MA, (n=5), mainly post authorization efficacy studies. Kymriah was approved initially in the EU for the indication on the treatment of B-cell acute lymphoblastic leukaemia (ALL), in paediatric and young adult patients whose cancer did not respond to previous treatment, has come back two or more times, or has come back after a transplant of stem cells and on the treatment of relapsed or refractory diffuse large B cell lymphoma (DLBCL) in adults [105]. In March of 2022 the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorization in order to include a new indication for the product, in the treatment of adult patients with relapsed or refractory follicular lymphoma (FL), after two or more lines of systemic therapy [106]. Serious and life-threatening adverse events, particularly cytokine release syndrome was observed in the majority of patients across indications, particularly within the first eight weeks following Kymriah infusion.

In addition to implemented risk minimization measures, post-authorization studies were deemed essential and required as Annex II conditions to further characterize the safety profile and long-term safety of Kymriah. Overall, a non-interventional PASS based on data from registries (EBMT and CIBMTR) was required to assess safety, including long-term safety of Kymriah in ALL and DLBCL patients (study CCTL019B24019) [105]. Moreover, four other studies, precisely PAES were required, including a subgroup analysis from the CCTL019B2401 registry, aiming to evaluate the efficacy and safety of Kymriah in patients below the age of 3 years with B-ALL treated in the commercial setting and another prospective observational PAES conducting a subgroup analysis from the CCTL019B2401 study, specifically focusing on evaluating the efficacy of Tisagenlecleucel in patients with r/r DLBCL, with efficacy outcome measures in line with those evaluated in the pivotal CCTL019C2201 study.

Furthermore, as part of the required post authorization efficacy studies, a 24-month follow-up and a 5-year follow-up from the pivotal phase 2 study CCTL019C2201 is included in conjunction with a phase 3 PAES, known as study CCTL019H2301, required to assess the long-term efficacy and safety of Kymriah in patients with relapsed/refractory DLBCL [105].

3.3.2.1. Annex II Conditions: objectives and studies design

Most of the Annex II conditions pertained to requests to conduct and submit results of observational studies 71% (n=24). Other requests, involved submitting results from ongoing clinical trials, accounting for 24% (n=8), and also to other requests, unrelated to interventional or observational studies. These included quality-related Annex II conditions, such as to further evaluate finished product specifications for Zolgensma upon the availability of additional patient data, and re-evaluation of acceptance criteria for potency tests for Zynteglo using batch release data and clinical results from patients treated with commercial batches.

The measures that have been imposed as Annex II conditions on the MA of the ATMPs comprised frequently for requests to further investigate either the long-term safety and efficacy or long-term safety.

Furthermore, the ATMPs safety concerns addressed through Annex II conditions were diverse, however there were some recurrent similarities observed, which often were related with the further characterization of identified risks, and further evaluation of potential risks, such as cytokine release syndrome, infections, induction of secondary malignancy, induction of immunogenic reactions, and serious neurological adverse reactions.

Missing information specially pertaining to long-term safety effects as well as effectiveness, such as long-term clinical response, also emerged as an aspect/concern in the summary of safety concerns in the RMP of the ATMPs and were also frequently addressed through imposed Annex II conditions.

3.3.2.2. Annex II conditions: completion rates

Among the 34 post-authorization measures listed as Annex II conditions, less than a quarter (21%, n=7) had been completed or fulfilled as of the final data verification cut-off of December 2023. The evidence of their fulfilment was identified in respective EPARs - Procedural steps taken and scientific information after authorization and on meetings minutes of EMA committees' where the submission of study results and fulfilment was explicitly stated. Updates to the Annex II.D of the product information to reflect their fulfilment (removal) were verified and, where applicable, new texts were added to the SmPC in order to include new relevant data.

The fulfilled Annex II conditions primarily revolved around the submission of preliminary efficacy results from ongoing clinical trials at the time of the marketing authorization application, e.g., the studies 20120325, 20110266, and 20110265 which were associated with measures imposed on the MA of medicinal product Imlygic to ensure the generation of additional efficacy data.

Furthermore, the fulfilment of MA Annex II conditions was also verified for two other medicinal products, Kymriah and Zolgensma. For Kymriah, the fulfilled MA Annex II conditions included the completion of a PAES consisting of a subgroup analysis derived from the observational study CCTL019B2401 to further evaluate the efficacy and safety of Kymriah in ALL patients below the age of 3 years, as well as a 24 month follow-up of all infused patients from study CCTL019C2201. Additionally, a PAES also as an Annex II condition consisting of a sub-analysis to assess efficacy in patients with relapsed or refractory diffuse large B-cell lymphoma based on data from the registry study CCTL019B2401 was also fulfilled.

Moreover, the Annex II condition concerning the medicinal product Zolgensma, requiring the submission of an evaluation of finished product specifications specified to take place once primary and key secondary endpoint data from additional patients with 2 copies of SMN2 became available, was fulfilled upon completion of the CL-302 and CL-304 cohort 1 studies.

In general, the fulfilled Annex II conditions primarily involved requests related to the submission of preliminary results and sub analysis of ongoing studies. These conditions had relatively shorter timeframes for completion as set by the EMA. There are still 27 Annex II conditions, either ongoing or planned, imposed on the selected ATMPs MA, as of the final data verification cut-off of December 2023. These ongoing/planned conditions primarily focus on the conduct and submission of observational studies aiming to assess the long-term efficacy and safety of the ATMPs and therefore have considerably longer completion timeframes.

The completion and submission of final study reports for the four Annex II conditions imposed at the withdrawn medicinal product Provenge were not explicitly documented in the medicine EPAR-Procedural steps taken and scientific information after authorization or committee minutes. However, their status was verified on the EU PAS register and ClinicalTrials.gov, indicating that some of these studies have a status of either planned, completed, or terminated. Specifically, one condition remains planned (Observational study P13-1, EU registry), while the observational study PROCEED/P10-3 - US Registry and study P-11 have been completed, and study P12-1 was terminated.

3.3.3. Specific Obligations: an in-depth analysis

The concept of conditional marketing authorization entails that less comprehensive data on the product for authorization is supplemented by additional post-authorization data obtained through specific obligations.

Among the seven medicinal products granted Conditional Marketing Authorization, namely Zolgensma, Tecartus, Abecma, Carvykti, Zynteglo, Roctavian and Hemgenix, sole the marketing authorization of Zolgensma have been converted from conditional to full

authorization while the MA of Tecartus, Abecma, Carvykti, Roctavian and Hemgenix are still conditional (as of the data verification cut-off of December 2023).

The marketing authorization holders of Carvykti, Abecma, and Roctavian were required to fulfil two specific obligations, while those of Zolgensma, Zynteglo, and Hemgenix were obligated to fulfil three. In the case of Tecartus, four obligations were required.

The specific obligations imposed by the CHMP for conditionally approved products concerned mainly to the submission of results from already ongoing clinical trials at MA application. Specifically, 84% (n=16) involved the submission of results from ongoing or completed clinical trials results while the remaining 16% (n=3), consisted of specific obligations to conduct and/or submit results of observational studies.

Initially, the majority of the marketing authorization applications were submitted for full authorizations. However, for Zynteglo, the applicant requested at first hand consideration of its application for a Conditional Marketing Authorization. The applicant of Zolgensma proposed a conditional MA during the evaluation process, after major objections were raised regarding the available efficacy and safety data, as well as concerns related to the commercial manufacturing process and the indication wording. Similarly, for Tecartus, Abecma, Carvykti, Roctavian and Hemgenix major concerns were raised during the assessment regarding the comprehensiveness of the data set, where considering these concerns, applicants requested considerations for a CMA as a response to the CAT/CHMP proposals during the assessment.

3.3.3.1. Specific obligations: objectives and studies design

All Specific obligations imposed under the CMAs were intended to address uncertainties concerning both efficacy and safety data. Among the 19 Specific obligations, 79% (n=15) were focused on confirming the efficacy and safety data of the medicinal products, while 21% (n=4) were specifically aimed at confirming long-term efficacy and safety data. Of the specific obligations that were imposed, more were observed associated with phase III trials (n=11), whereas a similar proportion was observed for phase II (n=3) and phase I/II trials (n=2). All clinical trials were open label, either randomised or not randomized with active control (n=3) or single arm (n=13). Three obligations associated with observational studies based on data from registries were requested to confirm the long-term efficacy and safety or confirm the efficacy and safety of the medicinal products Tecartus and Hemgenix.

More thoroughly, the clinical data of Tecartus was regarded not to be comprehensive due to uncertainties arising for instance from the short follow-up duration, the limited sample size and the possible differences in efficacy and safety related to gender, age and disease severity. However, with the benefits of the immediate availability of the ATMP outweighing the risks associated with the inherent uncertainties, a positive opinion on a conditional marketing

authorization was granted by the CHMP in October 2020 for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor [107]. Associated with this indication two specific obligations were imposed, namely, to submit results of a prospective study investigating Tecartus efficacy and safety based on data from a registry, namely the EBMT registry and a follow-up data of 24 months from all treated patients in cohort 1 of the pivotal study ZUMA-2.

In July 2022, the CAT recommended a variation to the terms of the marketing authorization, concerning the change to extend the approved indication to include the treatment of adult patients with relapsed or refractory (r/r) B-cell acute lymphoblastic leukemia (B-ALL). With the extension of indication, two other specific obligations were imposed and added to the RMP as well, referring to the submission of follow-up results of the ZUMA-3 clinical study (Part 1 and Part 2) and conduct and submit results of a prospective, observational study based on data from a registry in order to confirm the long-term efficacy and safety of Tecartus in adult patients with r/r ALL [108].

Concerning Hemgenix, three Specific obligations were requested in total. Two were intended to provide additional data on the durability of the effect, to further elucidate the durability and long-term safety, requiring the submission of final study results, including 5 years of follow-up, from the interventional studies CT-AMT-061-01 and CT-AMT-061-02. Additionally, another obligation associated with the observational post-authorization Long-term Follow-up Study CSL222_4001 was requested to confirm efficacy and safety by submitting a 1-year follow-up interim analysis report after enrolling the first 50 subjects [109].

3.3.3.2. Specific obligations: completion rates

Nine Specific obligations were fulfilled among the total overall 19 imposed obligations, specifically referring to the Specific obligations of the medicinal products Zolgensma, Tecartus, Abecma, Carvykti, and Zynteglo (as of the data verification cut-off of December 2023).

Moreover, during the second MA renewal of Zolgensma on March 24, 2022 (following the first renewal on March 25, 2021), the CAT/CHMP conducted a reassessment and confirmed a positive benefit-risk balance. Also, it was considered that all Specific obligations had been fulfilled, and no further grounds remained for the marketing authorization to remain conditional, with a recommendation been made to convert the marketing authorization to a full MA, therefore, no longer subject to Specific obligations.

Furthermore, the submission deadlines for Zolgensma Specific obligations data were met without delays. Namely, the final study data submission for AVXS-101-CL-303-CL-303 was due at the first annual CMA renewal, while the PAES AVXS-101-CL-302 and AVXS101-

CL-304 had deadlines for interim results submission at each annual renewal [110]. The studies were registered on Clinicaltrials.gov database with verified completion dates of 12th November 2019 (AVXS-101-CL-303-CL-303), 11th of September 2020 (AVXS-101-CL-302) and 15th of June 15, 2021 (AVXS101-CL-304). It is worth noting that the completion dates of these studies aligned with the estimated completion dates on the ClinicalTrials.gov database, where, upon examining the set deadlines for obligation fulfilment by the EMA, it was observed that the studies were completed significantly ahead of the renewal assessment. Particularly, the final results submission was evidenced for study AVXS-101-CL-302 in the CAT and CHMP minutes of July 2021, while all the others Specific obligations were stated completed at second annual renewal. The package leaflet of Tecartus was updated accordingly and the Annex II.E been updated to reflect completion of the Specific obligation concerning the study AVXS-101-CL-302. Importantly, the results of study AVXS-101-CL-302 were stated to be comparable to the results of the study CL-303, which was in the basis for the approval of the marketing authorization [111].

In the case of Tecartus, there have been three conditional marketing authorization renewals for the medicinal product. Out of the four Specific obligations imposed on the medicinal product MA, only one has been fulfilled as of the data verification cut-off of December 2023. The fulfilled Tecartus obligation pertained to the submission of a 24 months follow-up data from all treated patients in cohort 1 of the pivotal study ZUMA-2 (KTE-C19-102). The data was intended to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory mantle cell lymphoma. The request for the submission of follow-up data was originally due on March 31st, 2022, with results submission being evidenced in June 2022 [112].

With the obligation fulfilled, the sections 4.8 “Undesirable effects” and 5.1 “Pharmacodynamic properties” of the Summary of Product Characteristics (SmPC) were updated to include the latest safety and efficacy information based on the 24-month follow-up data. Additionally, the SmPC Annex II.E was updated by removing the previously listed obligation to accurately reflect their fulfilment. Regarding the other three Tecartus specific obligations addressing concerns related to the medicinal product in both approved indications, they are either currently ongoing or have planned actions in progress.

The conditional marketing authorizations for the advanced medicinal products Abecma and Carvykti have been renewed twice and once, respectively. Both obligations imposed on Abecma have been fulfilled. These concerned the submission of a 24 months post-Abecma infusion follow-up data in the enrolled and treated population of the pivotal study Karma (BB2121-MM-001) and the submission of results of the Phase 3 study KarMMa-3 (MM-003) comparing the efficacy and safety of Abecma vs. standard regimens in subjects with relapsed

and refractory multiple myeloma. The Specific obligations focused in confirming the efficacy and safety, with deadlines set for December 2021 (BB2121-MM-001) and January 2024 (MM-003). While the latter obligation's completion date was set after the data cutoff analysis, evidence of fulfilment was observed in the CAT minutes of October 2023 [113].

The fulfilment of the obligation associated with the study BB2121-MM-001 led to the update of section 5.1 “Pharmacodynamic properties” of the Summary of Product Characteristics and the removal of corresponding obligation from Annex II of the product information [114].

Regarding Carvykti, one of the two specific obligations imposed has been fulfilled, particularly the submission of the final study results of the pivotal study CARTITUDE-1 (MMY2001) with set date for December 2022. The results were effectively submitted within the specified timeframe as evidenced in the CAT and CHMP minutes of December 2022 [113].In the case of Carvykti, the SmPC sections 4.4 “Special warnings and precautions for use” and 4.8 “Undesirable effects” were updated. This update aimed to provide current warnings on cytokine release syndrome (CRS), neurologic toxicities, and the grading of related events, and to update the list of adverse drug reactions based on previously reviewed data from studies MMY2001 and MMY2003 as well as an additional internal characterisation of neurotoxicity risk [115][116].

With regard to Zynteglo, three specific obligations were requested, of which two have been fulfilled. These obligations were related to the submission of interim and final data from the clinical studies HGB207 and HGB-212. Evidence of fulfilment were observed in the CAT minutes of February 2022 [117]. No updates to the SmPC or further updates on the EPAR-Procedural steps taken and scientific information after authorization, were verified, possibly due to the withdrawal of the marketing Authorization in the EU in March 2022.

3.4. Additional pharmacovigilance activities: RMP Category 3 studies

3.4.1. RMP Category 3 studies: objectives, studies design, and completion rates

Category 3 studies in the Risk Management Plan (RMP) are mandated additional pharmacovigilance activities primarily aimed at investigating specific safety concerns or evaluating the effectiveness of risk minimization measures. These studies may include ongoing trials (e.g., providing a report from clinical trials) or planned studies involving the conduct of a planned study. The rationale for requiring additional pharmacovigilance activities (category 3 studies) is centred in the safety concerns of the ATMPs RMPs i.e., in potential and identified important risks or important missing information, such as the risks of a medicinal product use in patient populations for which safety information is limited or missing e.g., pregnant women, specific age groups or long-term safety data.

The Category 3, additional pharmacovigilance activities of the selected ATMPs were more commonly linked to clinical trials (n=20) compared to observational studies (n=8), studies assessing the effectiveness of Risk Minimization Measures – RMMs (n=7), or other measures such as quality-related or assay implementations (n=9).

Concerning the additional pharmacovigilance activities consisting of cross-sectional surveys aimed at evaluating the effectiveness of risk minimization measures, these were included in the RMP of six advanced products, namely for the CMA approved medicinal products, Tecartus, Carvykti, Roctavian and Hemgenix and also in the RMP of the medicinal products Yescarta and Imlygic. Four cross-sectional surveys were registered in the EU PAS Register. Notably, the surveys evaluating the effectiveness of the Carvykti healthcare professionals Educational Program and Product Handling Training, the healthcare professionals survey concerning Roctavian educational material, and the Hemgenix Survey (CSL222_5001) to assess the effectiveness of additional risk minimization measures for Hemgenix among EU prescribers, were exceptions.

Of the seven cross-sectional surveys, three have been completed and finalized. Specifically, the cross-sectional studies 20180099 and 20180062 conducted concerning the medicinal product Imlygic, and study KT-EU-471-0116 carried out for the medicinal product Yescarta. However, the remaining four cross-sectional surveys, namely study KT-EU-472-5966 for Tecartus has an ongoing status, and the surveys for Carvykti, Roctavian, and Hemgenix, still have a planned status according to the EPAR, as no EU PAS registrations were found.

The Carvykti survey specifically refers to a survey to measure the effectiveness of the HCP Educational Programme and the Product Handling Training. The survey serves as an additional risk minimization measure to provide guidance and enhance awareness among HCPs about the risks associated with cytokine release syndrome and neurologic toxicity, as well as strategies to mitigate these risks [118]. On the other hand, the ongoing cross-sectional survey study added to the RMP of the medicinal product Tecartus, referred to as the study (KT-EU-472-5966, EUPAS104052), has the primary objective of measuring healthcare professionals (HCPs) awareness and knowledge of RMMs for Tecartus. Precisely to measure HCPs knowledge of known important identified risks associated with Tecartus, assess whether HCPs understand how to identify and treat cytokine release syndrome or serious neurologic adverse events, and determine whether healthcare professionals understand the proper handling procedures and appropriate method of administration of Tecartus to effectively preserve the viability of the product. Additionally, to assess the level of awareness among HCPs regarding the patient alert card, as well as their adherence to distributing and adequately informing patients about the contents of the educational material [119].

Moreover, the healthcare professional survey, within the Roctavian RMP, was not assigned a specific identifier number. This survey aims to evaluate the effectiveness of provided educational materials, specifically addressing concerns related to hepatotoxicity, thromboembolic events, and transmission to third parties [120].

Regarding the Hemgenix survey, it aims to evaluate the extent to which healthcare professionals have received, utilized, and understood the additional RMM tools. This is assessed by determining the proportion of targeted HCPs who acknowledge receipt, usage, and comprehension of the tools, as well as providing accurate responses to questions concerning key risk messages outlined. The survey addresses concerns such as hepatotoxicity, the risk of malignancy due to vector integration, and thromboembolic events [121].

In general, the observational cross-sectional studies were geared towards evaluating the effectiveness of RMMs among both healthcare professionals and patients. However, it is noteworthy that the majority of these studies primarily focused on HCPs.

The medicinal product Imlygic was approved with educational materials targeting both physicians and patients. For physicians the primary additional risk minimization measure was the physician education booklet (PEB) with a PASS, category 3 in the RMP (survey) required to assess the effectiveness of the information provided in the PEB (Study 20180099, EUPAS31188). For patients the primary additional risk minimization measure was the Patient Safety Brochure and Patient Alert Card also with a PASS, category 3 in the RMP (survey) required to assess the effectiveness of the information provided in Patient Safety Brochure and Patient Alert Card (Study 20180062, EUPAS31213). Each study aimed to include approximately 50 eligible patients and physicians. These studies had secondary objectives focusing on different aspects for both HCPs and patients. For HCPs, the secondary objectives included assessing the receipt and reading of the education booklet, as well as understanding the requirements for distributing the Patient Information Leaflet (PIL), Patient Safety Brochure, and Patient Alert Card [122][123].

On the patient side, the secondary objectives involved evaluating the receipt, reading, and knowledge (understanding the purpose) of the Patient Alert Card. The knowledge assessment for both patients and physicians encompassed various domains, such as understanding the risks of disseminating herpetic infection in immunocompromised patients, the risk of spreading the Imlygic virus to close contacts, the risk of symptomatic herpes infection during or after treatment, knowledge regarding the use of Imlygic during pregnancy, among others [123].

Additionally, is noteworthy that both aforementioned post-authorization safety studies were registered EU PAS register in December 2019, virtually four years after the initial approval

of Imlygic. The results of the study targeting physicians (study 20180099) were posted on the EU PAS register in December 2020, approximately one year after their registration. On the other hand, the results of the study targeting patients (study 20180062), were posted in February 2022, around two years after the registration.

In the case of Yescarta, the survey study (KT-EU-471-0116, EUPAS28523) had the objective of measure the awareness and knowledge of RMMs for Yescarta, as described in the RMP, specifically, to conduct a survey to measure knowledge and understanding of the key messages in the HCP-directed additional RMMs and SmPC for Yescarta, including how to mitigate risk of CRS, neurotoxicity and how to correctly handle and administer the product to ensure product viability [124].

The inclusion criteria for the KT-EU-471-0116 survey comprised of HCPs in selected European countries who have received training on the additional RMMs and prescribe, dispense, handle, or administer Yescarta or manage patients experiencing Yescarta related adverse drug reactions [124]. The primary measure of success for the effectiveness endpoints was achieving a knowledge level of ≥ 80% among HCPs for each of the 20 key questions in the survey. The overall composite, weighted knowledge level across all 20 questions was determined to be 85.7%. These results indicate that HCPs exhibited a strong understanding of the important identified risks associated with Yescarta, as well as the correct handling and administration of the medication. Notably, the non-interventional, cross-sectional survey was initially registered on March 25, 2019, less than a year after the initial approval of Yescarta and the findings of the study were subsequently posted on the EU PAS register in June 2021 [124].

3.5. ENCePP and clinical trials registrations

To promote openness about both mandatory and voluntary post-authorization safety studies and to enable seamless communication of pharmacovigilance data among all relevant stakeholders, it is strongly recommended that MAHs ensure the availability of study information in the EU electronic register of Post-authorization Studies (EU PAS Register), including of studies conducted outside the EU, such as non-interventional studies requested by non-EU regulatory authorities [125].

Particularly, as a mandatory requirement all non-interventional PASS that are imposed as a condition to the marketing authorization (RMP category 1 and 2 studies) must be published in the register with studies protocols and final studies reports and its abstract of results. Protocols should be promptly uploaded upon their completion (protocol finalisation) and prior to the commencement of study data collection [125].

Moreover, the purpose of the register extends to non-imposed studies, such as those required as additional pharmacovigilance activities in the RMP (category 3). Therefore,

marketing authorization holders should also enter in the EU PAS Register all non-interventional PASS required in the risk management plan agreed in the EU or conducted voluntarily in the EU [125]. Moreover, it is advised to ensure that updates to the study protocol in the event of significant amendments, progress reports, and the final study report are promptly entered into the register, preferably within a two-week timeframe following their finalisation [125].

The analysis of the extracted data as of December 2023, revealed that a total of twenty (20) post authorization studies required or imposed by the EMA were entered on the European Union (EU) PAS Register held by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), by conducting a search using terms such as the brand name of the medicine, the international non-proprietary name (INN) of the substance, and the study title acronym or number/code, if available.

Fourteen (14), 70% of these studies comprise studies imposed as Annex II conditions to the MA and six (6), 30% required as additional pharmacovigilance activities in the RMP (category 3 studies). Four of the latter being cross sectional studies aiming to assess the effectiveness of RMMs. No studies imposed as a Specific obligation were identified in the register in the context of the selected advanced medicinal products under study with conditional marketing authorizations. As evident, a significant proportion of the registered studies are imposed studies required as Annex II conditions.

The registered post-authorization studies consisted of non-interventional post-authorization safety studies, which primarily employed a prospective cohort study design based on secondary use of data from existing data sources, mainly patient outcome registries, such as the EBMT and CIBMTR registries. No clinical studies associated with the selected ATMPs post authorization measures were identified to be registered, which is aligned with the register's primary focus on observational research.

Study protocols were available for 60% of the registered studies, totalling 12 post-authorization studies. Concerning studies without protocols associated, it is noteworthy that the absence of protocols may be attributed to various factors, for instance to study withdrawal. Specifically, this is the case of the planned non-interventional registry PASS of the medicinal product Provenge (EUPAS8254 - study START). Additionally, among the other studies for which protocols were not available, one had a planned status, namely the post-authorization safety study 68284528MMY4009 (EUPAS49370) evaluating the safety of multiple myeloma patients treated with the relatively recently approved medicinal product Carvykti. In addition, other studies with planned status were found to have no associated protocols, such as Roctavian studies 270-801/EUPAS49243 and 270-601/EUPAS49071, Hemgenix study EUPAS106066, and Zynteglo study REG 501/EUPAS36487.

Others corresponded to ongoing studies, where the data collection already had been started, including the study 68284528MMY4004 (EUPAS49218), a prospective non-interventional PASS concerning the medicinal product Carvykti, and the study 20130193 (EUPAS15128), a prospective cohort study of melanoma patients treated with Imlygic to assess the long-term safety and the risk of herpetic infection among patients, close contacts, and healthcare providers. Furthermore, the fact that protocols for these ongoing studies, which have already initiated data collection, were also unavailable in the EU PAS register, indicates a lack of adherence to the requirement set forth by the Guideline on good pharmacovigilance practices (GVP) – Module VIII and the ENCePP Code of Conduct, to enter the full study protocol before the commencement of data collection or extraction.

Moreover, it was verified that the publication of the study protocol for the study 20130193 of the medicinal product Imlygic was possibly postponed until study finalisation, as indicated in the register section for study protocol publication, that the protocol will be made available when the study is completed, as evidenced by “available when the study ends”.

Overall, out of the registered studies, there were (n=4) finalised studies, (n=7) with a planned status and (n=9) that are ongoing. Moreover, it is worth mentioning that for all finalised studies, the results have been appropriately uploaded and made available in the register.

Considering only newly studies referring to studies not already ongoing at the time of application, hence, to be initiated at post-authorization phase (opposite to ongoing continued studies) the analysis indicates that 13 observational studies required (voluntary) or imposed as post-authorization measures were not entered in the register. Among these non-registered studies, (n=2) account for specific obligations, specifically imposed under the conditional MA of the medicinal product Tecartus, (n=7) for Annex II conditions and (n=4) for additional pharmacovigilance activities in the RMP (category 3 studies). Incorporating the consideration of newly conducted clinical trials to be conducted in the post-authorization phase, it was revealed that (n=4) of these trials were not included in the register. Importantly, some of the post-authorization studies not registered in the EU PAS register can be associated with the EU withdrawal of medicinal products (Provenge and MACI).

Additionally, some of the non-interventional post-authorization studies not registered consisted of subgroup analysis from existing observational studies (Kymriah, subgroup analysis from CCTL019B2401), and follow-up studies of RCT participants (Luxturna, study AAV2-hRPE65v2-LTFU-01; Zolgensma, study AVXS-101-LT-001)

Upon review of registration on ClinicalTrials.gov, a total of 59 studies linked to post-authorization measures were identified, among them, the majority comprised interventional studies associated with PAMs (n=42), while a smaller subset consisted of observational studies associated to PAMs (n=17). Regarding the status of studies registered on

ClinicalTrials.gov, regardless of their design, 25 studies had a completed or terminated status, 23 were listed as not recruiting, and 11 were either enrolling by invitation or actively recruiting.

Table 5. Summary of extracted data from ENCePP and ClinicalTrials.gov.

ClinicalTrials.gov status	**(n=) studies**
Active, not recruiting	23
Recruiting	9
Enrolling by invitation	2
Terminated	3
Completed	22
Total registered	59
Study type	
Interventional	42
Observational	17
Associated study PAM category	**ClinicalTrials.gov (n=) studies**
Annex II condition	17
Specific obligation	16
Additional PhV RMP (category 3 study)	26
EU PAS register status	**(n=) studies**
Planned	7
Ongoing	9
Finalised	4
Total registered	20
Study type	
Interventional	0
Observational	20
Associated study PAM category	**EU PAS register (n=) studies**
Annex II condition	14
Specific obligation	0
Additional PhV RMP (category 3 study)	6
Registered in both databases	4

3.6. EU PAMs status

Through consultation of EU measures status information sources, including the EU PAS register, ClinicalTrials.gov database, and primarily through the review of evidence from study/measures submissions containing final or interim results found in the EPAR - Procedural steps taken and scientific information after authorization, as well as from Committees minutes, it was discerned that out of the total 97 EMA post-authorization measures, 59 were either ongoing or still planned, 22 were fulfilled, and 16 with an undisclosed or missing status as of December 2023, table 4. The “missing” adscription relates to post-authorization measures which had set dates reached, but no evidenced of their fulfilment was found.

Significantly, these pertained to Post-authorization Measures (PAMs) of the medicinal products MACI, Provenge, and Zynteglo, which are withdrawn from the European market, as

well as to Annex II conditions regarding the medicinal product Breyanzi. Although the latter post-authorization measures could potentially have been complied with and on time, updated public information was not available at the time of the data cut verification.

The fulfilled post-authorization measures were more frequently associated with ongoing clinical trials at MA application (n=15); however, these fulfilled measures were relatively evenly distributed among the categories, i.e., Annex II conditions, Specific Obligations, and category 3 studies in the RMP. Among the fulfilled measures (n=20), only three were associated with requests to conduct or submitted results of observational studies, with two of them comprising subgroup analyses derived from an ongoing observational study (Kymriah, PAES subgroup analysis from CCTL019B2401). The other remaining completed observational study related PAM pertains to study 20120139, a category 3 study in the RMP of Imlygic, which was already in progress/ongoing at the time of the MA application. This particular study was a multicenter, observational registry study aimed at evaluating the survival and long-term safety of subjects who have previously received Imlygic in clinical trials.

Table 6. Overview of the EMA PAMs and associated studies extracted.
PAM, Post-Autorization Measure; RCT, Randomized Clinical Trial; NRCT, Nonrandomized Clinical Trial; Missing, referring to information not available on consulted sources.

Product brand name	Study number or description	PAM Category	PAM Objectives	Observational study design	Interventional study: Phase Comparator Masking Allocation	Estimated subjects Sample Size	Status ClinicalTrials.gov based	Status EU PAS based	Submission status
Provenge	P13-1 (EU registry) | EUPAS8254	Annex II condition	Long term safety	Prospective study registry based		850	Not registered	Withdrawn - Planned	Missing
	PROCEED/P10-3 (US Registry)	Annex II condition	Long term safety	Prospective study registry based		1500	Completed	Not registered	Missing
	Study P-11	Annex II condition	Follow-up efficacy		Phase 3 Placebo Double blind RCT	159	Completed	Not registered	Missing
	Study P12-1	Annex II condition	Follow-up efficacy	Prospective Case-Only		2000	Terminated	Not registered	Missing
	Study P11-3	Additional PhV	Safety and efficacy		Phase 2 Active Open-label RCT	60	Completed	Not registered	Missing
	Study P13-2	Additional PhV	Safety		Phase 2 Missing Missing Missing	Missing	Not registered	Not registered	Missing
	Measure coagulation P13-2	Additional PhV	Safety			NA	NA	NA	Missing
	Re-evaluate the CD54 up regulation acceptance criterion, based on quality and clinical data from patient batches manufactured in EU	Additional PhV	Safety Quality			NA	NA	NA	Fulfilled
	Investigate and implement a rapid microbial detection	Additional PhV	Safety Quality			NA	NA	NA	Missing

	method for product release								
MACI	MACI00809	Additional PhV	Long term safety and efficacy	Prospective Cohort study	Active Open-label RCT	144	Completed	Not registered	Missing
	Study (55-1702-1)	Additional PhV	Safety		Phase 3 Active Open-label RCT	45	Recruiting	Not registered	Missing
	Study to validate a newly developed potency assay	Additional PhV	Safety Quality			NA	NA	NA	Missing
Imlygic	Study 20120325	Annex II condition	Efficacy		Phase 2 None Open-label Single-arm	110	Completed	Not registered	Fulfilled
	Study 20110266	Annex II condition	Safety and efficacy		Phase 2 Active Open-label RCT	150	Completed	Not registered	Fulfilled
	Study 20110265	Annex II condition	Efficacy		Phase 3 Placebo in combination with pembrolizumab Double blind RCT	110	Terminated	Not registered	Fulfilled
	Study 20120139 | EUPAS43115	Additional PhV	Long-term safety and efficacy	Prospective study registry based		186	Completed	Finalised	Fulfilled
	Study 20130193 | EUPAS15128	Additional PhV	Long-term safety and efficacy	Prospective study registry based		920	Recruiting	Ongoing	
	Study 20120324	Additional PhV	Biodistribution and shedding pharmacokinetics (safety)		Phase 2 None Open-label Single-arm	30	Completed	Not registered	Fulfilled
	Study 20180099 | EUPAS31188	Additional PhV	Safety Effectiveness of RMM - Assessing physician safety knowledge	Cross-sectional study		50	Not registered	Finalised	Fulfilled

	Study 20180062 | EUPAS31213	Additional PhV	Safety Effectiveness of RMM - Assessing patient safety knowledge	Cross-sectional study		50	Not registered	Finalised	Fulfilled
	Study 20110261	Additional PhV	Safety and tolerability		Phase 1 None Open-label NRCT	18	Completed	Not registered	Fulfilled
	Study to be determined	Additional PhV	Safety and efficacy		RCT Missing Missing RCT	Missing	Missing	Not registered	
	Testing of anti-granulocyte macrophage colony stimulating factor antibodies	Additional PhV	Safety				NA	NA	
	qPCR testing for talimogene laherparepvec DNA	Additional PhV	Safety				NA	NA	
Yescarta	KT-EU-471-0117 | EUPAS32539	Annex II condition	Long term safety	Prospective study registry based		750	Not registered	Ongoing	
	KT-EU-471-0116 | EUPAS28523	Additional PhV	Safety Effectiveness of RMM - Assessing prescribers knowledge	Cross-sectional study		1617	Not registered	Finalised	Fulfilled
	ZUMA-1	Additional PhV	Safety and efficacy		Phase 1/2 None Open-label Single-arm	124	Completed	Not registered	
	ZUMA-2	Additional PhV	Safety and efficacy		Phase 2 None Open-label Single-arm	70	Active, not recruiting	Not registered	
	ZUMA-3	Additional PhV	Safety and efficacy		Phase 1/2 None Open-label Single-arm	75	Active, not recruiting	Not registered	
	ZUMA-4	Additional PhV	Safety and efficacy		Phase 1/2 None Open-label	75	Active, not recruiting	Not registered	

					Single-arm				
	ZUMA-5	Additional PhV	Safety and efficacy		Phase 2 None Open-label Single-arm	50	Active, not recruiting	Not registered	
	ZUMA-6	Additional PhV	Safety and efficacy		Phase 1/2 None Open-label Single-arm	31	Completed	Not registered	
Kymriah	Study CCTL019B2401 | EUPAS32497	Annex II condition	Long-term safety	Prospective study registry based		3415	Not registered	Ongoing	
	PAES (ANX006) Subgroup analysis CCTL019B2401	Annex II condition	Safety and efficacy	Prospective study registry based - subgroup analysis from (B2401)		43	Not registered	Not registered	Fulfilled
	CCTL019B2401 Subgroup analysis	Annex II condition	Efficacy	Prospective study registry based - subgroup analysis from (B2401)		Missing	Not registered	Not registered	Fulfilled
	Follow up CCTL019C2201	Annex II condition	Long-term efficacy and safety		Phase 2 None Open-label Single-arm	100	Completed	Not registered	Fulfilled
	Study CCTL019H2301	Annex II condition	Long-term efficacy and safety		Phase 3 Active Open-label RCT	318	Active, not recruiting	Not registered	
	CCTL019A2205B	Additional PhV	Long-term efficacy and safety	Observational - Long Term Follow Up (LTFU) Study		500	Recruiting	Not registered	
Luxturna	SPKRPE-EUPASS | EUPAS31153 | CLTW888A12401	Annex II condition	Long term safety	Prospective study registry based		300	Active, not recruiting	Ongoing	
	AAV2-hRPE65v2-LTFU-01	Annex II condition	Long-term efficacy and safety	Observational - Long Term Follow Up (LTFU) Study		41	Active, not recruiting	Not registered	
Zolgensma	AVXS-101-RG001	Annex II condition	Long-term efficacy and safety	Prospective study registry based		500	Recruiting	Not registered	

	Further evaluate finished product specifications	Annex II condition	Consistency of product quality and optimal clinical outcome (quality and efficacy)				NA	NA	Fulfilled
	AVXS-101-CL-302	Specific obligation	Confirm efficacy, safety and tolerability		Phase 3 None Open-label Single-arm	30	Completed	Not registered	Fulfilled
	AVXS-101-CL-303	Specific obligation	Confirm efficacy, safety and tolerability		Phase 3 None Open-label Single-arm	15	Completed	Not registered	Fulfilled
	AVXS101-CL-304	Specific obligation	Confirm efficacy, safety and tolerability		Phase 3 None Open-label Single-arm	44	Completed	Not registered	Fulfilled
	AVXS-101-LT-001	Additional PhV	Long term safety	Observational - Long Term Follow Up (LTFU) Study		15	Active, not recruiting	Not registered	
	AVXS101-LT-002	Additional PhV	Long-term safety and efficacy	Observational - Long Term Follow Up (LTFU) Study		308	Active, not recruiting	Not registered	
Tecartus	KTE-EU-472-6036 | EUPAS45813	Annex II condition	Long-term safety and efficacy	Prospective study registry based		350	Not registered	Ongoing	
	Prospective study based on data from KTE-EU-472-6036 registry	Specific obligation	Confirm the long-term efficacy and safety	Prospective study registry based		Missing	Not registered	Not registered	
	24 months Follow up of the study KTE-C19-102/ZUMA-2	Specific obligation	Confirm the long-term efficacy and safety		Phase 2 None Open-label Single-arm	70	Active, not recruiting	Not registered	Fulfilled
	Follow-up ZUMA-3 (Part 1 and Part 2)	Specific obligation	Confirm the long-term efficacy and safety		Phase 1/2 None Open-label NRCT	75	Active, not recruiting	Not registered	
	Prospective study based on data from a registry - for r/r ALL	Specific obligation	Confirm the long-term efficacy and safety	Prospective study registry based		Missing	Not registered	Not registered	

	Prescriber Survey KT-EU-472-5966 | EUPAS104052	Additional PhV	Safety Effectiveness of RMM - Assessing prescribers knowledge	Cross-sectional study		100	Not registered	Ongoing	
	KTE-C19-108 (ZUMA-8)	Additional PhV	Safety and tolerability		Phase 1 None Open-label NRCT	108	Terminated	Not registered	
Abecma	24 months Follow up of the BB2121-MM-001/KarMMa	Specific obligation	Confirm efficacy and safety		Phase 2 None Open-label Single-arm	94	Active, not recruiting	Not registered	Fulfilled
	Study KarMMa-3 | (BB2121-MM-003)	Specific obligation	Confirm efficacy and safety		Phase 3 Active Open-label RCT	381	Active, not recruiting	Not registered	
	GC-LTFU-001	Additional PhV	Long-term safety		Phase 2/3 None Open-label Single-arm	200	Recruiting	Not registered	
	Transgene assay on patients that develop a secondary malignancy from GC-LTFU-001	Additional PhV	Safety				NA	NA	
	BB2121-MM-006 | EUPAS45152	Annex II condition	Long-term efficacy and safety	Prospective study registry based		1000	Not registered	Ongoing	
Carvykti	CARTITUDE-1 (MMY2001)	Specific obligation	Confirm Safety and efficacy		Phase 1/2 None Open-label Single-arm	84	Completed	Not registered	Fulfilled
	CARTITUDE-4 (MMY3002)	Specific obligation	Confirm Safety and efficacy		Phase 3 Active Open-label RCT	400	Active, not recruiting	Not registered	
	68284528MMY4002	Annex II condition	Long-term efficacy and safety	Observational - Long Term Follow Up (LTFU) Study		228	Recruiting	Not registered	
	68284528MMY4004 EUPAS49218	Annex II condition	Long-term efficacy and safety	Prospective study registry based		1500	Not registered	Ongoing	

	68284528MMY4009 EUPAS49370	Annex II condition	Long-term efficacy and safety	Prospective study registry based		300	Not registered	Planned	
	Survey	Additional PhV	Safety Effectiveness of RMM - Assessing clinical knowledge	Cross-sectional study		30	Not registered	Not registered	
Breyanzi	EUPAS103852 | CA082-1105 Submission of batch analysis and corresponding clinical safety and effectiveness data	Annex II condition	Product quality and clinical outcomes (quality and efficacy)	Prospective study registry based		30	NA	Planned	
	JCAR017-BCM-005 | EUPAS103855	Annex II condition	Long-term safety and efficacy	Prospective study registry based		750	Not registered	Planned	
	24 months Follow-up data of subjects in the study 017001	Annex II condition	Long-term safety and efficacy		Phase 1 None Open-label NRCT	70	Active, not recruiting	Not registered	Missing
	24 months Follow-up data of subjects in the study JCAR017-BCM-001 Cohort 1	Annex II condition	Long-term safety and efficacy		Phase 2 None Open-label Single-arm	124	Active, not recruiting	Not registered	Missing
	GC-LTFU-001	Additional PhV	Long-term safety and efficacy	Observational - Long Term Follow Up (LTFU) Study		200	Recruiting	Not registered	
	Transgene assay on patients that develop a secondary malignancy from GC-LTFU-001	Additional PhV	Safety				NA	NA	
Zynteglo	REG 501 | EUPAS36487	Annex II condition	Long-term safety and efficacy	Prospective study registry based		350	Not registered	Ongoing	

	Reevaluate the acceptance criteria for attributes related to potency tests	Annex II condition	Quality - safety				NA	NA	Missing
	Study HGB-207	Specific obligation	Confirm Safety and efficacy		Phase 3 None Open-label Single-arm	15	Completed	Not registered	Fulfilled
	Study HGB-212	Specific obligation	Confirm Safety and efficacy		Phase 3 None Open-label Single-arm	15	Completed	Not registered	Fulfilled
	LTF-303	Specific obligation	Confirm Safety and efficacy		Phase 3 None Open-label Single-arm	27	Active, not recruiting	Not registered	
Skysona	LTF-304	Annex II condition	Long-term safety and efficacy	Prospective Case-Only		17	Active, not recruiting	Not registered	
	REG-502	Annex II condition	Long-term safety and efficacy	Prospective study registry based		Missing	Not registered	Not registered	
	ALD-102	Additional PhV	Safety and efficacy		Phase 2/3 None Open-label Single-arm	15	Completed	Not registered	
	ALD-104	Additional PhV	Safety and efficacy		Phase 3 None Open-label Single-arm	20	Completed	Not registered	
Roctavian	Study 270- 401 (Follow-up study)	Annex II condition	Long-term safety and efficacy	Prospective Cohort study		172	Enrolling by invitation	Not registered	
	Study 270-801 EUPAS49243 GENEr8-GTR	Annex II condition	Long-term safety and efficacy	Retrospective study registry based		720	Not registered	Planned	
	Study 270-601 EUPAS49071 GENEr8-COAS	Annex II condition	Long-term safety and efficacy	Prospective Cohort study		200	Not registered	Planned	

	5 years follow-up of Study 270-301	Specific obligation	Confirm the efficacy and safety		Phase 3 None Open-label Single-arm	40	Active, not recruiting	Not registered	
	Final results of Study 270-303. Interim data from studies 270-203 and 270-205	Specific obligation	Confirm the efficacy and safety		Phase 3 None Open-label Single-arm	20	Active, not recruiting	Not registered	
	Study 270-201	Additional PhV	Dose-Escalation, Safety, Tolerability and Efficacy		Phase 1/2 None Open-label Single-arm	12	Active, not recruiting	Not registered	
	Study 270-302	Additional PhV	Efficacy and Safety		Phase 3 None Open-label Single-arm	40	Completed	Not registered	
	Healthcare professional Survey	Additional PhV	Safety Effectiveness of RMM - Assessing clinical knowledge	Cross-sectional study		Missing	Not registered	Not registered	
	Embryo-Foetal Developmental Toxicity Study	Additional PhV	Toxicity Study - safety			Missing	NA	NA	
	270-203	Additional PhV	Safety, Tolerability and Efficacy		Phase 1/2 None Open-label Single-arm	10	Active, not recruiting	Not registered	
	270-205	Additional PhV	Safety, Tolerability, and Efficacy		Phase 1/2 None Open-label Single-arm	20	Recruiting	Not registered	
Hemgenix	CSL222_4001 | EUPAS106066	Annex II condition	Long-term safety and efficacy	Prospective study registry based		500	Recruiting	Planned	
	Follow-up of the pivotal Study CT-AMT-061-01/CSL222_2001	Specific obligation	Confirm the efficacy and safety		Phase 2 None Open-label Single-arm	3	Completed	Not registered	

	Follow-up of the pivotal Study CT-AMT-061-02/ CSL222_3001	Specific obligation	Confirm the efficacy and safety		Phase 3 Active Open-label NRCT	56	Active, not recruiting	Not registered	
	1-year follow-up interim analysis of subjects enrolled in Study CSL222_4001	Specific obligation	Confirm the efficacy and safety	Prospective study registry based		50	Not registered	Not registered	
	Extension Study CSL222_3003	Additional PhV	Long-term safety and efficacy	Prospective Cohort study		56	Enrolling by invitation	Not registered	
	Survey - CSL222_5001	Additional PhV	Safety Effectiveness of RMM - Assessing clinical knowledge	Cross-sectional study		Missing	Not registered	Not registered	

3.7. Legally Binding Measures

Article 46 of Regulation (EC) No 1901/2006, commonly known as the 'Paediatric Regulation,' establishes the obligation for marketing authorization holders to submit any studies sponsored by them that concern to the use of an authorised medicinal product in the paediatric population. This requirement remains applicable irrespective of whether these studies are part of a paediatric investigation plan. For centrally authorised medicinal products, these studies are to be submitted to the EMA [87]. According to the Paediatric regulation, MAHs have the obligation to submit results of paediatric studies within 6 months after their completion.

Among the 15 ATMPs under study, four were granted with a full waiver to paediatric requirements, namely a class waiver for the medicinal product Provenge and product-specific full waivers for the medicinal products Tecartus, Abecma and Carvykti. For the medicinal product Yescarta an application for modification of the agreed paediatric investigation plan was submitted to the EMA on 19 November 2021 referring to extend the previously waiver to cover the remaining subsets of the paediatric population [126].

Other waivers were identified for the ATMPs PIPs which did not preclude the paediatric requirements completely (partial waivers), for instance, waivers for the specific medicines target conditions, referring to the paediatric population weighing or age limitations, administration routes or waivers granted on the grounds that medicinal products do not represent a significant therapeutic benefit over existing treatments for paediatric patients or do not represent a significant therapeutic benefit as clinical studies are not feasible.

A total of 23 clinical trials were identified within the paediatric investigation plans of the selected ATMPs, alongside additional non-clinical studies, extrapolation studies, observational research, and quality-related analyses. Additionally, 12 clinical trials were identified, through screening of the EU Clinical Trials Register, targeting the pediatric population and not associated with the ATMPs PIPs, but sponsored by the MAHs. These pediatric studies, unrelated to respective PIPs concerned the medicinal products Yescarta, Kymriah, Zolgensma, Breyanzi, Zynteglo, and Hemgenix.

The majority of clinical trials identified within the respective ATMPs PIPs were entered/registered in the EU Clinical Trials Register, totalling 14 pediatric trials (refer to Table 6). It is noteworthy that a non-PIP study (AVXS-101-CL-306) for the Zolgensma medicinal product was not found in the database, neither in the respective medicine PIP; however, was confirmed through the respective pediatric study-related variation assessment report, indicating the study completion and submission of the final report. Moreover, among the 14 registered trials, 9 have been completed, with their results available and reported.

Regardless of whether pediatric trials were PIP or non-PIP trials, among the completed registered trials with results, only three were found to have evidence of their results submitted and within the designated timeframe of 6 months from completion. This verification was done by comparing the trial end dates provided in the register with the dates of results submissions in the available assessment reports. This comparison was only performed for these trials, as no assessment variation reports were available for the other completed registered paediatric trials. Specifically, the three completed trials relate to the medicinal product Kymriah, namely the paediatric clinical studies CCTL019B2001X, CCTL019BUS03, CCLTL019C2202, and study 2 (14BT022/CCTL019B2205J).

Furthermore, another paediatric study, specifically PIP study 3 (CCTL019B2202) pertaining to the medicinal product Kymriah had final results reported through a variation assessment report (Type II variation EMEA/H/C/004090/II/0056). Notably, no updates were raised by the MAH in the procedure, and no regulatory actions were required [127].

The analysis presented here provide a considerably limited view of legally binding measures considered as PAMs. However, it suggests some compliance with registering trials in the EU Clinical Trials Register and for studies with data available, there is evidence of timely submission of results within six months of completion, indicating adherence to Article 46 of the Paediatric Regulation.

Table 7. Paediatric studies – PIP and non-PIP trials, analysis of LEGs.

ATMP	PIP Clinical Trials	EU Clinical Trials Register Status	Assessment report	Non-PIP Clinical Trials	EU Clinical Trials Register Status	Assessment report
MACI	Study (55-1702-1)	Not registered				
Imlygic	Study 3 (20110261)	Ongoing				
Yescarta	Not applicable (waivers)			KTE-C19-104	Ongoing	
Kymriah	Study 1 CCTL019B2101J/(CHP959)	Completed with results	Not found	CCTL019B2001X	Completed with results	Available
	Study 2 (14BT022/CCTL019B2205J)	Completed with results	Available	CCTL019BUS03	Completed with results	Available
	Study 3 (CCTL019B2202)	Completed with results	Available	CCLTL019C2202	Not registered	Available
	Study 5 (CCTL019G2201J)	Ongoing		CCTL019A2205B	Ongoing	
Luxturna	PIP P/0221/2015 was completed at the time of submission, no registered studies conduct by the MAH found					
Zolgensma	Study 1 AVXS-101-CL-101	Completed with results	Not found	AVXS-101-LT-002	Ongoing	
	Study 2 AVXS-101-CL-102	Completed with results	Not found	COAV101A12306	Ongoing	
	Study 3 AVXS-101-CL-302	Completed with results	Not found	COAV101A12308	Ongoing	
	Study 4 AVXS-101-CL-303	Completed with results	Not found	AVXS-101-CL-306	Not registered	Available
	Study 5 AVXS-101-CL-304	Completed with results	Not found			
	Study 8 OAV101B12301	Ongoing				
	Study 9 OAV101B12302	Ongoing				
Provenge, Tecartus, Abecma Carvykti: Not applicable (waivers)						
Breyanzi	Study 2	Not registered		JCAR017-BCM-004	Ongoing	
Zynteglo	Study 1 (HGB-207)	Ongoing		LTF-303	Ongoing	
	Study 3 (HGB-209)	Not registered				
	Study 4 (HGB-212)	Completed with results	Not found			
Skysona	P/0290/2018 was completed at the time of submission, no registered studies conduct by the MAH found					
Roctavian	Study 4	Not registered				
	Study 5	Not registered				
	Study 6	Not registered				
Hemgenix	Study 4	Not registered		CT-AMT-061-02	Ongoing	
	Study 5	Not registered				
	Study 6	Not registered				

3.8. Recommendations

Overall, during the assessment of MAs applications, recommendations to be addressed in the post authorization phase were identified for nearly all fifteen advanced therapies under study, primarily focusing on quality-related aspects not expectable to have impact on the benefit/risk balance of the ATMPs. The level of detail and information regarding these recommendations varied among the respective European Public Assessment Reports. As standout cases are the EPARs of Zolgensma and Hemgenix which particularly provided an extensive level of information regarding recommendations for future quality development, with detailed texts describing the specific recommendations. A total of 18 distinct points (Zolgensma) and 17 points (Hemgenix) for investigation were outlined in the medicine EPAR [109][110]. Noteworthy is also the case of Zynteglo EPAR, in which 14 recommendations for future quality development were mentioned, however, with far less detail [128]. For instance, included recommendations aimed at improving control of raw materials, providing additional stability data for starting materials and installing in process controls, among other.

Figure 3 provides a representation of the extent and characteristics of EMA committee(s) recommendations found in the ATMPs EPARs.

One of the recommendations provided to the applicant of Zolgensma was to develop and implement a release test for controlling the vector genome integrity, as well as the establishment of scientifically justified acceptance criteria (point for investigation 1) [110]. The applicant was advised to perform this action and re-evaluated the continued need for a release test for vector genome integrity once the results of the initial 30 batches, tested using MAH in-house method, become available [110]. Furthermore, the applicant was also advised to establish an independent assay control for the potency assay in order to monitor the performance of the assay and ensure the stability of reference standards (point for investigation 10). Notably, potency assays are designed to directly measure the therapy ability to produce the intended therapeutic effect, where correspond to a critical component of product development, manufacturing, and regulatory evaluation. The applicant was also committed to investigate the possible causes of the observed downward trends during stability (point for investigation 14). In this context, the available long-term stability data at the time of marketing authorization application of Zolgensma included a 12-month stability data for process performance qualification, supportive, and commercial final product lots stored at temperatures below -60°C. Although all acceptance criteria were met, certain downward trends were observed. The applicant pledged to continuously monitor changes in genomic titre during stability and assess potential underlying factors [110].

The EPAR of Imlygic and Abecma, in contrast, do not provide clarifying information regarding the recommendations for further development of the medicinal products. Nevertheless, it was indicated that the CAT recommended two points for further investigation in the case of Imlygic, and several points for further investigation for Abecma, yet detailed information on these recommendations is not evidenced in the respective EPARs.

Moreover, in the case of Yescarta and Skysona also no detailed textual description of recommendations was found in the product EPAR, yet it is highlighted that several points for investigation, including points related to the manufacturing process and control of the product were recommended. Notably, in the case of the Roctavian EPAR, it explicitly indicates that no recommendation has been issued regarding for future quality development.

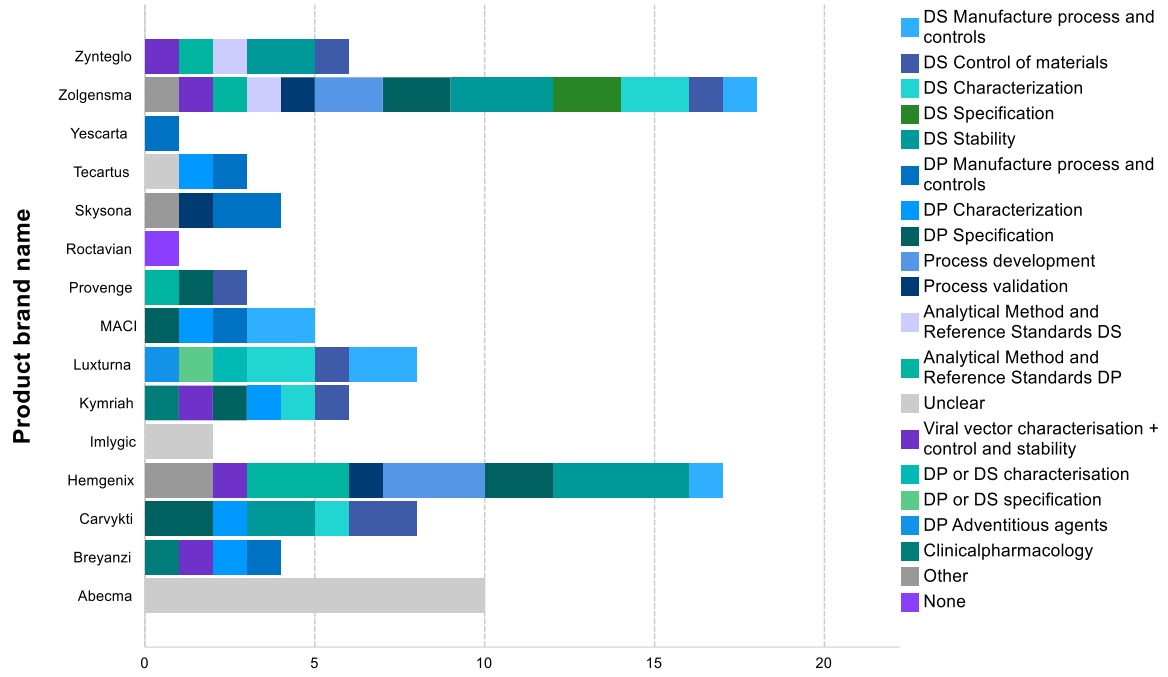

Figure 3. Frequent Recommendations stated at ATMPs EPARs. DS: Drug Substance; DP: Drug Product.

Despite the limitations on publicly available information regarding Recommendations in the ATMPs EPARs, it was possible to verify that recommendations were made to several key quality aspects involved in the development and manufacturing of the advanced therapies, including the control of materials, drug substance manufacture process and controls, characterisation of the drug substance and drug product, specifications, as well as referring to analytical methods, and reference standards.

The control of materials used in ATMPs is crucial to maintain consistency and integrity throughout the manufacturing process. This includes evaluation and selection of starting materials, excipients, and other components to ensure their quality, safety, and suitability for use in the therapy product. The source of the starting materials and raw materials used during

the manufacturing process needs to be chosen to avoid the risk of transmitting adventitious agents. For instance, in the case of the medicinal product Carvykti, the applicant committed to a recommendation referring to qualify and perform an additional identity test on the work cell bank, as in the case of Hemgenix, where the applicant was advised to include testing for porcine viruses into the testing panel for future master cell banks and master seed viruses.

Moreover, in the case of Kymriah, with a continuous manufacturing process without holding step, beginning with thawing of the leukapheresis starting material and ending with finished product formulation Recommendations were made for several points, including completing the characterisation and testing of the viral vector and the leukapheresis starting material.

Characterisation of the drug substance is another vital aspect, it involves a comprehensive analysis of the drug substance to determine its physical, chemical properties, biological activity, immuno-chemical properties, purity, and impurities by appropriate techniques to allow a suitable specification to be established. For example, in the case of Zolgensma, the applicant committed to develop a more sensitive and precise method for analysing protein impurities from drug substance and re-evaluate the specifications for impurities based on the sensitivity of the new method by the end of 2020 [110].

Specification setting is a critical step in the quality control process of medicines. Specifications define the acceptable limits for various quality attributes of the drug substance and drug product, such as purity, potency, and impurity levels. These specifications are established based on scientific knowledge, regulatory requirements, and the intended use of the medicinal product. They serve as benchmarks for quality assessment and help ensure consistent product quality and performance. In particular, for the medicinal product MACI, the applicant has proposed a potency assay specification which was deemed by the EMA consistent with the data used in the pivotal clinical trial (SUMMIT study). However, to further ensure the quality of batches manufactured, the applicant committed to develop a new potency assay validated against the ability to generate stable cartilage.

Analytical methods and reference standards are essential tools in quality control. Validated analytical methods are used to measure and assess various critical parameters and quality attributes of the drug substance and drug product. Reference standards, including reference materials and reference cells, are employed to ensure accurate and reliable measurement and comparison of results. These methods and standards contribute to the accuracy, reproducibility, and reliability of quality control testing. For instance, the medicinal product Zolgensma the applicant committed to establish an independent assay control for the potency assay by August 2020 and to monitor assay performance as well as reference standard stability [110].

The drug substance manufacture process and controls are carefully designed and implemented to ensure consistent production of high-quality therapies. Robust manufacturing processes and strict control measures are in place to minimize variations and ensure reproducibility. This includes process validation, equipment qualification, personnel training, and adherence to good manufacturing practices guidelines.

Overall, some common quality aspects raised for recommendation include, for instance, the insufficient product characterisation, inadequate control of starting materials, deficiencies in validation and qualification, and limited or insufficient stability data. Both the FDA and the EMA have acknowledged the distinctive nature and intricacy of ATMP/CGT development and have published several guidelines outlining specific requirements for quality, as well as for non-clinical, and clinical aspects of ATMPs/CGTs [129][130].

The present brief summary highlights the significance of quality matters, where becomes evident that various CMC aspects were recurrently addressed as future Recommendations during regulatory assessments of ATMPs. Although these recommendations may not directly affect the benefit/risk balance of the advanced products, the complexity of ATMPs manufacturing process and the unique challenges they present demand stringent quality standards. In this context, resolved Recommendations to be submitted as PAMs serve as essential in establishing the groundwork for therapies of quality, that are not only safe and effective but also reliable and consistent.

These recommendations serve as a supplementary guide for developers and manufacturers to further navigate the complexities of advanced therapy development and manufacturing in the post-authorization phase yet is important to acknowledge that the aforementioned examples represent only a partial perspective on potential Recommendations that were potentially proposed and committed to.

3.9. US PAMs on selected ATMPs: General characteristics

Overall, twenty-seven (27) post-marketing requirements and forty-three (43) post-marketing commitments points were identified from the FDA documents pertaining to the 15 selected ATMPs. The complete list of US post-marketing requirements is provided in table 8. With regards to PMCs, the significant majority (n=42) corresponded to non-reportable under section 506B (Non-506B Postmarketing Commitments), thus consisting of chemistry, manufacturing, and control (CMC) commitments, that are not required for approval and without a direct safety endpoint, table 10 (Annex1, supplementary information). An overall mean of 1.80 (SD ± 1.51; median: 1; IQR 1.00-2.50; range 0.00-5.00) PMRs were imposed per ATMPs regardless of statutory authority and a mean of 2.87 for PMCs either reportable or not (SD ± 3.07; median: 2; IQR 0.00-5.00; range 0.00-9.00) agreed per medicinal product.

Among the 27 PMRs, the most common category (20, in total) referred to PMRs required under the FDAAA authority section 505(o)(3), to assess a known serious risk, signs of serious risks, or unexpected serious risks related to the use or administration of the advanced therapies. The second most prevalent category consisted of the ones required under an Accelerated Approval to further describe and verify clinical benefit of the advanced products granted with this type of expedited approval, (6 PMRs in total). These latter PMRs were required under Accelerated Approval requirements, where applicable, to initial BLA approvals, but also verified for a few supplemental BLAs approvals linked new indications added. Additionally, only one study (clinical trial - study 55-1702-1) was required as a PMRs under the Pediatric Research Equity Act, to the medicinal product MACI.

Tecartus, Kymriah, and Skysona represented the medicinal products with the most post-marketing requirements, with 4 and 5 PMRs imposed, respectively, under both the FDAAA section 505(o)(3) and accelerated approval authorities. Additionally, the holder of Yescarta was obligated to conduct three (n=3) PMRs, also falling under both the FDAAA section 505(o)(3) and accelerated approval authorities. In contrast, Luxturna, Zolgensma, and Roctavian approvals were not subject to any post-marketing requirements. The majority of the remaining advanced products were subject to only one PMR, particularly under the FDAAA section 505(o)(3) authority.

Regarding the other existing categories of PMRs, no PMRs under the Animal Efficacy Rule were required for the selected ATMPs. This is attributed primarily to the fact that the marketing approvals of the ATMPs were not based on the use of data from adequate and well-controlled animal studies and also because the advanced products were developed for purposes other than reducing or preventing serious or life-threatening conditions resulting from exposure to toxic chemical, biological, radiological, or nuclear substances. Moreover, since the FDA Animal Rule inception in 2002 considering both CDER and CBER approvals, only 16 drugs have been approved under the program [131].

Moreover, considering the exemption of Pediatric Research Equity Act requirements for orphan drugs, it is important to note the case of Provenge (non-orphan product). In the evaluation of the medicinal product, pediatric study requirements were completely waived during the biologic license application assessment. This waiver stemmed from the recognition that conducting such studies would be either infeasible or highly impractical. Justification for the waiver rests on Provenge specific indication for treating asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer, a condition predominantly afflicting men aged 65 years and older. As a consequence of the highly unlikely occurrence of the condition among the pediatric population and the subsequent full waiver, there are no deferred post-marketing pediatric studies or clinical trials to pediatric populations for Provenge.

Moreover, delving into MACI requirements, as aforementioned a pediatric study (clinical trial - study 55-1702-1) for patients aged 10 to 17 was deferred as a post-marketing requirement under the Pediatric Research Equity Act until June 2025. This deferral is explained by the fact that at the time of BLA submission, data supporting approval for adult use was provided, however pediatric studies had not been completed. The respective deferred pediatric study (clinical trial - study 55-1702-1) is a prospective, open-label, randomized, phase 3 clinical trial comparing the efficacy and safety of MACI with arthroscopic microfracture in treating symptomatic patients with single or multiple full-thickness cartilage defects in the knee, with or without bone involvement [132].

Concerning the rationale behind seeking supplementary data at the post-authorization phase in the form of post-approval clinical trials and studies, most of the PMRs related to or required prospective observational studies under the FDAAA section 505(o)(3). Hence, the rationale behind their requirement was to characterize serious risks associated with the use of the ATMPs and frequently involved requests to conduct a registry or observational study based on data from existing registries. Additionally, a smaller number of clinical trials, specifically phases 3 and 2, were associated with PMRs, with the majority of these being required under Accelerated Approval, being the rationale for their requisition therefore related to the necessity for further verify and detail clinical benefits attributed to the advanced therapies during their initial assessment.

Considering the studies sample size, the number of subjects expected to be enrolled in either observational studies or clinical trials required as PMRs ranged from 24 to 1500 (median: 300; IQR 90.00-1500). The estimated median sample size of the clinical trials was 56 subjects (IQR: 37.50-85.00, ranging from 30 to 230 patients) while observational studies had a median estimated sample size of 960 subjects (IQR: 350-1500, ranging 120.00-1500.0).

3.9.1. PMRs under Food and Drug Administration Amendments Act (FDAAA), Section 505(o)(3): an in-depth analysis

Overall, the PMRs required under FDAAA section 505(o)(3)(B) were notably prevalent with a primary focus on evaluating long-term effects. Primary objectives typically centred on assessing potential serious risks linked to insertional mutagenesis-related secondary malignancies, while secondary objectives frequently included evaluations of cytokine release syndrome, neurologic toxicity, prolonged cytopenia, and infections.

The rationale behind these PMRs is substantiated by two key considerations, including that the FDA considered that relying solely on the analysis of spontaneous postmarketing adverse event reports would not sufficiently identify the serious risk of secondary malignancies and to the fact that the existing pharmacovigilance system established under section 505(k)(3)

of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) would not be sufficient to assess the specific serious risk(s). These PMRs with a particular emphasis on evaluating the potential serious risk of secondary malignancies represent a common FDA practice to ensure long-term follow-up and surveillance of human administered gene therapy products. The duration of all these studies a span period of 15 years after product administration. This timeframe is aligned with the need to ensure thorough monitoring of subjects for potential delayed adverse events that may occur following gene therapy exposure. The duration of all these studies spans a period of 15 years after product administration, aligned with the necessity for thorough monitoring of subjects for potential delayed adverse events that may occur following gene therapy administration.

Moreover, considering several factors, such as the limited number of subjects involved in clinical investigations of gene therapy products, the often incomplete 15-year duration of long-term follow-up for all recipients of investigational gene therapies, and the potential gaps in capturing all delayed adverse events in clinical trial safety data, it is not surprising that these studies were required as PMRs.

Furthermore, the majority of PMRs required under the Food and Drug Administration Amendments Act of 2007 - FDAAA authority, represented observational studies, frequently employing an observational, prospective, registry-based design (either primary data collection from a newly established registry, with or without blood/tissue collection and analysis, or secondary use of data from existing registries). The other remainder observational studies were described as prospective observational studies without further detail description about their design in the respective ATMPs FDA approval letters, summary of regulatory actions, clinical reviews or in the FDA PMC and PMR database. These studies had often briefly described study methodology information for which prevented a more granular design classification.

There were specifically four distinct cases from the required studies aimed at evaluating the risk of secondary malignancies. These cases were for instance associated with the cell therapy product Provenge and the gene therapy product Imlygic. In the case of Provenge, an observed increase in the incidence of cerebrovascular events among Provenge-treated subjects signalled a potential serious risk. Addressing this safety signal, the FDA required a PMR under the FDAAA authority (PROCEED Registry) to further assess the risk of cerebrovascular events. The postmarketing study used a cohort registry design, which, due to the Provenge target indication of metastatic castrate-resistant prostate cancer, was considered unethical and impractical to conduct as a randomized, concurrently controlled clinical trial.

On the other hand, regarding Imlygic, an injectable modified oncolytic herpes virus, the FDA highlighted the limited availability of viral shedding data. Untimely, this poses challenges

in accurately assessing the risk of Imlygic transmission to healthcare providers and patients close contacts. It was acknowledged that potential Imlygic-associated herpetic infections in patients or contacts, especially among immunocompromised individuals or pregnant women, could lead to rare but serious clinical consequences like encephalitis, keratitis, and life-threatening disseminated infection. Therefore, considering that the criteria for serious risk under section 505(o) of the FDAAA was met, the FDA required the conduction of a prospective observational cohort study on melanoma patients treated with Imlygic (Study 20130193) to characterize the risk of herpetic infection with detection of Imlygic DNA among patients, close contacts, and health care providers [133].

Other studies required under the section 505(o) of the FDAAA, not aimed at evaluating the risk of secondary malignancies included for instance CMC studies, nonclinical studies, or toxicology studies, for three medicinal products: Zynteglo, Skysona, and Hemgenix. For Zynteglo and Skysona, studies were to support the extractable and leachable data provided for the finished product bag, due to the serious risks of patient exposure to any unknown extractables and leachables [134][135]. For Hemgenix the PMRs referred to the validation of a highly sensitive and accurate assay for detecting anti-AAV5 neutralizing antibodies, while the other referred to a clinical trial to assess the association between the serious risk of bleeding and preexisting anti-AAV5 neutralizing antibodies to the vector (AAV5) capsid of Hemgenix [136].

3.9.2. PMRs under Accelerated Approval pathway Authority: an in-depth analysis

Considering the ATMPs under study, only two FDA Accelerated Approvals were granted based on initially submitted BLAs, particularly for the medicinal products Tecartus and Skysona, for the treatment of adult patients with relapsed/refractory mantle cell lymphoma and for slowing the progression of neurologic dysfunction in boys with early active cerebral adrenoleukodystrophy, respectively [137]. Two other Accelerated Approvals were granted, but through supplemental BLA submissions adding the indications of relapsed or refractory follicular lymphoma, to the medicinal products Yescarta and Kymriah, each respectively.

Within the accelerated approvals, four efficacy PMRs, namely 2 consisting of phase III controlled clinical trials and 2 phase II uncontrolled trials were required to confirm and describe clinical benefits of the medicinal products Yescarta, Kymriah and Tecartus on the aforementioned indications. Moreover, two other efficacy PMRs were required by the FDA under the Accelerated Approval for Skysona: one referred to a follow-up of all subjects who received Skysona in the studies ALD-102 and ALD-104, to assess event-free survival or the need for hematopoietic stem cell transplant for a minimum of ten years following administration; the other compelled an investigation into the event-free survival for a minimum of five years

post-treatment in newly treated 24 boys with more advanced, early active, cerebral adrenoleukodystrophy [134].

Some of these PMRs were linked to ongoing clinical trials, rather than being trials required to be conducted during the post-marketing phase. This is the case of the PMRs under accelerated approval requirements for the medicinal product Tecartus to confirm clinical benefit in patients with relapsed or refractory mantle cell lymphoma, namely an additional follow-up of all 68 subjects treated in ZUMA-2 cohort 1 and a single arm study of subjects who have not been exposed to a Bruton tyrosine kinase inhibitor. The latter single arm study comprises of a new cohort (cohort 3) of Bruton tyrosine kinase inhibitor-naive subjects introduced to ZUMA-2, with a minimum follow-up of 18 months after first objective disease response [137].

Patients with relapsed/refractory mantle cell lymphoma - r/r MCL, have poor outcomes, particularly if their cancer returns or does not respond to previous treatments such as BTK inhibitors. The FDA clinical data assessment point-out that there was a lack of available data to determine the efficacy of Tecartus in patients with r/r MCL who had not been previously exposed to BTK inhibitors. This absence of data prompted the FDA clinical team to examine the ZUMA-2 trial for subjects with limited or no exposure to BTK inhibitors in order to inform a decision regarding expansion of the indicated treatment population to r/r MCL regardless of BTK inhibitor exposure. According to the ZUMA-2 eligibility criteria, only one subject met the specified parameters. As a result, meaningful conclusions could not be drawn. Nevertheless, the FDA considered that there was no apparent mechanistic reason to suggest that patients with r/r MCL who had not been exposed to BTK inhibitors would experience a decreased rate, depth, or durability of response to Tecartus compared to those who had been exposed. Based on the FDA clinical team's recommendation to grant accelerated approval for the broad indication of relapsed/refractory mantle cell lymphoma, which was contingent on assumptions about Tecartus efficacy in BTK inhibitor-naive patients, it was therefore recommended that the efficacy of Tecartus in BTK inhibitor-naive subjects should be confirmed through the ZUMA-2 cohort 3, which would provide substantial evidence to support the consideration of converting the accelerated approval to traditional approval. As of December 2023, this postmarketing requirement is currently ongoing and its status is reflected in both the PMC and PMR database (ongoing) and on ClinicalTrials.gov (Active, not recruiting participants). The FDA has set a completion deadline of April 30, 2025, for the PMR, and the corresponding study report is expected to be submitted to the agency by October 31, 2025.

Moreover, as of December 2023, the only postmarketing requirement that had been fulfilled under accelerated approval was the follow-up of treated subjects in ZUMA-2 Cohort 1 to a minimum of 18 months from the time of first response (medicinal product Tecartus). The follow-up PMR was imposed considering that the primary efficacy FDA review issue of

Tecartus pointed out was the lack of sufficient follow-up to adequately assess duration of response. While treatment with Tecartus demonstrated a favourable overall response rate in the pivotal study ZUMA-2, the data did not establish a sufficient duration of response to demonstrate clinical benefit and support regular approval. At the time of the initial BLA, the median duration of response had not yet been reached after following all subjects in the efficacy-evaluable population with relapsed/refractory mantle cell lymphoma for a minimum of six months after first objective response. The FDA considered that there was reasonable likelihood of clinical benefit, but further evidence was needed, therefore the follow up PMR was required to further assess durability of response.

The marketing approval conversion to traditional approval of the cell-based gene therapy, Tecartus, has not yet been achieved as the fulfilment of efficacy requirements and confirmation of clinical benefits are thus far to be verified. No labelling changes/updates were observed referring to the findings of the follow up completed PMR of subjects treated in ZUMA-2 Cohort 1. However, for this specific PMR concerns of clinical benefit may be considered cleared as of conclusions summarized by a published study reporting outcomes after a 3-year follow-up of the pivotal ZUMA-2 study in relapsed/refractory MCL. The study suggests that Tecartus induced durable long-term responses with manageable safety in patients with relapsed/refractory MCL [138].

To further evaluate the measurement of clinical benefit and associated PMRs following initial drug approval through the Accelerated Approval pathway, it would be necessary to have access to additional publicly available FDA data. These would possibly provide insights and allow for a more extensive review on the FDA assessment of completed postmarketing requirements and of how clinical benefit is measured after the initial approval via this program.

3.9.3. Postmarketing Commitments: an in-depth analysis

In general, the majority of the postmarketing commitments identified related to quality aspects, and consisted of chemistry, manufacturing, and control studies, agreed to be conducted, therefore, non-reportable (non-506B PMCs). These are not subject to reporting requirements, and neither are required for approval yet are important in order to provide complete quality information.

The exception lies in a specific reportable postmarketing commitment associated with the medicinal product Abecma. The respective postmarketing commitment involves submitting an integrated final report that consolidates data from the clinical trials MM-002 and MM-003. The purpose of this report is to further characterize the safety and efficacy of Abecma specifically among African Americans with multiple myeloma. The primary objective of the analysis is to evaluate the effectiveness of Abecma in the subpopulation of African Americans

with multiple myeloma in comparison to the subpopulation of Caucasian patients, with the secondary objective to assess safety, considering that approximately 20% of the population diagnosed with myeloma in the US is African American. The deadline for submitting the final report was November 30, 2023. However, as of the data cut-off in December 2023, the PMC report was still with a pending status in the FDA's online database for post-marketing commitments and requirements, indicating that the study has not been initiated [139].

Regarding the scope of the identified PMCs, no specific precise association/trends was observed among them. Instead, a variety of distinct quality requests were agreed upon, including e.g., commitments involving quality activities related to methods development and validation, to updated or revise acceptance criteria, documentation updates and revision, such as standard operating procedures, revalidation, qualification, and requests for assay inclusion or optimization. Additionally, the analysis of the collected data on PMCs was very much limited due to redactions implemented by the FDA in accordance with the Freedom of Information Act. These were applied to certain sections of the data considered as sensitive or as confidential information.

3.10. Status and registration on ClinicalTrials.gov and on PMC and PMR database

As of December 2023, 8 out of the 27 FDA PMRs studies identified were registered on ClinicalTrials.gov. Among these PMRs, 6 are clinical trials, while 2 consist of observational studies. The final rule, or title 42 of the Code of Federal Regulation (CFR) Part 11, details the requirements for submitting registration and summary results information, including adverse event information to ClinicalTrials.gov, to improve public access to information about clinical research and promote public trust [140]. However, the low registration rate of PMR studies on ClinicalTrials.gov may be attributed to the predominance of observational studies as PMRs, while the ClinicalTrials.gov registry primarily caters to interventional studies.

Specifically, out of the studies registered on ClinicalTrials.gov, a total of (n=3) studies have been completed with results posted. In contrast to these completed studies, all the remaining registered studies, either trials or observational studies, were found to be ongoing and actively recruiting participants or active, but not recruiting.

The three completed studies as indicated by ClinicalTrials.gov status, were not found to be registered in the FDA PMC and PMR database. This suggests that the availability of these completed trials in the PMC and PMR database has exceeded the maximum one-year database timeframe. Specifically, one such completed study is PROCEED, a postmarketing study based on a registry design aimed at assessing the risk of cerebrovascular events in Provenge treated subjects. Additionally, the other completed studies pertain to the PMRs requiring the completion of an ongoing single-arm trial at the initial BLA application of Imlygic

(study 20120324) that evaluates the biodistribution and shedding of Imlygic in treated subjects, and the aforementioned additional follow-up of subjects from Cohort 1 of ZUMA-2 (Tecartus).

All these completed PMRs were required under the FDAAA authority and in the case of the completed/fulfilled Imlygic PMR (study 20120324) the results were reported on ClinicalTrials.gov outside the period set by the FDA for PMR final results report submission. The FDA set the final study report to be submitted on September 30, 2016, where on ClinicalTrials.gov results were firstly posted on June 2019. This fact may be related to a potential delay in the study completion as the FDA set the applicant to complete the study by December 31, 2015, where on ClinicalTrials.gov, the “actual study completion date” is of January 17, 2017. No information from the FDA is available to evaluate delays beyond the status displayed in the FDA PMC and PMR database, and historical status cannot be accessed.

Overall, the status of the PMRs registered on ClinicalTrials.gov was found to be consistent with the status displayed in the PMC and PMR database.

Considering the status and registration on the FDA PMR/PMC database, the majority of PMRs were found to be registered. However, there were five exceptions, related to studies concerning the medicinal product Kymriah and the aforementioned completed studies/PMRs of Imlygic, Provenge and Tecartus. Moreover, as for the particular studies of Kymriah, which were required under accelerated supplemental BLAs adding new indications for the treatment of adult patients with relapsed or refractory follicular lymphoma – FL and adult patients with relapsed or refractory diffuse large B-cell lymphoma, these were not registered either in the database or on ClinicalTrials.gov.

Essentially, as of December 2023, most of the 27 PMR studies were registered on the FDA PMR/PMC database (n=22), and PMRs either had a “submitted” status (n=1), “pending” status (n=9), indicating that the studies had not been initiated, or were “ongoing” (n=12); none of the ongoing studies were behind their original schedules. The 5 exceptions relate to the 3 aforementioned completed studies/PMRs, concerning Imlygic, Provenge and Tecartus and also to PMRs studies concerning the medicinal product Kymriah.

The analysis, in general, highlights the FDA efforts towards transparency and the dissemination of study information to the public. Furthermore, the availability of this publicly information, derived from FDA letters and annual status reports submitted by applicants, suggests that applicants have actively reported on the progress of postmarketing requirements.

Table 8. Overview the FDA Post-marketing requirements extracted.

PMR, Postmarketing Requirement; FDA PMRs authorities: Postmarketing requirement under FDAAA Section 505(o)(3) authority; Postmarketing requirement under Pediatric Research Equity Act authority; Postmarketing requirement under Accelerated approval; FDAAA - Food and Drug Administration Amendments Act; PREA, Pediatric Research Equity Act; RCT, Randomized Clinical Trial; sBLA, supplemental Biologic License Application (BLA); CALD, Active Cerebral Adrenoleukodystrophy; Nab, neutralizing antibody; NA; Not Applicable; Missing, referring to information not available on consulted sources.

Product	Study	PMR Authority	Objectives	Observational study design	Interventional study phase	Comparator	Masking	Allocation	Estimated subjects Sample Size	Status PMR/PMC Database
Provenge	PROCEED Registry	FDAAA Section 505(o)(3)	Long term safety	Prospective study registry based					1500	Not registered
MACI	Pediatric Clinical Study under PREA (55-1702-1)	Pediatric Research Equity Act	Safety and efficacy		Phase 3	Active	Open label	RCT	45	Ongoing
Imlygic	20130193	FDAAA Section 505(o)(3)	Long-term safety	Prospective study registry based					920	Ongoing
	20120324	FDAAA Section 505(o)(3)	Biodistribution and shedding pharmacokinetics		Phase 2	None	Open-label	Single-arm	30	Not registered
Yescarta	KTE-C19-110	FDAAA Section 505(o)(3)	Long-term safety	Prospective study registry based					1500	Ongoing
	PMR on sBLA 125643/248 for Follicular Lymphoma indication	FDAAA Section 505(o)(3)	Long-term safety	Prospective study registry based					300	Ongoing
	KT-US-473-0133	Accelerated Approval	Efficacy		Phase 3	Active	Open-label	RCT	230	Ongoing
Kymriah	CCTL019B2401	FDAAA Section 505(o)(3)	Long-term safety	Prospective study registry based					1000	Ongoing
	PMR on sBLA 125646/76 for Diffuse Large B-cell Lymphoma indication	FDAAA Section 505(o)(3)	Long-term safety	Prospective study registry based					1500	Not registered
	PMR on sBLA 125646/663 for Follicular Lymphoma indication	Accelerated Approval	Efficacy		Phase 3	Active	Missing	RCT	Missing	Pending

	PMR on sBLA 125646/663 for Follicular Lymphoma indication	FDAAA Section 505(o)(3)	Long-term safety	Prospective study registry based					300	Not registered
Luxturna	No PMRs required.									
Zolgensma										
Tecartus	Additional follow-up from ZUMA-2 Cohort 1	Accelerated Approval	Efficacy		Phase 2	None	Open-label	Single-arm	70	Not registered
	Additional Cohort 3 to ZUMA-2	Accelerated Approval	Efficacy		Phase 2	None	Open-label	Single-arm	90	Ongoing
	KT-US-472-5655	FDAAA Section 505(o)(3)	Long-term safety	Prospective study registry based					500	Ongoing
	PMR on sBLA 125703/91 for Acute Lymphoblastic Leukemia indication	FDAAA Section 505(o)(3)	Long-term safety	Prospective study registry based					500	Ongoing
Abecma	Prospective Observational study	FDAAA Section 505(o)(3)	Long term-safety	Prospective study registry based					1500	Pending
Carvykti	68284528MMY4004	FDAAA Section 505(o)(3)	Long term-safety	Prospective study registry based					1500	Ongoing
Breyanzi	JCAR017-DLBCL-001	FDAAA Section 505(o)(3)	Long term-safety	Prospective study registry based					1500	Ongoing
Zynteglo	REG501	FDAAA Section 505(o)(3)	Long-term safety	Prospective study registry based					150	Pending
	Study to justify the sample processing steps. Extractables and leachables study for the bag and submit a toxicological risk assessment	FDAAA Section 505(o)(3)	Safety							Ongoing

Skysona	Follow up of subjects from Studies ALD-102 and ALD-104	Accelerated Approval	Efficacy	Prospective cohort study					Missing	Pending
	Study to assess event-free survival for at least five years post-treatment in 24 boys with more advanced early active CALD	Accelerated Approval	Efficacy	Missing					24	Pending
	Study to support the extractable data provided for the bag and an appropriate identification process used for the extractables	FDAAA Section 505(o)(3)	Safety						NA	Pending
	Study to evaluate leachables of the bag over the duration of the shelf-life	FDAAA Section 505(o)(3)	Safety						NA	Pending
	REG-502	FDAAA Section 505(o)(3)	Long-term safety	Prospective study registry based					120	Pending
Roctavian	No PMR required.									
Hemgenix	Validation of a sensitive and accurate assay for the detection of anti-AAV5 neutralizing antibodies, specifically to detect anti-AAV5 NAb titers up to 1:1400 or higher	FDAAA Section 505(o)(3)	Safety						NA	Submitted
	CSL222_3005	FDAAA Section 505(o)(3) - PMR	Safety		Phase 3b	None	Open-label	Single-arm	35	Pending

3.11. EU vs. US PAMs on selected ATMPs: Discussion

Between 2009 and 2023, for the 15 ATMPs studied, a total of 53 EMA-imposed PAMs, covering both Annex II conditions and Specific Obligations were identified. Furthermore, 44 non-imposable measures “required”, specifically category 3 studies within the risk management plans, were also identified, contributing to an overall total of 97 post-authorization measures from the EMA. In contrast, 27 FDA-imposed PAMs were identified, falling primarily under the purview of the FDAAA section 505(o)(3) and the Accelerated Approval authorities, while 43 agreed-upon postmarketing commitments were identified. Nevertheless, the results reveal a noteworthy difference between regulatory agencies - in the EU, the marketing authorizations of the ATMPs were accompanied by a substantially higher number of post-authorization measures compared to the approvals of the same medicinal products in the US. Hence, considering primarily the count of imposed measures, it appears to be less emphasis on mandatory post-marketing data collection via PMRs to address existent uncertainties at the time of ATMP-approval in the US.

This should be contextualized within the confines of a limited sample size of fifteen advanced medicinal products under study as well as the inclusion of the distinct post-authorization measures categories from the EMA and the FDA, with their specific frameworks as applied by each region. Notably, it is important to emphasize that the FDA and EMA could address uncertainties surrounding the safety, efficacy, and quality of medicinal products by using distinct post-authorization measures categories. The categories, as implemented by the FDA and EMA, not only vary in distribution/count but also differ in the underlying purposes guiding their respective requests rationale.

In the EU, the EMA can impose Annex II conditions at the time of marketing authorization grant or later especially considering these to be key to the benefit/risk balance of a product, therefore considering the generation of additional data for the purposes of specifically further continuing medicines balance of benefits and risks evaluation. Wherefore, for conditionally authorised medicinal products and under exceptional circumstances, Specific obligations are imposed based on the less comprehensive data presented. Therefore, the generation of additional data serve the purposes to medicine-specific remaining uncertainties that need to be addressed and precluded the continuation or renewal of the CMA. Moreover, additional pharmacovigilance activities in the RMP (category 3 studies) are required to investigate a safety concern of a medicinal product, either aimed at identifying and characterising risks, or at assessing the effectiveness of risk-minimisation activities.

In the US, a distinct measures scenario can be found. FDA post-marketing requirements under the FDAAA section 505(o)(3) authority imply the collection of data after

approval for any or all of three purposes, i.e.; to investigate a known serious risk, signals of serious risks, and to detect any unexpected serious risks when available data indicate the potential for a serious risk. Hence, the FDA can require through the latter authority a study or clinical trial that is adequate to address a serious safety concern. Other circumstances that fall into the FDA imposable PAMs require PMRs to support clinical benefit of medicines that were approved under the Accelerated Approval pathway, or those approved on preclinical data under the Animal Efficacy Rule and deferred post-marketing paediatric studies that are required under the Paediatric Research Equity Act. While, post-marketing commitments are agreed upon with applications and can concern clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology, therefore being reportable, or also non-reportable commitments relating to CMC aspects, in this case.

Study findings suggest that the nature of each category of measures have implications for the types of requests. For instance, the EMA MA Annex II conditions were frequently associated with the completion and submission of results from ongoing studies or the conduction and submission of results from new/planned studies; whereas Specific obligations primarily entailed requests for the submission of results from already ongoing clinical trials at the time of MA application, including the submission of interim and/or final data. PMRs under the FDAAA section 505(o)(3) authority were linked to the conduction and submission of new/planned observational studies whereas PMRs under the Accelerated Approval pathway authority were often associated with the completion and/or submission of results from ongoing clinical trials. Moreover, the fact that the submissions of results from ongoing clinical trials were frequently observed aligns with the majority of the selected ATMPs target orphan indications, where trials are often not yet completed at the time of marketing authorization and biologics license application submissions. Consequently, they continue in the post-Authorization setting, with requests for completion and results submission.

Furthermore, when taking into account the imposable measures in both the EU and the US, findings underline that, in the EU, EMA-imposed PAMs frequently comprised requests for data collection that spread across quality, efficacy, and safety aspects, whereas in the US, the FDA-imposed PAMs were more often limited to specific matters, such as long-term safety and clinical benefit.

For instance, within the study sample, most of the identified FDA PMRs were required under FDAAA section 505(o)(3) and focused primarily on assessing the long-term safety of the gene therapy products, specifically the potential serious risk of insertional mutagenesis-related secondary malignancies, or, less often, the assessment of specific short-term adverse events. By contrast, the type of PAM most frequently imposed by the EMA (Annex II conditions) often

emphasized a more global assessment, to further characterize and confirm the long-term safety and efficacy of ATMPs.

Additionally, the fact a significant number of ATMPs marketing authorizations were subjected to Annex II conditions aligns with the understanding that these medicinal products may pose meaningful uncertainties at the time of approval. Consequently, it is not surprising that the continuous assessment of these products' efficacy and safety profile in the postmarketing setting was deemed crucial within the ATMPs landscape, with marketing authorizations being subjected to conditions which are key in further assessing the benefit-risk balance.

Moreover, when comparing the EMA Specific Obligations imposed under CMA with the FDA Post-Marketing Requirements under the jurisdiction of Accelerated Approval, obligations imposed by the EMA also focused on a broader spectrum, addressing both the efficacy and safety of the ATMPs. In contrast, those required by the FDA concentrate specifically on efficacy, thereby aiming to describe and verify the predicted clinical benefit. Of note that in the EU, either Annex II Conditions or Specific Obligations can be applied to impose further efficacy data collection, while in the US, remaining efficacy concerns appear to be exclusively addressed through a single imposable measure category - PMRs under the Accelerated Approval pathway authority.

Apart from an analysis of the diverse underlying characteristics, rationale and objectives dictating both the EMA and FDA measures categories, the observed variation in quantities, particularly regarding the directly comparable measures (imposed EMA and FDA PAMs), may be further explained by the difference between the number of CMAs and Accelerated Approvals granted in the medicines study sample.

Within the 15 ATMPs included in this analysis, in the US, Accelerated Approvals were granted through initial summited BLAs of the medicinal Tecartus and Skysona. Furthermore, two additional Accelerated Approvals were granted, through supplemental BLAs submissions that introduced new indications to the medicinal products Yescarta and Kymriah, resulting in a total of 4 ATMPs with Accelerated Approvals in US. In contrast, under the similar approval mechanism in the EU, i.e. CMA, seven medicinal products – Zolgensma, Tecartus, Abecma, Carvykti, Zynteglo, Roctavian and Hemgenix, were granted conditional approval, and each ATMP was accompanied by at least two Specific obligations. Therefore, owing to the increased frequency of CMAs for the ATMPs under study (EU), as opposed to Accelerated Approvals (US), there is also a notable increase in the number of PAMs imposed by the EMA vs. the FDA.

While the FDA Accelerated Approval pathway and the EMA CMA share similar foundations, meaningful differences need to be considered. The Accelerated Approval

Program relies on surrogate or intermediate clinical endpoints, presumed to accurately predict clinical benefit, while the CMA relies on the premise that the benefit of immediate availability of the medicine is greater than the associated risk of requiring additional data [141][142]. Moreover, unlike the FDA, the EMA only grants a CMA to first authorizations and not for “new” indications submitted as part of a variation or extension procedure. It should be noted however, if a product already has a CMA, it is possible to modify (including extend) the indication and related Specific Obligation, provided that any modifications that are based on less comprehensive data comply with the requirements for a CMA [143].

These contrasts may highlight the regulatory variations between the EMA and the FDA concerning efficacy concerns and subsequent type of authorization grant. This discrepancy is further accentuated by the predominant trend of submissions being made in the US first. Yet, to better understand and to accurately drawn inferences, a thorough evaluation of assessments of the selected ATMPs would be necessary.

Furthermore, another possible reason associated with the fewer identified FDA PMRs, is the fact that remaining safety concerns in the US ATMPs clinical data assessments are potentially as well as addressed through other surveillance activities and risk-minimization procedures, rather than relying on post-marketing requirements. In addition to data generated through routine pharmacovigilance activities, other strategies can be implemented to generate data, address concerns and ensure the safe use of medicines. These for instance, may include the use of active surveillance programs, studies conducted by the sponsor on a voluntary basis, risk mitigation through adequate medication prescribing information (PI) measures, Risk Evaluation and Mitigation Strategy (REMS), including or not Elements To Assure Safe Use (ETASU), and other potential activities in postmarketing plans proposed by applicants. In the EU, similar tools and initiatives are in place. Also, in addition to data derived from routine pharmacovigilance activities, these for instance include risk management plans, voluntary post-authorization safety studies, and additional risk minimization measures. However, this which were frequently implemented did not hinder the EMA from imposing an increased number of measures.

Nonetheless, it was noted for some ATMPs, particular studies associated with MA-binding obligations in the EU were frequently included in the product’s pharmacovigilance plans in the US, as applicant proposed voluntary studies forming additional pharmacovigilance activities. For example, the studies AAV2-hRPE65v2-LTFU01 and AVXS-101-RG-001 were included as US planned pharmacovigilance activities for Luxturna and Zolgensma, respectively, while in the EU, they were associated with Annex II conditions. Another example is the study 68284528MMY4002, present in the US pharmacovigilance plan for Carvykti, while in the EU, the same study was associated with a Specific Obligation. Similarly, for Zynteglo,

US additional pharmacovigilance activities (namely, long-term follow-up study LTF-303 and clinical studies HGB-207 and HGB-212) were associated with Specific Obligations, which requested the submission of interim and final data and/or a 5-year follow-up. For Roctavian, US pharmacovigilance activities, specifically the follow-up study 270-401 and voluntary observational post-marketing studies 270-601 and 270-801, were all imposed as Annex II conditions in the EU. A similar case was observed with Hemgenix, where studies present in the US pharmacovigilance plan of this ATMP (voluntary registry study CSL222_4001 and interventional long-term follow-up extension study from subjects of the CSL222_2001 and CSL222_3001 trials) were imposed as Annex II conditions and Specific Obligations in the EU, respectively.

Moreover, in the US, any PMRs for the medicinal products Luxturna, Zolgensma and Roctavian were issued, where voluntary post-marketing studies were implemented but not imposed. In the EU context, oppositely, besides voluntary studies like those classified as category 3 studies in the RMP, various other imposed PAMs were identified for the same medicinal products, biding to marketing authorizations. Specifically, including both Annex II conditions and Specific obligations, there were two EMA-imposed PAMs for Luxturna, five for Zolgensma, and another five for Roctavian.

In the US, routine pharmacovigilance activities are generally deemed adequate for post-marketing surveillance and risk assessment across most products. Nevertheless, an US pharmacovigilance plan will delineate efforts that extend beyond routine post-marketing spontaneous reporting, to enhance and accelerate the applicant capacity to gather safety information (34). In the aforementioned cases, this may indeed be the case, where according to statutory provisions under the FDAAA section 505(o)(3), before requiring a PMR study, the FDA must determine that the reporting of adverse events and the new pharmacovigilance system established under section 505(k)(3) of the Food, Drug and Cosmetic Act will not be enough to achieve and fulfil any or all of the three purposes correlated to serious risks. This inference may also account for the absence of FDA PMRs in any authority for the medicinal products Luxturna, Zolgensma and Roctavian where further from routine pharmacovigilance activities, other voluntary pharmacovigilance plan studies as aforementioned described were implemented for postmarketing surveillance yet were not considered to fulfil the purposes listed on the FDAAA, section 505(o)(3)(B); i.e., purposes correlated to serious risks.

A question that can arise from these distinct approaches between the EMA and the FDA for the management of post-approval data gathering is the potential implication on data reporting and completion requirements penalties legally bounded. In the US, for each PMR, section 901 of the FDAAA requires applicants to periodically report to the FDA on the status of the required study within 60 days of the anniversary of the medicine's approval [92].

Consequently, the FDA will oversee PMR-related submissions for timely closure. Noncompliance (such as missing final protocol, study/clinical trial completion, or final report submission milestones) may lead to FDA enforcement actions, such as warnings or untitled letters, misbranding charges, and civil monetary penalties [92]. Hence, PMRs not only allow the FDA to proactively address emerging safety concerns and the need for additional information, but they are also subjected to more stringent reporting requirements (and highlighted penalties), compared to studies incorporated in the pharmacovigilance plan. Upon completion, study reports (and, if appropriate, interim reports) should be submitted according to the milestones within the pharmacovigilance plan, which might align with regulatory milestones, e.g. PSURs, annual reassessment, and license renewals [63]. Furthermore, concerning the enforcement of imposable PAMs in the EU context, the EMA maintains a record of post-authorization measures and their respective deadlines. Regarding Specific obligations, the agency conducts annual assessments to ensure compliance, both during the annual renewal process for conditional marketing authorizations and during the annual reassessment for marketing authorizations under exceptional circumstances. In instances where non-compliance with a post-authorization measure is identified, the responsible EMA committee will consider and have the authority to take a range of actions, including sending a formal letter to the MAH from the committee chair, arranging for the MAH to provide an oral explanation to the committee, initiating a referral procedure with the intention to vary/suspend/revoke the MA, and conducting inspections upon request of the committee(s) [23].

However, even studies which are required by the FDA through PMRs are not always carried out, or may encounter setbacks in achieving milestones [144][145][146]. Generally, these circumstances can significantly impact the ability to answer remaining questions and to generate new information about the benefit–risks profile.

Findings did not reveal EMA and FDA Post-authorization measures fulfilment delays, nevertheless, due to the withdrawal of some medicines from the European market, the fulfilment of their associated measures, or evidence thereof, was sometimes not identified, and also in other cases in part due to the availability of publicly updated information. Considering the registration and reporting of measures studies, it is overall evidenced registration adherence on EU PAS Register and ClinicalTrials.gov from the industry. However, it is important to emphasize certain points. For instance, certain protocols of ongoing studies linked to imposed PAMs, where data collection had already been initiated, were found to be missing from the EU PAS register. This may underscore the potential significance of greater industry publication, aligning with regulatory requirements outlined in Article 10 or 10a of Regulation (EC) No 726/2004, or Articles 21a or 22a of Directive 2001/83/EC.

Moreover, it is also essential to note the significance of PMRs in evaluating new drug and biologic safety and effectiveness as part of lifecycle evaluation efforts. In this context, there could be greater improved publicly dissemination and oversight regarding PMRs and reportable PMCs, entailing providing more detailed descriptions of postmarketing requirement studies and reporting of results within the PMRs and PMCs database, for instance, since the status and a short description are already displayed on this platform.

Within the matter, distinctions between platforms became evident. Notably, a significant contrast was observed, particularly in the analysis of observational studies: the EU PAS register allows for more detailed study descriptions, with frequently available study protocols. In contrast, for FDA-required studies, varied data sources were used, such as the PMR/PMC database and also to each products' Summary of Regulatory Actions, Approval Letters and Clinicaltrials.gov. In all these data sources details about observational designs were not as comprehensive and clearly described. This gains relevance considering that, apart from PMRs under the authority of Accelerated Approval, PMR-related studies were mainly observational studies.

The FDAAA details that, in the post-authorization setting, the FDA may only require a randomized clinical trial when sufficient information cannot be derived from an observational study [91][92]. Therefore, the statute explicitly specifies a priority for observational study designs, which is further substantiated by study results. This is somehow similar with the EU scenario, where the Annex II conditions most often pertained to requests to conduct and submit results of new observational studies, especially for safety assessment.

Moreover, among the select ATMPs considered, there is a shared presence of class-specific adverse effects, with varying degrees of occurrence, such as cytokine-release syndrome, neurotoxicity, and cytopenias. In addition, one of the major safety concerns in one class of such therapies, Gene Therapy Products, is the potential risk of insertional mutagenesis leading to oncogenesis, which may take several years to develop. Moreover, these comprise the vast majority of the study sample. For these products, regulatory agencies will typically require the conduction of LTFU studies, which can be crucial to assess the long-term safety, and monitor potential delayed effects or reactivation of gene therapies, under real-world conditions. Our study reveals that both the EMA and FDA often imposed PAMs comprising requests for LTFU studies, with submission timelines extending up to 15 years, aligning with the need for extended safety monitoring of these products.

Considering the less frequently identified US PAMs categories, such as PMRs under the Animal Efficacy Rule and the Paediatric Research Equity Act authorities it is noted that only one study (clinical trial - study 55-1702-1) was required as a PMRs under the Pediatric Research Equity Act authority, to the medicinal product MACI. This is consistent with the

observation that the majority of the selected advanced therapies were granted with US orphan drug designations, except for MACI and Provenge. Notably, the FDA has not implemented regulations that enforce the application of the Pediatric Research Equity Act to orphan-designated indications. As a result, the biological products with orphan drug designations were granted exemptions from pediatric requirements, and therefore is mainly not observed deferred pediatric studies as PMR. Additionally, no PMRs were required for the selected ATMPs under the Animal Efficacy Rule. This is because their marketing approvals were not based on data from animal studies, and they were not developed for reducing serious conditions from exposure to toxic substances.

Overall, both the EMA and FDA prioritize post-marketing data collection for ATMPs, but with differences in the quantity and nature of imposed PAMs. The EMA emphasizes a broader assessment covering efficacy, safety, and quality aspects, imposing a higher number of PAMs. In contrast, the FDA focuses on specific safety concerns, like gene therapy-associated secondary malignancies, leading to PMR requirements. Overall, observed variations between regulatory jurisdictions reflect differences in the organizational structures and approaches adopted for post-authorization data collection by each regulatory agency rather than differences in initial benefit/risk assessments.

Moreover, in general, the non-reportable postmarketing commitments (non-506B PMC) for the selected ATMPs can be regarded as analogous to EU Recommendations, as both represent categories of measures associated with quality aspects of advanced products. Furthermore, the focus on quality aspects within these categories of PAMs aligns with the novelty and complexity of these products. For example, challenges related to quality and production include variability in biologic starting materials, and other starting materials throughout the manufacturing process, as well as ensuring consistency and validation of the manufacturing process and comparability.

From a global perspective, considering the findings from part II, Roctavian was notable for having multiple allocated mechanisms, incorporating PRIME and along combinations of with FTD, BTD or/and RMAT. Similarly, is observed for Zynteglo, Breyanzi, Zolgensma and Kymriah. In addition, it is also verified the presence of Accelerated Assessments and Priority Reviews for the products. This diverse allocation of expedited mechanisms indicates that these products benefited from a range of regulatory pathways designed to expedite their development and approval processes. This aspect did not appear to have an influence on agencies decisions for post-authorization measures. For instance, the holder of Roctavian was not required to conduct any US postmarketing requirement, while the holder of Breyanzi was required to conduct solely one PMR. Similarly, in the EU, this aspect did not seem to have a

direct impact, as post-authorization measures trends were consistent within the advanced medicinal products sample.

PART IV

Real World data as applied to the EMA and FDA PAMs

4. Background

The present dissertation sample revolves around ATMPs with frequently multiple targeting rare indications, most of them being refractory and recurrent stages of a disease that lacks effective therapeutic alternatives. Moreover, with ATMPs that can cover unmet needs and address life-threatening diseases it is recognized the use of a delicate balance between the urgency of providing rapid access to these treatments and the imperative to gather comprehensive data on their benefits and risks.

As a consequence, and as explored in earlier discussed sections, this balance has also been associated with an intrinsic uncertainty on effectiveness and safety, where often as a condition to the marketing authorizations of these medicinal products, additional data collection and continuous surveillance is required, to address specific safety, efficacy or quality concerns that were not further assessed or/and identified during the initial regulatory evaluation due to limited comprehensive available data. Such impositions typically involve conducting post-authorization studies, where certain treatment aspects can only be adequately assessed under real-world conditions and over an extended period.

Hence, in such instances, real-world data may serve to gain a more comprehensive understanding of how these treatments function outside of clinical trials, providing real world safety and effectiveness insights, and in assisting post-authorization assessments.

Real-World Evidence – RWE, refers to the information derived from the analysis of Real-World Data - RWD, while RWD refers to routinely collected data relating to a patient's health status or the delivery of health care from a variety of sources other than traditional clinical trials [147].

The 21st Century Cures Act has prompted the FDA's Real-World Evidence Program, and accordingly the FDA defines real-world data as the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. On the other hand, Real-World Evidence is accordingly defined as the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD; where is possible to note that in scope of this definition of RWE, as applied by the FDA, medicines evaluation seems to be also in focus [148].

However, currently there is no standardized and agreed-upon definition of RWD and RWE, where these terms have been highlighted for their inconsistent usage and occasional interchangeability [148].

The tenet of RWD includes various data elements gathered from patient electronic health records (EHRs), hospital or insurance company administrative and claims data, directly from patients or providers in the course of an observational study, from sources of patient-generated information outside of clinical settings, and in registries [149].

Conversely, the term RWE is commonly used to denote the findings derived from the analysis of RWD using well validated and appropriate methods, which may combine design elements of observational studies and clinical trials [148].

The FDA and the EMA have created frameworks and guidance documents for efficient harnessing of RWE while acknowledging several challenges in RWD collection and analysis. Examples of such guidance include the FDA guidance document, titled *"Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products"* where recommendations on how to select relevant data sources and define and validate study variables are provided; and the FDA guidance on designing or leveraging an existing registry in the context of regulatory decisions, document titled *"Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products - Guidance for Industry"*. The FDA also issued guidance addressing considerations into the use of data standards, which are currently supported by the FDA, in drug submissions incorporating study data obtained from RWD sources, document titled *"Data Standards for Drug and Biological Product Submissions Containing Real-World Data - Guidance for Industry"* [150]. Other FDA existent guidance outlines the agency expectations for clinical studies employing RWD when submitted to support a regulatory decision concerning a drug effectiveness and safety, guiding document titled *"Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products"* [150].

Within the sphere of the European Union, efforts have been continuously underway to enhance the collection of Real-World data, e.g. as through the use of registries. The EMA Initiative for Patient Registries, initiated in September 2015, is focused on enhancing and streamlining the use of existing patient registries for the benefit risk evaluation of medicinal products. As part of this initiative, the EMA has issued guidance on the methodological, regulatory, and operational aspects involved in using registry-based studies to support regulatory decision-making, namely the EMA guideline, *Guideline on registry-based studies - Scientific guideline* [151].

In addition, the European Medicines Agency qualified the Cellular Therapy module of the EBMT Registry as suitable for performing pharmacoepidemiological studies for regulatory purposes, concerning Chimeric Antigen Receptor (CAR) T- cell therapies for haematological malignancies. Hence, the CHMP considered that the status of the Cellular Therapy module of the EBMT registry (coverage, core dataset, governance, quality assurance approaches, and completeness of core variables), may allow its use as a data source for regulatory purposes in the context of drug utilisation, drug efficacy/effectiveness and drug safety evaluation studies concerning CAR-T cell therapies authorised for haematological malignancies [152].

In the context of drug safety evaluation studies, the cellular therapy module of the EBMT registry emerges as a valuable tool for gathering safety data related to CAR-T cell therapy. This module is particularly focused on monitoring early and late-stage adverse events of special interest, including neurological events, cytokine release syndrome, and drug-related (grade 3-4) adverse events.

Post-authorization obligations with evidence of use of RWD regarding the long-term safety and/or effectiveness were included for all the advanced therapy products under the present study. This indicates the significance of Real-World Data as a complementary source of the clinical development data collected in the context of investigational ATMPs, where one possible approach to accomplish post-authorization obligations is via creation of a registry and/or conduct registry-based studies.

Recently, the EMA Committee for Advanced Therapy has prioritized gaining understanding of the use of RWD, including natural history data, retrospective patient level treatment data and registry-based data, for regulatory decision making pre-and post-authorization and for patient access to advanced therapy medicinal products [153].

It is worth noting that RWD and RWE have a broader scope beyond medicines evaluation, as they find application in diverse domains, including health technology assessment, health economics, patient-reported outcomes, and disease epidemiology [147].

4.1. Post-Authorization Measures for Advanced Medicinal Products: An Analysis of Real-World Data use

Table 9 presents a list of all the ATMPs studied, identifying instances where study designs incorporating real-world data were conducted as part of post-authorization measures/post-marketing requirements. The table contains the respective descriptions/identifiers of the ATMP studies, alongside the corresponding category of the EU/US post-authorization measures and the primary rationale for requesting the study. Additionally, it includes the design of the non-interventional studies and the sources of RWD data which were identified. It is important to note that sources of RWD are presented according to the descriptions provided in the sources. However, limitation on information is evident. For instance, the option for prospective patient-based data collection was often observed to be included in studies based on a registry, however, these descriptions lack clarity regarding the specific data collection instruments used. In addition, a distinction is made between registries and studies conducted as registry-based studies.

Overall, a total of 39 measures incorporating real-world data were identified, namely 30 from the EMA and 15 from the FDA, where six of these were required by both the EMA and FDA. Namely the measures associated with the study PROCEED (Provenge), study 20130193

(Imlygic), study CCTL019B2401 (Kymriah), study 68284528MMY4004 (Carvykti), study REG-501 (Zynteglo) and study REG-502 (Skysona). The difference in number aligns with the distinct categories of included PAMs and the overall number of measures identified in each region. The higher number of measures identified in the EU may also correlate to the observed variance.

It is noted that the EMA and the FDA measures frequently sourced RWD from pre-existing patient outcome registries, primarily through registry-based studies. Moreover, it is possible to obverse that the associated measures studies incorporating real-world data were required by the FDA as postmarketing requirements under the FDAAA authority, and, in the EU, these were primarily imposed as Annex II conditions. This indicates the significance of employing RWD designs to further evaluate benefit and risks, particularly in the context of long-term safety follow up of ATMPs.

While the identification of RWD sources was not always straightforward, it is noteworthy to emphasize the indication of the use of patient registries and product registries i.e., registry focused on patients receiving a specific ATMP of interest; followed by medical records and patient-reported outcomes. These RWD sources were predominantly included to support safety assessment objectives.

4.1. Discussion

The present section briefly explored the RWD use to support/contribute to studies within post-authorization measures, revealing that data drawn from registries is a prevalent RWD source among both EU and US RWD post-authorization requests.

This observed fact is supported by a prior study on the use of RWD in postmarketing surveillance activities, particularly of PMCs or PMRs for products that received a marketing authorization by the EMA and the FDA. In this study, out of 165 products, 85% involved postmarketing activities in the US sourced from product registries, and 12% from patient registries. On the other hand, for the EMA, 49% of these activities were sourced from patient registries, and 48% from product registries [186].

Moreover, this may closely correlate to the EU approach promoted by the EMA Initiative for Patient Registries, focusing in enhancing the use of existing patient registries, where is advised to limit the establishment of new registries if current existing patient registries are insufficient or unavailable. Hence, the EMA regulators prioritizing existing patient registries over for instance specific product registries due to known issues associated with multiple registries requests, such as inefficiency and duplication of efforts and discrepancy between data collected and the data requested [187].

Interestingly, holders may prefer to establish individual product registries instead of using existing patient registries due to various challenges in using such latter registries for regulatory studies. These challenges include recruitment difficulties, such as a lack of physician engagement because of administrative burdens, issues with patient consent, low product usage, and competing registries. Additionally, there are concerns related to data quality, such as the representativeness of the registry population, missing data, and the lack of consistent data quality control as well as sustainability issues [187].

While there are no explicit references indicating the FDA stance on enhancing the use of existing patient registries or establishing new registries, it is plausible that this fact likely relates to FDA considerations for the challenges faced by the holders, providing an explanation for their notable requirement for the establishment of such registries.

Moreover, in accordance with the FDA guidance document titled *"Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products"*, in general, registries are better suited as a data source for regulatory purposes when sponsors aim to capture objective endpoints, such as death or hospitalization and subjective endpoints, such as pain, can be collected in a registry, but standardizing such measurements poses additional challenges. However, the observed US stablished product registries frequently serve the purpose of assessing long-term safety by evaluating adverse events and the risk of secondary malignancies, both of which are important objective endpoints.

The submission of RWD within post-authorization measures of the ATMPs approved by both the EMA and the FDA were predominantly imposed to be fulfilled within a long-term period, reflecting on both the EMA and the FDA often imposed submission timelines extending up to 15 years. This untimely aligning with the extended safety monitoring required in the product class of the majority of advanced products in study (gene therapies).

Furthermore, given that the medicinal products included in the research sample were approved relatively recently, there is not many verified fulfilled post-authorization measures and a clear evidence of real word data generating RWE supporting agencies actions/decisions, in the form, for example of Product Information and Prescribing Information updates, especially as many studies still are in planned phases. In addition, would be important to further study the progress of these studies, as manufacturers have shown their capability to organize short-term clinical follow-ups for a restricted number of patients involved in clinical trials. However, conducting long-term follow-ups of large patient cohorts during the post-authorization phase is anticipated to be more challenging.

However, there were instances of complete data collection and fulfilment of post-authorization measures, specifically for the medicinal products Provenge and Kymriah.

Particularly, during the review of available RWD from subgroup analysis of the study CCTL019B2401, a patient registry for Kymriah, the CHMP issued opinions supporting changes to the Summary of Product Characteristics. The changes incorporated new texts referencing real-world analysis findings in the paediatric population, demonstrating that Kymriah's safety profile in this population was generally consistent with the previously known safety profile determined for the medicine.

Regarding the data extraction for the present analysis purposes, the identification of RWD sources was more easily performed among EU required/imposed studies, as the majority were identified within the EU PAS register, where study information, mainly studies protocols were frequently available providing a greater level of detail on the studies. Regarding the US required studies, information was limited to the products Summary of Regulatory Actions, Approval letters, and also the Clinicaltrails.gov. the PMRs and PMCs databases, when found to be registered. In these US data sources, information about the real-world data was not as ample and clearly described. Frequently the PMR description simply described requests for prospective observational safety study designs, which frequently suggested the case of LTFU registries. In other instances, throughout extensive documents texts revisions the term "registry" was found to be associated with specific PMRs. However, there was a lack of precise information regarding study designs, particularly whether requirements pertained to the establishment of a new register or to the use of existing registries, as well as further information concerning real-world data elements.

In addition, acknowledging the significance of the present section analysis limitations, it is important to note that requests for RWD collection were only gather within post-authorization measures/requirements which possibly left out other instances where RWD was potentially applied, and RWE potentially followed generated, such as, in studies included in the FDA ATMPs pharmacovigilance plans which do not necessarily compose PMRs or PMCs, and were therefore not extracted.

RWD was indicated as an essential tool for benefit-risk profiles evaluation of advanced therapy medicinal products. This is accentuated by the recognized data limitations at the time of marketing authorizations, underlining the critical tenancy of leveraging RWD and RWE in regulatory evaluations.

Table 9. Summary of RWD studies.

The studies were distinguished by region by a colour coding system, where rows highlighted in ▭ refer to studies required by the U.S. Food and Drug Administration - FDA, while rows highlighted in ▭ pertain to studies mandated by the European Medicines Agency - EMA. KOOS - Knee injury and Osteoarthritis Outcome Score. * Described as observational safety studies without further identified information on RWD elements. Note: studies design presented were based on studies descriptions.

ATMP	Study identifier/description	EU/US PAM category	Objective of studies	Design of studies	Sources
PROVENGE	P13-1 (EU registry)	Annex II condition	Long term safety	Prospective study registry based	Patient-based registry primary data collection
	PROCEED/P10-3	Annex II condition	Long term safety	Prospective study registry based	Patient-based registry primary data collection
	PROCEED	PMR under FDAAA Section 505(o)(3)	Long term safety	Prospective study registry based	Patient-based registry primary data collection
MACI	MACI00809	Additional PhV in the RMP (category 3 study)	Long term safety and efficacy	Prospective observational study	Patient reported outcome questionnaire (KOSS)
IMLYGIC	20120139	Additional PhV in the RMP (category 3 study)	Long-term safety and efficacy	Prospective study registry based	Patient-based primary data collection from eCRFs
	20130193	Additional PhV in the RMP (category 3 study)	Long-term safety and efficacy	Prospective study registry based	Patient-based primary data collection - Exposure registry
	20130193	PMR under FDAAA Section 505(o)(3)	Long-term safety	Prospective study registry based	Patient-based primary data collection - Exposure registry
YESCARTA	KT-EU-471-0117	Annex II condition	Long term safety	Prospective study registry based	Patient data from EBMT registry – (Data Collection Forms)
	KTE-C19-110	PMR under FDAAA Section 505(o)(3)	Long-term safety	Prospective study registry based	Patient-based registry primary data collection
	sBLA 125643/248 PMR for FL	PMR under FDAAA Section 505(o)(3)	Long-term safety	Prospective study registry based	Patient-based registry primary data collection
KYMRIAH	Study CCTL019B2401	Annex II condition	Long-term safety	Prospective study registry based	Patient data from EBMT and CIBMTR registries - (Data Collection Forms)
	CCTL019A2205B	Additional PhV in the RMP (category 3 study)	Long-term efficacy and safety	Observational - Long Term Follow Up (LTFU) Study	Patient data collection*
	Study CCTL019B2401	PMR under FDAAA Section 505(o)(3)	Long-term safety	Prospective study registry based	Patient data from EBMT and CIBMTR registries - (Data Collection Forms)
	sBLA 125646/76 for DLBCL PMR	PMR under FDAAA Section 505(o)(3)	Long-term safety	Prospective study registry based	Patient Registry data collection*

	sBLA 125646/663 for FL PMR	PMR under FDAAA Section 505(o)(3)	Long-term safety	Prospective study registry based	Patient Registry data collection*
LUXTURNA	SPKRPE-EUPASS	Annex II condition	Long term safety	Prospective study registry based	Patient-based registry primary data - collection from medical notes, electronic medical records, and hospital discharge files, ocular assessments, patient, and caregiver reported outcome questionnaire
	AAV2-hRPE65v2-LTFU-01	Annex II condition	Long-term efficacy and safety	Observational - Long Term Follow Up (LTFU) Study	Patient reported outcome questionnaire*
ZOLGENSMA	AVXS-101-RG001	Annex II condition	Long-term efficacy and safety	Prospective study registry based	Patient registry data collection*
	AVXS-101-LT-001	Additional PhV in the RMP (category 3 study)	Long term safety	Observational - Long Term Follow Up (LTFU) Study	Patient data collection*
	AVXS101-LT-002	Additional PhV in the RMP (category 3 study)	Long-term efficacy and safety	Observational - Long Term Follow Up (LTFU) Study	Patient data collection*
TECARTUS	KTE-EU-472-6036	Annex II condition	Long-term safety and efficacy	Prospective study registry based	Patient data from EBMT registry – (Data Collection Forms)
	Prospective study based on data from KTE-EU-472-6036 registry	Specific obligation	Confirm the long-term efficacy and safety	Prospective study registry based	Patient data from EBMT registry – (Data Collection Forms) *
	Prospective study based on data from a registry - for r/r ALL	Specific obligation	Confirm the long-term efficacy and safety	Prospective study registry based	Patient registry data collection*
	KT-US-472-5655	PMR under FDAAA Section 505(o)(3)	Long-term safety	Prospective study registry based	Patient data from CIBMTR registry – (Data Collection Forms)
	sBLA 125703/91 for ALL PMR	PMR under FDAAA Section 505(o)(3)	Long-term safety	Prospective study registry based	Patient data from CIBMTR registry – (Data Collection Forms)
ABECMA	BB2121-MM-006	Annex II condition	Long-term efficacy and safety	Prospective study registry based	Patient data from EBMT and CIBMTR registries - (Data Collection Forms)
	PMR Prospective Observational study	PMR under FDAAA Section 505(o)(3)	Long term-safety	Prospective study registry based	Patient registry data collection*
CARVYKTI	68284528MMY4002	Annex II condition	Long-term efficacy and safety	Observational - Long Term Follow Up (LTFU) Study	Patient data collection*

	68284528MMY4009	Annex II condition	Long-term efficacy and safety	Prospective study registry based	Patient-based data primary collection - medical records Adverse events spontaneously reported
	68284528MMY4004	Annex II condition	Long-term efficacy and safety	Prospective study registry based	Patient data from 68284528MMY4009 Patient data from CIBMTR registry – (Data Collection Forms) Spontaneous reporting
	68284528MMY4004	PMR under FDAAA Section 505(o)(3)	Long term-safety	Prospective study registry based	Patient data from 68284528MMY4009 Patient data from CIBMTR registry – (Data Collection Forms) Spontaneous reporting
BREYANZI	CA082-1105	Annex II condition	Product quality and clinical outcomes	Prospective study registry based	Patient data from EBMT and CIBMTR registries - (Data Collection Forms). Applicant internal batch quality database
	JCAR017-BCM-005	Annex II condition	Long-term safety and efficacy	Prospective study registry based	Patient data from CIBMTR registry – (Data Collection Forms)
	JCAR017-DLBCL-001	PMR under FDAAA Section 505(o)(3)	Long term-safety	Prospective study registry based	Patient data from EBMT and CIBMTR registries - (Data Collection Forms)
ZYNTEGLO	REG-501	Annex II condition	Long-term safety and efficacy	Prospective study registry based	Patient-based data collection from Rare Anaemia Registry, Germany
	REG-501	PMR under FDAAA Section 505(o)(3)	Long term-safety	Prospective study registry based	Patient Registry data collection*
SKYSONA	LTF-304	Annex II condition	Long-term safety and efficacy	Prospective case-only	Patient data collection*
	REG-502	Annex II condition	Long-term safety and efficacy	Prospective study registry based	Patient data from EBMT and CIBMTR registries - (Data Collection Forms)
	PMR - Follow up of subjects from Studies ALD-102 and ALD-104	PMR under Accelerated Approval	Efficacy (clinical benefit)	Prospective cohort study	Patient data collection*
	REG-502	PMR under FDAAA Section 505(o)(3)	Long term-safety	Prospective study registry based	Patient data from EBMT and CIBMTR registries - (Data Collection Forms)
ROCTAVIAN	Study 270-401 (Follow-up study)	Annex II condition	Long-term safety and efficacy	Prospective cohort study	Patient data collection*

	Study 270-801	Annex II condition	Long-term safety and efficacy	Retrospective study registry based	The WFH Gene Therapy Registry EUHASS - Blood disorders American Thrombosis and Hemostasis Network
	Study 270-601	Annex II condition	Long-term safety and efficacy	Cohort study	Prospective and retrospective patient data collection*. Electronic health record systems
HEMGENIX	CSL222_4001	Annex II condition	Long-term safety and efficacy	Prospective study registry based	Patient-based data collection* ATHN Transcends: A Natural History Study of Non-Neoplastic Hematologic Disorders (Hemophilia Cohort, Gene Therapy Outcomes Arm and Natural History Arm)
	Extension Study CSL222_3003	Additional PhV in the RMP (category 3 study)	Long-term safety and efficacy	Prospective Cohort study	Patient data collection*

5. Study limitations

The following limitations are acknowledged: (a) findings relied on publicly available data obtained from agency websites, where the information may not be entirely updated or provided; thus analysis may be hindered by discrepancies in the availability of public information; (b) the study focused on a limited sample size, composed of advanced medicinal products approved both in the EU and the US until 2023; (c) comparisons primarily relied on the descriptive overview used to characterize measures; (d) in some instances, achieving a comparison between the EU and US measures was hindered by differences in the nature of considered categories.

6. Opportunities for future research

There are several opportunities to further expand the research covered in this dissertation. The most immediate would be the follow-up of the assessed measures until their fulfilment and the availability of associated study results. It would be possible to ascertain whether planned milestones were met, and consequently, whether measures were completed within agreed timeframes or as imposed by regulators.

In addition, compelling into a study including an expanded sample of advanced medicinal products, comprising those approved in the respective regions, even if not necessarily approved in both, could enhance the robustness and generalizability of the findings achieved.

Furthermore, it would be important to investigate what actions followed the submission of results, in both jurisdictions, to understand how measures contributed to the knowledge maturation of the advanced medicinal products and whether it lead to preventive actions, such as RMM and labelling changes. Based on this analysis, it would also be crucial to further estimate the extent to which the use of real-world data and generated evidence contributed to the achievement of the objectives set for these measures. Assessing granular details was significantly hindered by the level of information provided on the sources of data used. For example, detailed descriptions of observational study design methodologies, ambiguous or non-uniform classification terminologies between identical study designs, as well as more detailed descriptions of real-world data sources, were observations that made it difficult to discern intricacies. Considering the well-established history of real-world data use, notably in post-authorization activities, an expectation arises for a potential increase in harmonization of terminologies among diverse jurisdictions, accompanied by an elevation in descriptive detail. This advancement is anticipated to potentially facilitate improved accuracy in communication and interpretation and facilitate further research.

7. Final considerations

Regulatory agencies in both the European Union and in the United States employ a variety of post-marketing strategies to manage uncertainties, often using similar approaches. These frequently involve requests for additional data collection post-approval through ongoing clinical trials and observational studies. In both the EMA and FDA contexts, these requests, known post-authorization measures and as post-marketing requirements and commitments, are crucial mechanisms for addressing uncertainties.

In the EU, a significant count of post-authorization measures were identified in contrast to the US. This observation seems to be primarily connected to distinct regulatory structures across the agencies for further data collection, thus, different structures of decision to require post-approval data, rather than disparities in benefit/risk assessments. Expedited mechanisms and long-term uncertainties urge authorities to cautiously consider and enforce appropriate post-marketing risk management and collection of confirmatory evidence.

The vast majority of advanced products under study were designated as orphan drugs, and Breakthrough and PRIME designations were commonly granted. This underscores the widespread utilization of expedited clinical development programs across regions for these products, a trend similarly observed in expedited review mechanisms.

Throughout the present dissertation, several guidelines have been highlighted, illustrating how regulatory agencies are actively adapting their procedures to keep up with the needs in the realm of advanced therapies, and committed to support their development.

Data obtained from registries was a predominant source of real-world data in both EU and US post-authorization requests for advanced therapies. Registries play a crucial role in capturing long-term patient outcomes and treatment effectiveness, contributing valuable insights into the real-world performance of these innovative therapies. This reliance on registry data highlights its significance in informing post-authorization evaluations and ensuring the ongoing safety and efficacy of advanced therapies.

References

[1] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (Text with EEA relevance) [Internet]. 2007 [cited 2021 Oct 3] p. 1. Available from: https://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF

[2] Carvalho M, Sepodes B, Martins AP. Regulatory and Scientific Advancements in Gene Therapy: State-of-the-Art of Clinical Applications and of the Supporting European Regulatory Framework. Frontiers in Medicine. [Internet]. 2017 [cited 2022 Oct 25]. Available from: Regulatory and Scientific Advancements in Gene Therapy: State-of-the-Art of Clinical Applications and of the Supporting European Regulatory Framework - PubMed (nih.gov)

[3] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (Text with EEA relevance) [Internet]. 2007 [cited 2021 Oct 3] p. 4-5. Available from: https://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF~

[4] Department of Health and Human Services Food and Drug Administration Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products [Internet]. [cited 2022 Aug 7] p. 3. Available from: https://fda.report/media/76647/Application-of-Current-Statuatory-Authorities-to-Human-Somatic-Cell-Therapy-Products-and-Gene-Therapy-Products.pdf

[5] Guidance for Industry Biologics License Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System [Internet]. 2014 [cited 2022 Aug 7] p. 5. Available from: https://www.fda.gov/media/86387/download

[6] US Food and Drug Administration. Presentation on the regulation of cellular therapies. [Internet]. [cited 2022 Aug 8]. Available from: https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Cellular-Therapy-Products.pdf

[7] US Food and Drug Administration. Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products Draft Guidance for Industry and Food and Drug Administration Staff [Internet]. 2014 Dec [cited 2022 Aug 8] p. 17. Available from: https://alliancerm.org/sites/default/files/ARMComments_MinimalManipulation_FINAL.pdf

[8] US Food and Drug Administration. CFR - Code of Federal Regulations Title 21 [Internet]. www.accessdata.fda.gov. [cited 2022 Aug 7]. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=601

[9] Public Health Service Act. title iii-general powers and duties of public health service part a-research and investigation in general [Internet]. 2020 [cited 2022 Aug 19] p. 328. Available from: https://www.govinfo.gov/content/pkg/COMPS-8773/pdf/COMPS-8773.pdf

[10] FDA Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P's) Product List. FDA [Internet]. 2019 Apr 5 [cited 2022 Aug 10]. Available from: https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products/fda-regulation-human-cells-tissues-and-cellular-and-tissue-based-products-hctps-product-list

[11] US Food and Drug Administration. Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use Guidance for Industry and Food and Drug Administration Staff [Internet]. 2020 [cited 2022 Aug 10] p 1-17. Available from: https://www.fda.gov/media/109176/download

[12] Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing,

preservation, storage and distribution of human tissues and cells [Internet]. [cited 2022 Aug] p 1. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32004L0023&from=EN
[13] Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use [Internet]. 2003 [cited 2002 Aug 20] p 45-46. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32003L0063&from=en
[14] Commission Directive 2009/120/EC of 14 September 2009 Amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products (Text with EEA relevance) [Internet]. 2009 [cited 2022 Aug 20] p. 2–3. Available from: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:242:0003:0012:EN:PDF
[15] Public Health Service Act. title iii-general powers and duties of public health service part a-research and investigation in general [Internet]. 2020 [cited 2022 Aug 19] p. 328. Available from: https://www.govinfo.gov/content/pkg/COMPS-8773/pdf/COMPS-8773.pdf
[16] Center for Biologics Evaluation and Research. What Are “Biologics” Questions and Answers. FDA [Internet]. 2019 Feb 28 [cited 2022 Aug 19]; Available from: https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-answers
[17] Department of Health and Human Services. Food and Drug Administration Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products [Internet]. [cited 2022 Aug 20] p. 3–4. Available from: https://www.fda.gov/media/76647/download
[18] European Medicines Agency. Reflection paper on a proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines (PRIME) [Internet]. 2015 [cited 2022 Aug 12] p. 6. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/draft-reflection-paper-proposal-enhance-early-dialogue-facilitate-accelerated-assessment-priority_en.pdf
[19] US Food and Drug Administration. Guidance for Industry Expedited Programs for Serious Conditions -Drugs and Biologics [Internet]. 2014 [cited 2022 Aug 10] p. 9, 18, 25. Available from: https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf
[20] European Medicines Agency. European Medicines Agency Guidance for applicants seeking access to PRIME scheme [Internet]. [cited 2021 Oct 20]. Available from: https://www.ema.europa.eu/en/documents/other/european-medicines-agency-guidance-applicants-seeking-access-prime-scheme_en.pdf
[21] Food and Drug Administration Center for Biologics Evaluation and Research. Expedited Programs for Regenerative Medicine Therapies for Serious Conditions Guidance for Industry [Internet]. 2019 Feb [cited 2021 Oct 21] p. 4–10. Available from: https://www.fda.gov/media/120267/download
[22] EMA Committee for Medicinal Products for Human Use (CHMP). Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products [Internet]. 2018 Jan [cited 2021 Oct 25] p. 13–4. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-safety-efficacy-follow-risk-management-advanced-therapy-medicinal-products-revision_en.pdf
[23] European Medicines Agency. European Medicines Agency post-authorisation procedural advice for users of the centralised procedure [Internet]. 2009 Jul [cited 2021 Oct 26] p. 203-222. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-post-authorisation-procedural-advice-users-centralised-procedure_en.pdf
[24] Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). Guidance for Industry Postmarketing Studies and Clinical Trials - Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act Drug Safety [Internet]. 2011 Apr [cited 2021 Oct 26] p. 6–7. Available from: https://www.fda.gov/media/131980/download

[25] Wallach JD, Luxkaranayagam AT, Dhruva SS, Miller JE, Ross JS. Postmarketing commitments for novel drugs and biologics approved by the US Food and Drug Administration: a cross-sectional analysis. BMC Medicine [Internet]. 2019 Jun 17 [cited 2021 Nov 7];17(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6572730/
[26] Wallach JD, Egilman AC, Dhruva SS, McCarthy ME, Miller JE, Woloshin S, et al. Postmarket studies required by the US Food and Drug Administration for new drugs and biologics approved between 2009 and 2012: cross sectional analysis. BMJ [Internet]. 2018 May 24. [cited 2021 Nov 7]. Available from: https://www.bmj.com/content/361/bmj.k2031
[27] Skydel JJ, Zhang AD, Dhruva SS, Ross JS, Wallach JD. US Food and Drug Administration utilization of postmarketing requirements and postmarketing commitments, 2009–2018. Clinical Trials, Journal of the Society for Clinical Trials [Internet]. 2021 April 16. [cited 2021 Nov 7]. Available from: https://journals.sagepub.com/doi/abs/10.1177/17407745211005044
[28] Hoekman J, Klamer TT, Mantel-Teeuwisse AK, Leufkens HGM, De Bruin ML. Characteristics and follow-up of postmarketing studies of conditionally authorized medicines in the EU. British Journal of Clinical Pharmacology [Internet]. 2016 Jul 1 [cited 2021 Nov 8];82(1):213–26. Available from: https://pubmed.ncbi.nlm.nih.gov/26992001/
[29] SALCHER-KONRAD M, NACI H, DAVIS C. Approval of Cancer Drugs With Uncertain Therapeutic Value: A Comparison of Regulatory Decisions in Europe and the United States. The Milbank Quarterly [Internet]. 2020 Oct 6. [cited 2021 Nov 8]. Available from: https://pubmed.ncbi.nlm.nih.gov/33021339/
[30] Zeitoun J-D, Baron G, Vivot A, Atal I, Downing NS, Ross JS, et al. Post-marketing research and its outcome for novel anticancer agents approved by both the FDA and EMA between 2005 and 2010: A cross-sectional study. International Journal of Cancer [Internet]. 2017 Oct 12 [cited 2021 Nov 8];142(2). Available from: https://pubmed.ncbi.nlm.nih.gov/28929484/
[31] Food and Drug Administration. Approved Cellular and Gene Therapy Products [Internet]. 2023 [cited 2023 Dec 20]. Available online at: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products
[32] European Medicines Agency. Human Medicines Division, CAT quarterly highlights and approved ATMPs, October 2023 [Internet]. 2023 [cited 2023 Dec 20] p. 3-4. Available from: https://www.ema.europa.eu/en/documents/committee-report/cat-quarterly-highlights-and-approved-atmps-october-2023_en.pdf
[33] Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells [Internet]. [cited 2022 Aug] p 1. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32004L0023&from=EN
[34] Postmarket Requirements and Commitments [Internet]. www.accessdata.fda.gov. Available from: https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm
[35] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use [Internet]. [cited 2022 Feb 6]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32001L0083&from=en
[36] Regulation (EC) No 726/2004 Regulation of 31 March 2004 Laying down Community Procedures for the Authorisation and Supervision of Medicinal Products for Human and Veterinary Use and Establishing a European Medicines Agency (Text with EEA relevance) [Internet]. 2004 [cited 2022 Jan 6]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32004R0726&from=EN
[37] Regulation (EC) No 1394/2007 of The European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (Text with EEA relevance) [Internet]. [cited 2022 Jan 6]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32007R1394&from=EN

[38] Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use (Text with EEA relevance) [Internet]. 2003 [cited 2022 Jan 10]. p43-46. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32003L0063&from=PT
[39] Regulation (EC) No 1394/2007 of The European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (Text with EEA relevance) [Internet]. [cited 2022 Jan 10]. p.18.Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32007R1394&from=EN
[40] European Parliament. Policy Department: Economic and Scientific Policy. Proposal for a Regulation of the European Parliament and of the Council on Advanced Therapy Medicinal Products and amending Directive 2001/83/EC & Regulation (EC) No.726/2004 (COM (2005)567) (IP/A/ENVI/OF/2005-053) Briefing Note [Internet]. [cited 2022 Jan 10] p. 19. Available from: https://www.europarl.europa.eu/RegData/etudes/note/join/2006/373574/IPOL-ENVI_NT(2006)373574_EN.pdf
[41] Regulation (EC) No 1394/2007 Regulation of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (Text with EEA relevance) [Internet]. [cited 2022 Jan 10]. p.11-12. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32007R1394&from=EN
[42] Committee for Advanced Therapies (CAT) Procedural advice on the evaluation of advanced therapy medicinal product in accordance with Article 8 of Regulation (EC) No 1394/2007 (EC) NO 1394/2007 [Internet]. 2009 [cited 2022 Jan 10] p. 3. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/draft-procedural-advice-evaluation-advanced-therapy-medicinal-products-accordance-article-8/2007_en.pdf
[43] EMA. Committee for Advanced Therapies (CAT) Rules of Procedure [Internet]. [cited 2022 Jan 10] p.4-11. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/cat-rules-procedure_en.pdf
[44] Reflection paper on classification of advanced therapy medicinal products [Internet]. [cited 2022 Jan 10] p. 3-6. Available from: https://www.fdanews.com/ext/resources/files/06/06-14-EMA-ATMP-guidance.pdf
[45] Report from the commission to the European Parliament and the council in accordance with Article 25 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 [Internet]. Publications Office of the EU. 2014 [cited 2023 Mar 15]. p.3. Available from:https://op.europa.eu/en/publication-detail/-/publication/2dc18b82-b6c8-11e3-86f9-01aa75ed71a1/language-en
[46] Carvalho MABR. Advanced therapy medicinal products: new strategies for clinical applications of cell and gene therapy [Internet]. repositorio.ul.pt. 2020 [cited 2023 Mar 15]. p.116. Available from: https://repositorio.ul.pt/handle/10451/48501
[47] Committee for advanced therapies (CAT) Procedural advice on the certification of quality and non- clinical data for small and medium sized enterprises developing advanced therapy medicinal products [Internet]. 2016 [cited 2022 August 6] p. 3–5. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/procedural-advice-certification-quality-non-clinical-data-small-medium-sized-enterprises-developing_en.pdf
[48] Consumers H, ECORYS Nederland BV, University Utrecht, Schothorst M van, Weeda J, Schiffers K, et al. Study on the regulation of advanced therapies in selected jurisdictions: final report [Internet]. Publications Office of the European Union. LU: Publications Office of the European Union; 2016 [cited 2023 Feb 14]. p.24-43. Available from: https://op.europa.eu/en/publication-detail/-/publication/78af6082-bc4a-11e6-a237-01aa75ed71a1
[49] Food and Drug Administration. Frequently Asked Questions About Therapeutic Biological Products. FDA [Internet]. 2019 Feb 8 [cited 2023 Feb 12]; Available from:

https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/frequently-asked-questions-about-therapeutic-biological-products
[50] Bailey AM, Arcidiacono J, Benton KA, Taraporewala Z, Winitsky S. United States Food and Drug Administration Regulation of Gene and Cell Therapies. Advances in Experimental Medicine and Biology [Internet]. 2023 Feb 12 [cited 2019 Apr 10];1–29. Available from: https://link.springer.com/chapter/10.1007/978-3-319-18618-4_1
[51] Code of Federal Regulations. Federal Register - 21 CFR Chapter, Subchapter F, Biological products [Internet]. federalregister.gov. [cited 2023 Feb 12]. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-F
[52] US Food and Drug Administration. Interactions with Office of Tissues and Advanced Therapies. FDA [Internet]. 2022 Jun 23 [cited 2023 Feb 12]; Available from: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/interactions-office-tissues-and-advanced-therapies
[53] Food and Drug Administration - Division of Cellular and Gene Therapies Office of Tissues and Advanced Therapies. Overview Office of Tissues and Advanced Therapies and Division of Cellular and Gene Therapies Research Program [Internet]. 2020 [cited 2023 Feb 12]. Available from: https://www.fda.gov/media/140940/download
[54] European Medicines Agency. Reflection paper on classification of advanced therapy medicinal products [Internet]. p. 4–17. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-classification-advanced-therapy-medicinal-products_en-0.pdf
[55] Department of Health and Human Services Food and Drug Administration. Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy. Human Gene Therapy. 1998 [Internet]. p. 6. Available from: https://www.fda.gov/media/72402/download
[56] EMA. Advanced therapies: post-authorisation [Internet]. European Medicines Agency. 2018 [cited 2023 Apr 12]. Available from: https://www.ema.europa.eu/en/human-regulatory/postauthorisation/advanced-therapies-postauthorisation#:~:text=The%20European%20Medicines%20Agency%27s%20scientific%20and%20regulatory%20guidance
[57] Post-authorisation - European Medicines Agency [Internet]. European Medicines Agency. 2018 [cited 2023 Apr 12]. Available from: https://www.ema.europa.eu/en/human-regulatory/post-authorisation
[58] Food and Drug Administration. Biologics Post-Market Activities [Internet]. FDA. 2019 [cited 2023 Feb 12]. Available from: https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-post-market-activities
[59] EMA. Pharmacovigilance for advanced therapies [Internet]. European Medicines Agency. 2018 [cited 2023 Feb 11]. Available from: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/advanced-therapies/pharmacovigilance-advanced-therapies
[60] Committee for Medicinal Products for Human Use (CHMP) - Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products, Draft [Internet]. 2018 [cited 2023 Feb 11] p. 3–17. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-safety-efficacy-follow-risk-management-advanced-therapy-medicinal-products-revision_en.pdf
[61] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance. Directive 2001/83/EC on the Community code relating to medicinal products for human use [Internet]. 2010 [cited 2023 Dec 11]. Available from: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF
[62] Regulation (EU) No 1235/2010 of the European Parliament and of the Council of of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use. Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products

[Internet]. [cited 2023 Dec 11]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32010R1235
[63] Food and Drug Administration. Guidance for Industry E2E Pharmacovigilance Planning [Internet]. 2005 [cited 2023 Feb 14] p. 5–12. Available from: https://www.fda.gov/media/71238/download
[64] Food and Drug Administration. Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment Clinical Medical [Internet]. 2005 [cited 2023 Feb 12]. p.21-23. Available from: https://www.fda.gov/media/71546/download
[65] Food and Drug Administration. What's in a REMS? FDA [Internet]. 2018 Nov 3 [cited 2023 Feb 13]; Available from: https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/whats-rems
[66] FDA's Sentinel Initiative [Internet]. FDA. 2022 [cited 2023 Feb 12]. Available from: https://www.fda.gov/safety/fdas-sentinel-initiative
[67] Center for Biologics Evaluation and Research. CBER Biologics Effectiveness and Safety (BEST) System [Internet]. U.S. Food and Drug Administration. 2019 [cited 2023 Feb 12]. Available from: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-biologics-effectiveness-and-safety-best-system
[68] Office of the Commissioner. MedWatch: FDA Safety Information & Adverse Event Reporting Program [Internet]. U.S. Food and Drug Administration. 2019 [cited 2023 Feb 12]. Available from: https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program
[69] Regulation (EC) No 1394/2007 of the European Parliament and of the council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (Text with EEA relevance) [Internet]. [cited 2023 Jan 8] p. 7. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32007R1394
[70] Food and Drug Administration. Cellular & Gene Therapy Guidances. FDA [Internet]. 2021 Jan 19 [cited 2023 Feb 12]; Available from: https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances
[71] Food and Drug Administration Center for Biologics Evaluation and Research. Long Term Follow-Up After Administration of Human Gene Therapy Products Guidance for Industry [Internet]. 2020 [cited 2023 Feb 12]. Available from: https://www.fda.gov/media/113768/download
[72] Werther, W., Loughlin, A.M. (2022). Post-Approval Regulatory Requirements. In: Piantadosi, S., Meinert, C.L. (eds) Principles and Practice of Clinical Trials. Springer, Cham. [cited 2023 Feb 12]. p.699–725. Available from: https://doi.org/10.1007/978-3-319-52636-2_256
[73] Consumers H, ECORYS Nederland BV, University Utrecht, Schothorst M van, Weeda J, Schiffers K, et al. Study on the regulation of advanced therapies in selected jurisdictions: final report [Internet]. Publications Office of the European Union. LU: Publications Office of the European Union; 2016 [cited 2023 Feb 14]. p.24-43. Available from: https://op.europa.eu/en/publication-detail/-/publication/78af6082-bc4a-11e6-a237-01aa75ed71a1
[74] Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). Guidance for Industry Expedited Programs for Serious Conditions -Drugs and Biologics [Internet]. 2014 [cited 2021 Nov 20] p. 1-25. Available from: https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf
[75] Commission Regulation (EC) No 507/2006 of 29 March 2006. on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council (Text with EEA relevance) [Internet]. 2006 [cited 2021 Nov 8] p. 3. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32006R0507&from=IT
[76] Food and Drug Administration Center for Biologics Evaluation and Research. Expedited Programs for Regenerative Medicine Therapies for Serious Conditions Guidance for Industry

[Internet]. 2019 [cited 2021 Nov 20] p.1-5. Available from: https://www.fda.gov/media/120267/download
[77] European Medicines Agency. Guidance for applicants seeking access to PRIME scheme. [Internet]. 2018. [cited 2021 Nov 20]. Available from: https://www.ema.europa.eu/en/documents/other/european-medicines-agency-guidance-applicants-seeking-access-prime-scheme_en.pdf. 2018.
[78] European Medicines Agency. Guideline on the scientific application and the practical arrangements necessary to implement the procedure for accelerated assessment pursuant to Article 14(9) of Regulation (EC) No 726/2004 [Internet]. 2016 [cited 2021 Dec 1]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-scientific-application-practical-arrangements-necessary-implement-procedure-accelerated/2004_en.pdf
[79] Center for Biologics Evaluation and Research. SOPP 8401.2: Administrative Processing of BLA and NDA Supplements [Internet]. 2024 [cited 2024 Feb 15]. Available from: https://www.fda.gov/media/108895/download
[80] Regulation (EC) No 726/2004 of the European Parliament and of the council of 31 March 2004. laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (Text with EEA relevance) [Internet]. 2004 [cited 2021 Dec 5] p. 8. Available from: https://health.ec.europa.eu/system/files/2016-11/reg_2004_726_en_0.pdf
[81] European Medicines Agency. Zynteglo Withdrawal of the marketing authorisation in the European Union [Internet]. 2022 [cited 2023 Dec]. Available from: https://www.ema.europa.eu/en/documents/public-statement/public-statement-zynteglo-withdrawal-marketing-authorisation-european-union_en.pdf
[82] European Medicines Agency. EU/3/12/1003 - orphan designation for treatment of adrenoleukodystrophy | European Medicines Agency [Internet]. www.ema.europa.eu. [cited 2023 Dec]. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu-3-12-1003
[83] European Medicines Agency. MACI Referral - Closure of EU manufacturing site for MACI [Internet]. European Medicines Agency. 2014 [cited 2022 Aug 19]. Available from: https://www.ema.europa.eu/en/documents/referral/maci-article-20-procedure-closure-eu-manufacturing-site-maci_en.pdf
[84] European Medicines Agency. Public statement Provenge [Internet]. 2015 May [cited 2022 Oct 8]. Available from: https://www.ema.europa.eu/en/documents/public-statement/public-statement-provenge-withdrawal-marketing-authorisation-european-union_en.pdf
[85] Committee for Orphan Medicinal Products Orphan designation withdrawal assessment report [Internet]. 2022 [cited 2022 Oct 16]. Available from: https://www.ema.europa.eu/en/documents/orphan-maintenance-report/breyanzi-orphan-designation-withdrawal-assessment-report-initial-authorisation_en.pdf
[86] Committee for Medicinal Products for Human Use (CHMP) Assessment report [Internet]. 2022 [cited 2022 Oct 16] p. 20. Available from: https://www.ema.europa.eu/en/documents/assessment-report/breyanzi-epar-public-assessment-report_en.pdf
[87] European Medicines Agency. European Medicines Agency post-authorisation procedural advice for users of the centralised procedure [Internet]. 2009 Jul [cited 2021 Oct 26] p. 168-221. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-post-authorisation-procedural-advice-users-centralised-procedure_en.pdf
[88] Guideline on good pharmacovigilance practices (GVP) Module V -Risk management systems (Rev 2) [Internet]. 2017 [cited 2023 Feb 5] p. 20–22. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf
[89] Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies [Internet]. 2017 [cited 2023 Feb 5] p. 5. Available from:

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf
[90] European Medicines Agency. EU PASS/PAES Requirements for Disclosure [Internet]. [cited 2023 Mar 15]. Available from: https://www.ema.europa.eu/en/documents/presentation/presentation-eu-pass/paes-requirements-disclosure-thomas-goedecke_en.pdf
[91] Guidance for Industry Postmarketing Studies and Clinical Trials - Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act Drug Safety [Internet]. 2011 [cited 2022 Apr 20] p. 9. Available from: https://www.fda.gov/media/131980/download
[92] Postmarketing Requirement/Commitment Related Submissions -Administrative Handling, Review, and CBER Reporting [Internet]. 2022 [cited 2022 Apr 20] p. 2. Available from: https://www.fda.gov/media/90205/download
[93] Federal Register. CRF Title 21 Chapter I Subchapter F Part 601 Subpart E [Internet]. unblock.federalregister.gov. [cited 2023 Feb 18]. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-F/part-601/subpart-E
[94] CFR - Code of Federal Regulations Title 21 subpart H of 21 CFR part 314 [Internet]. www.accessdata.fda.gov. [cited 2023 Feb 18]. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=314&showFR=1&subpartNode=21:5.0.1.1.4.8
[95] CFR - Code of Federal Regulations Title 21 PART 601 -LICENSING Subpart C - Biologics Licensing Sec. 601.27 Pediatric studies. [Internet]. www.accessdata.fda.gov. [cited 2023 Feb 18]. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=601.27#:~:text=%28b%29%20Deferred%20submission.%20%281%29%20FDA%20may%2C%20on%20its
[96] Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases Guidance for Industry [Internet]. 2018 [cited 2023 Feb 18] p. 1–6. Available from: https://www.fda.gov/files/about%20fda/published/Clarification-of-Orphan-Designation-of-Drugs-and--Biologics-for-Pediatric-Subpopulations-of-Common-Diseases.pdf
[97] Federal Register. Title 21 Chapter I Subchapter F Part 601 Subpart H [Internet]. unblock.federalregister.gov. [cited 2023 Feb 18]. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-F/part-601/subpart-H
[98] Federal Register. Title 21 Chapter I Subchapter D Part 314 Subpart I 314.610 [Internet]. unblock.federalregister.gov. [cited 2023 Feb 18]. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-314/subpart-I/section-314.610
[99] Guidance for Industry Reports on the Status of Postmarketing Study Commitments - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 [Internet]. 2006 [cited 2022 Apr 20] p. 14. Available from: https://www.fda.gov/media/72535/download
[100] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Assessment report Imlygic [Internet]. 2015 p. 127–50. Available from: https://www.ema.europa.eu/en/documents/assessment-report/imlygic-epar-public-assessment-report_en.pdf
[101] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Assessment report Provenge/Sipuleucel-T [Internet]. 2013 [cited 2023 Jan 17] p. 126–35. Available from: https://www.ema.europa.eu/en/documents/assessment-report/provenge-epar-public-assessmentreport_en.pdf
[102] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Assessment report MACI [Internet]. 2013 [cited 2023 Jan 17]. p.3-107Available from: https://www.ema.europa.eu/en/documents/assessment-report/maci-epar-public-assessment-report_en.pdf
[103] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Assessment report YESCARTA [Internet]. 2018 [cited 2023 Jan 17] p. 48-127. Available from:

https://www.ema.europa.eu/en/documents/assessment-report/yescarta-epar-public-assessment-report_en.pdf
[104] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Yescarta study KT-EU-471-0117. PASS Protocol Lisocabtagene maraleucel. View Study [Internet]. www.encepp.eu. [cited 2023 Feb 9]. https://www.encepp.eu/encepp/openAttachment/fullProtocolLatest/50253
[105] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Assessment report kymriah [Internet]. 2018 [cited 2023 Feb 9] p. 182–97. Available from: https://www.ema.europa.eu/en/documents/assessment-report/kymriah-epar-public-assessmentreport_en.pdf
[106] European Medicines Agency. Committee for Advanced Therapies (CAT) Committee for Medicinal Products for Human Use (CHMP) Assessment report Kymriah [Internet]. 2022. [cited 2023 Feb] Available from: https://www.ema.europa.eu/en/documents/variation-report/kymriah-h-c-4090-ii-0044-epar-assessment-report-variation_en.pdf
[107] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) CHMP assessment report Tecartus [Internet]. 2020 p. 121–31. Available from: https://www.ema.europa.eu/en/documents/assessment-report/tecartus-epar-public-assessment report_en.pdf
[108] European Medicines Agency. Committee for Advanced Therapies (CAT) Committee for Medicinal Products for Human Use (CHMP) Assessment report Tecartus [Internet]. 2022 [cited 2023 Feb] p. 106–19. Available from: https://www.ema.europa.eu/en/documents/variation-report/tecartus-h-c-005102-ii-0008-gepar-assessment-report-variation_en.pdf
[109] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Assessment report Hemgenix [Internet]. 2022 [cited 2023 Dec] p. 149–22. Available from: https://www.ema.europa.eu/en/documents/assessment-report/hemgenix-epar-public-assessment-report_en.pdf
[110] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Committee for Advanced Therapies (CAT) Assessment report Zolgensma [Internet]. 2020 [cited 2023 Feb 16] p. 134–25. Available from: https://www.ema.europa.eu/en/documents/assessment-report/zolgensma-epar-public-assessment-report_en.pdf
[111] European Medicines Agency. Committee for Advanced Therapies (CAT) Committee for Medicinal Products for Human Use (CHMP) Assessment report [Internet]. 2022[cited 2023 Feb] p. 8. Available from: https://www.ema.europa.eu/en/documents/variation-report/tecartus-h-c-005102-ii-0008-g-epar-assessment-report-variation_en.pdf
[112] European Medicines Agency. Committee for Advanced Therapies (CAT) Committee for Medicinal Products for Human Use (CHMP) Assessment report [Internet]. 2022 [cited 2023 Feb] p. 9. Available from: https://www.ema.europa.eu/en/documents/minutes/minutes-cat-meeting-15-17-june-2022_en.pdf
[113] European Medicines Agency. Committee for Advanced Therapies (CAT) Minutes of the meeting on 30-31 October 2023 [Internet]. [cited 2023 Dec]. Available from: https://www.ema.europa.eu/en/documents/minutes/minutes-cat-meeting-30-31-october-2023_en.pdf
[114] European Medicines Agency. Abecma, Procedural steps taken and scientific information after the authorisation. Assessment report [Internet]. p 4. Available from: https://www.ema.europa.eu/en/documents/procedural-steps-after/abecma-epar-procedural-stepstaken-scientific-information-after-authorisation_en.pdf
[115] European Medicines Agency. Committee for Advanced Therapies (CAT) Committee for Medicinal Products for Human Use (CHMP) Assessment report [Internet]. 2022 [cited 2023 Feb] Available from: https://www.ema.europa.eu/en/documents/minutes/minutes-cat-meeting-7-9-december-2022_en.pdf
[116] European Medicines Agency. Carvykti, Procedural steps taken and scientific information after the authorisation. Assessment report [Internet]. [cited 2023 Feb] p 4. Available from

https://www.ema.europa.eu/en/documents/procedural-steps-after/carvykti-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf
[117] European Medicines Agency. Committee for Advanced Therapies (CAT) Minutes of the meeting on 16-17 February 2022 [Internet]. [cited 2023 Dec]. Available from: https://www.ema.europa.eu/en/documents/minutes/minutes-cat-meeting-16-17-february-2022_en.pdf
[118] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Assessment report Carvykti [Internet]. 2022. Available from: https://www.ema.europa.eu/en/documents/assessment-report/carvykti-epar-public-assessmentreport_en.pdf
[119] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Study Protocol of non-interventional post-authorisation safety study PASS, study title: Tecartus Survey: Quantitative Testing of Health Care Professional Knowledge About Tecartus® Risk Minimisation Measures [Internet]. [cited]. Available from: https://www.encepp.eu/encepp/openAttachment/fullProtocol/104051
[120] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Assessment report Roctavian [Internet]. 2022 [cited 2023 Dec] p. 137–63. Available from: https://www.ema.europa.eu/en/documents/assessment-report/roctavian-epar-public-assessment-report_en.pdf
[121] Committee for Medicinal Products for Human Use (CHMP) Assessment report Hemgenix [Internet]. 2022 [cited 2023 Dec] p. 129–49. Available from: https://www.ema.europa.eu/en/documents/assessment-report/hemgenix-epar-public-assessmentreport_en.pdf
[122] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Final Study Report of non-interventional post-authorisation safety study PASS, study title: A Cross-sectional Survey to Evaluate Physician Knowledge of Safety Messages included Physician Education Booklet (PEB) with for IMLYGIC ® [Internet]. [cited]. Available from: https://www.encepp.eu/encepp/openAttachment/studyResult/38847;jsessionid=Wi08OiiF2qiEuqOfkEvshmwgRFmYz09dMV1Heitpcp5sPu2P_skd!-1783076594
[123] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Final Study Report of non-interventional post-authorisation safety study PASS, study title: A Cross-sectional Survey to Evaluate Patient Knowledge of Safety Messages Included in the Patient Safety Brochure and Patient Alert Card for IMLYGIC ® [Internet]. [cited]. Available from: https://www.encepp.eu/encepp/openAttachment/studyResult/45943
[124] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Final Study Report of non-interventional post-authorisation safety study PASS, study title: Quantitative Testing of Healthcare Provider Knowledge about YESCARTA (axicabtagene ciloleucel) Risk Minimisation Measures [Internet]. [cited 2023]. Available from: https://www.encepp.eu/encepp/openAttachment/studyResult/43869
[125] European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module VIII - Post-authorisation safety studies (Rev 2) [Internet]. 2015 [cited 2023] p. 7–8. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies_en.pdf
[126] European Medicines Agency. Opinion of the Paediatric Committee on the acceptance of a modification of an agreed Paediatric Investigation Plan and on the granting of a product-specific waiver [Internet]. [cited 2023] p. 5. Available from: https://www.ema.europa.eu/en/documents/pip-decision/p/0114/2022-decision-13-april-2022-acceptance-modification-agreed-paediatric-investigation-plan_en.pdf
[127] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Assessment report Kymriah [Internet]. 2022 [cited 2023]. Available from: https://www.ema.europa.eu/en/documents/variation-report/kymriah-h-c-004090-p46-022-epar-assessment-report_en.pdf

[128] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Assessment report Zynteglo [Internet]. 2019 [cited 2023 Dec] p. 25–143. Available from: https://www.ema.europa.eu/en/documents/assessment-report/zynteglo-epar-public-assessment-report_en.pdf
[129] U.S. Food and Drug Administration. Center for Biologics Evaluation and. Cellular & Gene Therapy Guidances. FDA [Internet]. 2021 Jan 19; Available from: https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances
[130] EMA. Guidelines relevant for advanced therapy medicinal products [Internet]. European Medicines Agency. 2018. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/advanced-therapies/guidelines-relevant-advanced-therapy-medicinal-products
[131] Food and drug administration. CDER drug and biologic animal rule approvals [Internet]. Available from: https://www.fda.gov/media/150191/download
[132] A Study of MACI in Patients Aged 10 to 17 Years With Symptomatic Chondral or Osteochondral Defects of the Knee - Full Text View - ClinicalTrials.gov [Internet]. clinicaltrials.gov. [cited 2023 Mar 22]. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT03588975?term=Autologous+Cultured+Chondrocytes+on+a+Porcine+Collagen+Membrane&draw=2&rank=3
[133] Food and Drug Administration. Summary Basis for Regulatory Action talimogene laherparepvec [Internet]. 2015 [cited 2023 Mar] p. 19. Available from: https://wayback.archive-it.org/7993/20190425013447/https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM473103.pdf
[134] U.S. Food and Drug Administration. Elivaldogene autotemcel Approval letter BLA 125755/0 [Internet]. 2022 [cited 2023 Dec]. Available from: https://www.fda.gov/media/161665/download?attachment
[135] U.S. Food and Drug Administration. Summary Basis for Regulatory Action, betibeglogene autotemcel [Internet]. 2022 [cited 2023 Dec] p. 18. Available from: https://www.fda.gov/media/161472/download?attachment
[136] U.S. Food and Drug Administration. Office of Tissues and Advanced Therapies (OTAT), Division of Cellular and Gene Therapies (DCGT). Hemgenix Summary Basis for Regulatory Action [Internet]. 2022 [cited 2023 Dec]. p. 17 Available from: https://www.fda.gov/media/164094/download?attachment
[137] U.S. Food & Drug Administration. Brexucabtagene autoleucel Summary Basis for Regulatory Action [Internet]. Available from: https://www.fda.gov/media/141093/download
[138] Wang M, Munoz J, Goy A, Locke FL, Jacobson CA, Hill BT, et al. Three-Year Follow-Up of KTE-X19 in Patients with Relapsed/Refractory Mantle Cell Lymphoma, Including High-Risk Subgroups, in the ZUMA-2 Study. Journal of Clinical Oncology. 2022 Jun 4. [Internet]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9870225/
[139] Food and Drug Administration, Office of Tissues, and Advanced Therapies. Summary Basis for Regulatory Action idecabtagene vicleucel [Internet]. 2021 p. 27. Available from: https://www.fda.gov/media/147627/download
[140] ClinicalTrials.gov. FDAAA 801 and the Final Rule [Internet]. clinicaltrials.gov. [cited 2023 Dec]. Available from: https://clinicaltrials.gov/policy/fdaaa-801-final-rule
[141] U.S. Food and Drug Administration. Accelerated Approval Program [Internet]. FDA. 2023 [cited 2023 Dec]. Available from: https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approvalprogram#:~:text=The%20FDA%20instituted%20its%20Accelerated,based%20on%20a%20surrogate%20endpoint.%22
[142] Committee for Medicinal Products For Human Use (CHMP) Guideline On The Scientific Application And The Practical Arrangements Necessary To Implement Commission Regulation (EC) No 507/2006 On The Conditional Marketing Authorisation For Medicinal Products For Human Use Falling Within The Scope Of Regualtion (EC) No 726/2004 CHMP [Internet]. 2006 [cited 2023 Nov]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/draftguideline-scientific-

application-and-practical-arrangements-necessary-implement-commission-regulation-ec-no-5072006-conditional-marketing-authorisation-medicinal-products-human-use-f_en.pdf
[143] European Medicines Agency. European Medicines Agency post-authorisation procedural advice for users of the centralised procedure [Internet]. 2023 [cited 2024] p. 69. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-post-authorisation-procedural-advice-users-centralised-procedure_en.pdf
[144] Moneer O, Brown BL, Avorn J, Darrow JJ, Mitra-Majumdar M, Joyce KW, et al. New Drug Postmarketing Requirements and Commitments in the US: A Systematic Review of the Evidence. Drug Safety. 2022 Feb 19;45(4):305–18. Available from: https://link.springer.com/article/10.1007/s40264-022-01152-9
[145] Choi L, Etchey B, Billings M, Lee C, Weil KM, Boxwell D, et al. A descriptive analysis of postmarketing requirement studies and clinical trials. Pharmacoepidemiology and Drug Safety. 2023 Nov 23; Available from: https://onlinelibrary.wiley.com/doi/10.1002/pds.5725
[146] Brown BL, Mitra-Majumdar M, Darrow JJ, Moneer O, Pham C, Avorn J, et al. Fulfillment of Postmarket Commitments and Requirements for New Drugs Approved by the FDA, 2013-2016. JAMA Internal Medicine. 2022 Nov 1;182(11):1223. Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2797103
[147] The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (Revision 11). EMA/95098/2010. [Internet]. [cited 2023]. p.126-131. Available from: https://encepp.europa.eu/document/download/f6e403a6-8033-4c22-a5ff-195ba3666299_en?filename=01.ENCePPMethodsGuideRev.11.pdf
[148] U.S Food and Drug Administration. Framework for FDA's Real-World Evidence Program [Internet]. 2018. [cited 2023]. Available from: https://www.fda.gov/media/120060/download
[149] A Framework for Regulatory Use of Real-World Evidence [Internet]. Center for Health Policy at Duke University. [cited 2023]. Available from: https://healthpolicy.duke.edu/publications/framework-regulatory-use-real-world-evidence
[150] U.S. Food and Drug Administration. Real-World Evidence Guidances [Internet]. U.S. Food and Drug Administration. 2019. Available from: https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence
[151] European Medicines Agency. Inspections and Human Medicines Pharmacovigilance Division Initiative for patient registries Strategy and pilot phase [Internet]. 2015 [cited 2023]. Available from: https://www.ema.europa.eu/en/documents/other/initiative-patient-registries-strategy-pilot-phase_en.pdf#:~:text=The%20main%20objective%20of%20the%20initiative%20for%20patient
[152] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Qualification opinion on Cellular therapy module of the European Society for Blood & Marrow Transplantation (EBMT) Registry. EMA/CHMP/SAWP/792574/2018 [Internet]. 2019 [cited 2023]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/qualification-opinion-cellular-therapy-module-european-society-blood-marrow-transplantation-ebmt_en.pdf
[153] European Medicines Agency. Committee for Advanced Therapies (CAT): Work Plan 2023 [Internet]. [cited 2023] p. 4–6. Available from: https://www.ema.europa.eu/en/documents/other/committee-advanced-therapies-cat-work-plan-2023_en.pdf
[154] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Non-Interventional Study Protocol V07, CTL019/Tisagenlecleucel/CCTL019B2401 [Internet]. www.encepp.eu. [cited 2023 March 25]. Available from: https://www.encepp.eu/encepp/viewResource.htm?id=42020
[155] Food and Drug Administration. [homepage on the Internet]. Approval letter - Kymriah. U.S. Food and Drug Administration Center for Biologics Evaluation and Research (CBER); 2017 [cited 2023 March 3]. Available from: https://www.fda.gov/media/106989/download

[156] Food and Drug Administration. [homepage on the Internet]. Biologics License Application (BLA) Clinical Review and Evaluation, STN: 125646/663 (Tisagenlecleucel). Food and Drug Administration. 2022 [cited 2023 March 3]. Available from: https://www.fda.gov/media/159700/download
[157] Committee for Medicinal Products for Human Use (CHMP) Assessment report Procedural steps taken and scientific information after the authorisation [Internet]. 2023 [cited 2023 March 3] Available from: https://www.ema.europa.eu/en/documents/procedural-steps-after/kymriah-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf
[158] Annex I summary of product characteristics [Internet]. [cited 2023 Mar 12]. Available from: https://www.ema.europa.eu/en/documents/product-information/kymriah-epar-product-information_en.pdf
[159] Committee for Medicinal Products for Human Use (CHMP) Assessment report [Internet]. 2018 [cited 2023 Feb 15] p. 76–96. Available from: https://www.ema.europa.eu/en/documents/assessment-report/luxturna-epar-public-assessment-report_en.pdf
[160] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. CLTW888A12401 v01, Protocol/Voretigene neparvovec [Internet]. www.encepp.eu. [cited 2023 Feb 15]. Available from: https://www.encepp.eu/encepp/openAttachment/fullProtocol/31152
[161] Long-term Follow-up Study in Subjects Who Received Voretigene Neparvovec-rzyl (AAV2-hRPE65v2) ClinicalTrials.gov ID NCT03602820 [Internet]. clinicaltrials.gov. [cited 2023 Feb 15]. Available from: https://clinicaltrials.gov/study/NCT03602820?tab=table
[162] Registry of Patients with a Diagnosis of Spinal Muscular Atrophy (SMA) - ClinicalTrials.gov [Internet]. clinicaltrials.gov. [cited 2023 Feb 16]. Available from: https://classic.clinicaltrials.gov/ct2/show/record/NCT04174157?term=AVXS-101-RG-001&draw=2&rank=1
[163] Long-Term Follow-up Study for Patients From AVXS-101-CL-101 - Full Text View - ClinicalTrials.gov [Internet]. clinicaltrials.gov. [cited 2023 Feb 15]. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT03421977?term=AVXS-101-LT-001&draw=2&rank=1
[164] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Study protocol. Study Title Long-term, non-interventional study of recipients of Tecartus for treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) [Internet]. 2021 [cited 2023]. Available from: https://www.encepp.eu/encepp/openAttachment/fullProtocol/45816
[165] U.S. Food and Drug Administration. Office of Tissues and Advanced Therapies. Tecartus/brexucabtagene autoleucel. Summary Basis for Regulatory Action. Available from: https://www.fda.gov/media/141093/download
[166] U.S. Food and Drug Administration. Tecartus/Brexucabtagene Approval letter BLA 125703/91, supplement approval. Available from: https://www.fda.gov/media/152696/download
[167] Press- Kite's Tecartus® CAR T-cell Therapy Demonstrates 78% Complete Response Rate and 90% Overall Response Rate in Largest Real-World Evidence Analysis for Relapsed/Refractory Mantle Cell Lymphoma [Internet]. www.kitepharma.com. [cited 2023 Dec]. Available from: https://www.kitepharma.com/news/press-releases/2023/6/kites-tecartus-car-tcelltherapy-demonstrates-78-complete-response-rate-and-90-overall-response-rate-in-largest-realworld-evidence-analysis-for-r
[168] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Abecma ® (idecabtagene vicleucel) BB2121-MM-006 Study protocol [Internet]. 2021 [cited 2023]. Available from: https://www.encepp.eu/encepp/openAttachment/fullProtocol/45498
[169] U.S. Food and Drug Administration, Office of Tissues, and Advanced Therapies. Summary Basis for Regulatory Action, idecabtagene vicleucel/ABECMA [Internet]. 2021 p. 15–27. Available from: https://www.fda.gov/media/147627/download
[170] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Assessment report Carvykti [Internet]. 2022. Available from:

https://www.ema.europa.eu/en/documents/assessment-report/carvykti-epar-public-assessment-report_en.pdf
[171] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Carvykti study 68284528MMY4004. View Study [Internet]. www.encepp.eu. [cited 2023]. Available from: https://www.encepp.eu/encepp/viewResource.htm?id=49219
[172] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Carvykti study 68284528MMY4009. View Study [Internet]. www.encepp.eu. [cited 2023]. Available from: https://www.encepp.eu/encepp/viewResource.htm?id=50187
[173] U.S. Food and Drug Administration. Office of Tissues and Advanced Therapies. Summary Basis for Regulatory Action, ciltacabtagene autoleucel/CARVYKTI [Internet]. p. 9–14. Available from: https://www.fda.gov/media/156999/download
[174] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Assessment report Breyanzi [Internet]. 2022 p. 238–252. Available from: https://www.ema.europa.eu/en/documents/assessment-report/breyanzi-epar-public-assessment-report_en.pdf
[175] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Breyanzi study CA082-110 Protocol. PAES Protocol Lisocabtagene maraleucel. View Study [Internet]. www.encepp.eu. [cited 2023]. Available from: https://www.encepp.eu/encepp/openAttachment/fullProtocol/104025
[176] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Breyanzi study JCAR017-BCM-005. PASS Protocol Lisocabtagene maraleucel. View Study [Internet]. www.encepp.eu. [cited 2023]. Available from: https://www.encepp.eu/encepp/openAttachment/fullProtocol/104026
[177] U.S. Food and Drug Administration. Office of Tissues and Advanced Therapies. Breyanzi Summary Basis for Regulatory Action [Internet]. 2021 [cited 2023]. Available from: https://www.fda.gov/media/146242/download
[178] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Yescarta study KT-EU-471-0117. PASS Protocol Lisocabtagene maraleucel. View Study [Internet]. www.encepp.eu. [cited 2023]. https://www.encepp.eu/encepp/openAttachment/fullProtocolLatest/50253
[179] U.S. Food and Drug Administration. Office of Tissues and Advanced Therapies. Yescarta Summary Basis for Regulatory Action [Internet]. 2017. Available from: https://www.fda.gov/media/108788/download
[180] U.S. Food and Drug Administration. Yescarta Approval letter BLA 125643/248, supplement approval. Available from: https://www.fda.gov/media/148510/download
[181] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Talimogene laherparepvec/Imlygic clinical study report 20120139. [Internet]. www.encepp.eu. [cited 2023]. Available from: https://www.encepp.eu/encepp/openAttachment/studyResult/47497
[182] Brittberg M, Recker D, Ilgenfritz J, Saris DBF, SUMMIT Extension Study Group. Matrix-Applied Characterized Autologous Cultured Chondrocytes Versus Microfracture: Five-Year Follow-up of a Prospective Randomized Trial. The American Journal of Sports Medicine [Internet]. 2018 May 1;46(6):1343–51. Available from: https://pubmed.ncbi.nlm.nih.gov/29565642/
[183] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Assessment report Provenge/Sipuleucel-T [Internet]. 2013 p. 126–35. Available from: https://www.ema.europa.eu/en/documents/assessment-report/provenge-epar-public-assessment-report_en.pdf
[184] U.S. Food and Drug Administration. Office of Tissues and Advanced Therapies. Summary Basis for Regulatory Action Provenge [Internet]. 2010 [cited 2023]. Available from: http://wayback.archive-it.org/7993/20170723023808/https:/www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM213114.pdf

[185] Higano CS, Armstrong AJ, Sartor AO, Vogelzang NJ, Kantoff PW, McLeod DG, et al. Real-world outcomes of sipuleucel-T treatment in PROCEED, a prospective registry of men with metastatic castration-resistant prostate cancer. Cancer. 2019 Sep 4;125(23):4172–80.
[186] Mofid S, Winona Rei Bolislis, Kühler TC. Real-World Data in the Postapproval Setting as Applied by the EMA and the US FDA. Clinical Therapeutics. 2022 Jan 1;44(2):306–22.
[187] European Medicines Agency. Use of disease registries for benefit- risk evaluation of medicines: A regulatory perspective [Internet]. 2018. Available from: https://www.ema.europa.eu/en/documents/presentation/presentation-registry-initiative-april-2018_en.pdf

Annex 1 – Supplementary information

Table 1. FDA Postmarketing commitments extracted.

Product brand name	Category	PMC Description	Focus	PMC Due date
Provenge	non-reportable (non-506B PMC)	The CMC review team determined that in lieu of CBER lot release testing, the sponsor should submit summary analyses and data trending of lot release testing conducted for all lots generated during a manufacturing year. ----------b(4)----------	CMC - Quality	Missing
MACI	non-reportable (non-506B PMC)	1. a Develop a quantitative method and validation of the method. 1. b. Provide an initial release specification. 1. c. Provide in Annual Reports to the BLA, summary data for b (4) quantitation. 1. d. Provide updated acceptance criteria for b(4) testing. Add b(4) testing for future validation.	CMC - Quality	To implement/complete by: 30/06/2017.
		2. To perform the following to complete the implementation of testing as an ACI-Maix collagen membrane quality inspection item: a,b,c,d and e points	CMC - Quality	To implement/complete by: 31/03/2017
		3. Complete updates to all standard operating procedure (SOP) documentation requiring revision due to obsoleted procedures and to implement the revised SOPs.	CMC - Quality	To implement/complete by 28/02/2017

Kymriah	non-reportable (non-506B PMC)	commits to submit a Prior Approval Supplement with revised Percentage of Viable T cells lot release criterion in alignment with the demonstrated tisagenlecleucel commercial manufacturing capability.	CMC - Quality	Final Report Submission: July 31, 2022
	non-reportable (non-506B PMC)	Revalidation of Mycoplasma Testing validation for vector (initial approval)	CMC - Quality	Final Report Submission: 30/06/2018
Luxturna	non-reportable (non-506B PMC)	Shipping validation study protocol of the Drug Product	CMC - Quality	Final Report Submission: 30/06/2018
		Verification studies for essays - tests for particulate matter for the Drug Product and Diluent, performed	CMC - Quality	Final Report Submission: 31/03/2018
		Analysis of the lot release test results obtained from all Drug Substance (DS) and Drug Product (DP) and evaluate if the acceptance criteria for lot release tests provide adequate quality control for DS and DP	CMC - Quality	Final Report Submission: 31/03/2020.
		Stability studies s on the HEK293 (MCB) used for Drug Substance manufacture	CMC - Quality	Final Report Submission: 31/03/2018.
		Qualification of (b) (4)	CMC - Quality	Final Report Submission: 31/03/2018.
		Revise procedures for visual inspection to incorporate statistically sound sampling plans. The sampling plan will include appropriate acceptance criteria for critical and major defects.	CMC - Quality	Final Report Submission: 30/06/2018
		Revised procedure for performing cleaning verification.	CMC - Quality	Final Report Submission: 30/09/2018

Zolgensma	non-reportable (non-506B PMC)	Agrees to develop and qualify a suitable method for quantifying (b) (4) providing the method qualification report and providing an additional process validation report for (b) (4)	CMC - Quality	Final Report Submission: 31/12/2019
		Agrees to validate the robustness of the (b) (4) assay per protocol REC2566 and will provide the validation report.	CMC - Quality	Final Report Submission: 31/12/2019
		Update the (b) (4) assay to include the assay validity criterion for the reference standard and provide the supplemental validation report for robustness	CMC - Quality	Final Report Submission: 31/12/2019
		agrees to revise the Bioburden Determination operating procedure (SOP-085) to be compliant with(b) (4) , including (b) (4) on(b) (4) . Agrees to implement the revised SOP-085 for all bioburden tests and to provide the revised SOP-085.	CMC - Quality	Final Report Submission: 01/07/2019
Abecma	506B-Reportable PMC	commits to submit an integrated final report containing data from clinical trials MM-002 and MM-003 to further characterize the safety and efficacy of idecabtagene vicleucel among African-Americans/ Blacks with multiple myeloma. The primary objective of this analysis is to evaluate the efficacy of idecabtagene vicleucel in the subpopulation of African-Americans/Blacks with multiple myeloma compared to the subpopulation of Whites, and the secondary objective is safety. Ensure that the representation of the African American subpopulation in the studies is reflective of the Black	Efficacy and safety	Final analysis by: 30 April 2025. Final Report Submission: 31/10/2025

		population in the geographical location/country. Therefore, approximately 15% of the population that is enrolled from the US should comprise of African Americans. Prespecify an analysis plan for safety and efficacy with a justification/rationale of prespecified assumptions for efficacy outcomes.		
	non-reportable (non-506B PMC)	Comparability study between methods (b) (4) to provide assurance that the alternate method is equal to or greater than the assurances provided by the method for ide-cel and will provide the final study report.	CMC - Quality	Final Report Submission: August 31, 2021
Breyanzi	non-reportable (non-506B PMC)	Commits to prospectively validate (b) (4) and provide report	CMC - Quality	Final Report Submission: 30/09/2021
Zynteglo	non-reportable (non-506B PMC)	CMC – commitments 8 points: 3. commits to qualify a test of their to provide greater assurance of their final drug product and to submit these qualification results as a supplement to their file on or before March 31 of 2023. 4. commits to establish the sensitivity of method for the bag. 5. commits to perform the additional assessments of the assays as described in BLA 125717. 6. commits to add testing of beti-cel cryopreserved drug product (DP) for as described in BLA 125717. 7. commits to perform a supplemental study of beti-cel assessing the under the intended conditions as described in BLA 125717.	CMC - Quality	3. Final Report Submission: March 31 4. Final Report Submission: February 28, 2023 5. Final Report Submission: June 30, 2023 6. Final Report Submission: February 28, 2023 7. Final Report Submission: February 28, 2023 8. Final Report Submission: February 28, 2023 9. Final Report Submission: December 31, 2022

		8. commits to assess the feasibility of The feasibility assessment will include a proposed path forward for completing a leachable study for the (b) (4), including a date the final leachable study report will be submitted to the FDA. 9. commits to conducting testing following the conditions outlined in and provide justifications for the test method, results, and conclusions as part of a complete test report. 10. commits to perform a study to evaluate drug product bag integrity following (b) (4)		10. Final Report Submission: December 31, 2022
Skysona	non-reportable (non-506B PMC)	6. commits to qualify a test of their to provide greater assurance of their final drug product and to submit these qualification results as a supplement to their file on or before March 31 of 2023. 7. commits to providing a final report of the qualification results of from the drug product manufacturing facility. 8. commits to establish the sensitivity of method for the bag. 9. commits to perform the additional robustness assessments of the assays as described in BLA 125755. 10. commits to add testing of eli-cel cryopreserved drug product (DP) for as described in BLA 125755. 11. commits to perform a supplemental in-use stability study of eli-cel assessing the stability of under the intended conditions as described in BLA 125755. 12. bluebird bio, Inc., commits to assess the feasibility of detecting	CMC - Quality	6. Final Report Submission: March 31, 2023 7. Final Report Submission: October 31, 2022 8. Final Report Submission: February 28, 2023 9. Final Report Submission: June 30, 2023 10. Final Report Submission: February 28, 2023 11. Final Report Submission: March 31, 2023 12. Final Feasibility Assessment Report Submission: February 28, 2023 13. Final Report Submission: December 31, 2022 14. Final Report Submission: December 31, 2022

		(b) (4) The feasibility assessment will include a proposed path forward for completing a leachable study for the , including a date the final leachable study report will be submitted to the FDA. 13. commits to conducting testing following the conditions outlined in and provide justifications for the test method, results, and conclusions as part of a complete test report. Complete test reports for this testing on the bag will be submitted as a final study report by December 31, 2022. 14. commits to perform a study to evaluate drug product bag integrity following (e.g., The testing will include. Complete test reports for this testing will be submitted as a final study report by December 31, 2022.		
Hemgenix	non-reportable (non-506B PMC)	3. Validate a suitable method for release testing of etranacogene dezaparvovec-drlb drug product for. A final assay validation report will be submitted in conjunction with the introduction of release testing with appropriate acceptance criteria	CMC - Quality	Final Report Submission: December 31, 2023
	non-reportable (non-506B PMC)	4. Assay validation report linked to (3)	CMC - Quality	Final Report Submission: December 31, 2023
	non-reportable (non-506B PMC)	5. CSL Behring commits to include (b)(4) assay for release testing of etranacogene dezaparvovec-drlb drug product. A final assay validation report will be submitted in conjunction with the introduction of release testing with appropriate acceptance criteria	CMC - Quality	Final report submission: July 30, 2023

	non-reportable (non-506B PMC)	6. CSL Behring commits to perform a long-term leachables study of the intended drug product container closures at the intended storage conditions	CMC - Quality	Final report submission: April 30, 2024
	non-reportable (non-506B PMC)	7. CSL Behring commits to complete (b)(4) validation for (b)(4)assays.	CMC - Quality	Final report submission: December 31, 2022
	non-reportable (non-506B PMC)	8. re-evaluate the acceptance criteria for release testing of etranacogene dezaparvovec-drlb drug substance and drug product based on manufacturing experience when additional data from (b)(4) drug substance and drug product commercial batches are available and revise if appropriate. A final (b)(4)acceptance criteria report after re-assessment will be submitted as a “PMC Submission-Final Study Report.	CMC - Quality	Final report submission: June 30, 2024