Universidade de Lisboa

Faculdade de Farmácia

Critical Analysis of the Worldwide Regulatory Tools for Expedited Marketing Authorization

Regina Simões Dias

Dissertação orientada pelo Professor Doutor Bruno Miguel Nogueira Sepodes e coorientada pelo Professor Doutor João Pedro Fidalgo Rocha.

Mestrado em Regulação e Avaliação de Medicamentos e Produtos de Saúde

2021

Universidade de Lisboa

Faculdade de Farmácia

Critical Analysis of the Worldwide Regulatory Tools for Expedited Marketing Authorization

Regina Simões Dias

Dissertação orientada pelo Professor Doutor Bruno Miguel Nogueira Sepodes e coorientada pelo Professor Doutor João Pedro Fidalgo Rocha.

Mestrado em Regulação e Avaliação de Medicamentos e Produtos de Saúde

2021

Resumo

Nos últimos anos, as ferramentas regulamentares, alinhadas com legislação nova ou revista sobre procedimentos ou programas de aprovação acelerada de medicamentos (químicos, biológicos ou terapias avançadas) foram melhoradas de forma a permitir uma disponibilização mais rápida de medicamentos inovadores em todo o mundo. As Agências Regulamentares dos Estados Unidos da América (EUA) e da União Europeia (UE) têm liderado o tema nas últimas três décadas, juntamente com a Agência Regulamentar do Japão, que publicou nova legislação e implementou novas ferramentas regulamentares mais recentemente.

Neste documento, analisamos as ferramentas regulamentares para agilizar a concessão de Autorizações de Introdução no Mercado (AIM) no contexto regulamentar da UE, EUA e Japão, avaliando as diferentes limitações das vias de aprovação *standard*. Foram analisadas informações em regulamentos, *guidelines*, relatórios, estatutos, entre outros documentos oficiais relacionados com as ferramentas regulamentares para aprovação de novos medicamentos, publicados pelas três Agências Regulamentares. Adicionalmente, também foi consultada literatura publicada, relacionada com o tema, para consolidação da informação. Consequentemente, as ferramentas regulamentares de cada mercado foram categorizadas, com base em requisitos de dados clínicos pré ou pós-AIM, aprovação com base num número limitado de doentes ou indicação, ou programas de suporte ao desenvolvimento de medicamentos. Foi considerado relevante o exemplo de Keytruda®, Veklury® e Kymriah® para avaliar o impacto da utilização destas ferramentas regulamentares de aprovação acelerada. Estes três casos enfatizam a diminuição dos prazos de avaliação e aprovação dos pedidos de AIM, permitindo um acesso mais rápido de medicamentos inovadores aos doentes para tratar necessidades médicas não satisfeitas. A FDA representa a Agência Regulamentar com o menor tempo mediano de aprovação e a PMDA e a EMA também têm vindo a melhorar este indicador durante a última década.

A utilização efetiva de procedimentos e programas de aprovação acelerada é crucial para dar resposta em áreas de necessidades médicas não satisfeitas e outras emergências de saúde pública, tal como a pandemia por COVID-19. A inovação e as questões emergentes de saúde pública exigem uma melhoria contínua das vias e processos de avaliação e aprovação, garantindo que os medicamentos inovadores são rigorosamente avaliados e estão mais rapidamente disponíveis para os doentes.

Palavras-chave: expedited pathways; regulatory review; FDA; EMA; PMDA.

Abstract

In the past years, regulatory tools aligned with revised or new legislation for expedited approval pathways and programs for medicines (chemical, biologics or advanced therapies) have been endorsed to allow faster availability of innovative medicines around the world. Regulatory Agencies in the United States of America (USA) and the European Union (EU) have been leading this topic during the last three decades, along with the Japanese Regulatory Agency, which has published new legislation and implemented new tools more recently.

Here we analyze the regulatory tools for expedited Marketing Authorizations (MAs) in the context of the EU, the USA and Japan regulatory landscape, evaluating how they address the limitations of standard approval pathways. Analysis of information on regulation, guidelines, reports, statutes, and other published documents by these three Regulatory Agencies related to the regulatory tools for approval of new medicines was performed. In addition, published literature related to this topic were also consulted for consolidation of information. Consequently, regulatory tools from each market were categorized, based on pre- or post-marketing authorization clinical data requirements, approval based on limited patient cohort or indication and development support programs. The example of Keytruda®, Veklury® and Kymriah® were considered valuable to evaluate the impact of using such expedited tools. The three cases emphasize the decrease in timelines for review and approval of MA applications, allowing a faster access of innovative medicines to patients to treat unmet medical needs. The FDA represents the Regulatory Agency with the shortest median time for approval and PMDA and EMA have been also improving this indicator during the last decade.

The effective application of expedited pathways and programmes is crucial in addressing areas of unmet medical need and other public health emergencies such as the Coronavirus Disease 2019 (COVID-19) pandemic. Innovation and emerging issues of public health require continuous improvement of pathways and processes of review and approval, granting that innovative medicines are scrupulously assessed and readily available to patients.

Keywords: expedited pathways; regulatory review; FDA; EMA; PMDA.

Agradecimentos

Ao Professor Doutor Bruno Sepodes agradeço as preciosas ideias e recomendações, e por nunca desistir de me incentivar a chegar à fase final do trabalho. Agradeço a sua compreensão e sempre tão gentil suporte ao longo desta longa jornada. Agradeço a sua revisão e incentivo, ainda mais por mim valorizados por reconhecer a sua limitação de disponibilidade pela crítica e exigente contribuição para a comunidade Europeia num contexto pandémico sem precedentes.

Ao Professor Doutor João Rocha, pela sua dedicada co-orientação neste trabalho, e pelas considerações que muito tive em conta para melhorar a versão final deste trabalho.

À minha equipa da MSD Portugal. Porque em todo o momento me entusiasmaram a continuar e a levar a bom porto este projeto. À compreensão e suporte que nunca hesitaram em dar-me. Agradeço o tanto que aprendi convosco e que criou em mim um carinho tão especial pela área regulamentar, e sobretudo, pelo que ela significa e contribui para melhorar a vida das pessoas. Só no seio de uma equipa tão especial e genuína se pode ser tão feliz a trabalhar e a aprender.

Aos meus amigos. Àqueles que sofrem as minhas ausências, e que ainda assim eu sei que me apoiam incondicionalmente. Àquelas que não hesitam em dar-me uma dose extra de motivação e trazem no sorriso o meu elixir de tantos momentos felizes. Obrigada, meus queridos!

À minha família! À de sangue e à de coração. Aquela que é o meu maior suporte e abrigo em todo o momento, o núcleo forte e coeso que se apoia e ergue. Obrigada por tornarem mais leves as batalhas, e darem muito mais significado a todas as conquistas. Estou e sou tão grata por vos ter.

Uma vez mais, a todos vocês, o meu sincero obrigada!

Table of contents

List of Figures

List of Tables

List of abbreviations

AIDS	Acquired immunodeficiency syndrome
AR	Assessment Report
ATC	Anatomical Therapeutic Chemical
ATMP	Advanced Therapy Medicinal Product
BLA	Biologic License Application
CAT	Committee for Advanced Therapies
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CIRS	Centre for Innovation in Regulatory Science
CMC	Chemistry manufacturing and Controls
COMP	Committee for Orphan Medicinal Products
COVID-19	Coronavirus disease 2019
EC	European Commission
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EUA	Emergency Use Authorization
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
FDASIA	Food and Drug Administration Safety and Innovation Act
FIH	First in Human
FRP	Facilitated regulatory pathway
GAIN	Generating Antibiotic Incentives Now
GCP	Good Clinical Practices
GMP	Good Manufacturing Practices
GTMP	Gene Therapy Medicinal Product
HCP	Host Cell Protein
HCT/P	Human Cells, Tissues, or Cellular or Tissue-based Products
HIV	human immunodeficiency virus
HLH	Haemophagocytic Lymphohistiocytosis
HTA	Health Technology Assessment
ICH	International Council for Harmonisation
IMI	Innovative Medicines Initiative
IMM	irreversible morbidity or mortality
IND	Investigational New Drug
IVD	in-vitro diagnostics
JAR	Joint Assessment Report
LoOI	List of Outstanding Issues

LoQ	List of Questions
MA	Marketing Authorization
MAH	Marketing Authorization Holder
MAPP	Medicines Adaptive Pathways to Patients
MHLW	Ministry of Health, Labour and Welfare
MID-NET	Medical Information Database Network
NAS	New Active Substance
NCA	National Competent Authorities
NDA	New Drug Application
NIHS	National Institute of Health Sciences
PAES	Post-authorization efficacy study
PAFSC	Pharmaceutical Affairs and Food Sanitation Council
PAL	Pharmaceutical Affairs Law
PASS	Post-authorisation safety study
PDCO	Paediatric Committee
PDUFA	Prescription Drug User Act
PHS	Public Health Service
PMD Act	Pharmaceuticals and Medical Devices Act
PMDA	Pharmaceutical and Medical Devices Agency
POC	Proof of Concept
PRAC	Pharmacovigilance Risk Assessment Committee
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
PSUR	Periodic Safety Update Report
QIDP	Qualified Infectious Disease Product
QMS	Quality Management System
R&D	Research and Development
REMS	Post marketing risk evaluation and mitigation strategies
RMAT	Regenerative Medicine Therapies
RMP	Risk Management Plan
RMPs	Regenerative Medicine Products
RPDD	Rare Paediatric Disease Designation
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAWP	Scientific Advice Working Party
SCTMP	somatic cell therapy medicinal product
SME	micro-, small and medium enterprises
SOC	Standard of Care
TEP	Tissue Engineered Product
TGA	Therapeutic Goods Administration
USA	United States of America
WHO	World Health Organization

1 Introduction and objectives

In past years, with special emphasis on the last two decades, Regulatory Agencies have developed pathways and programs to expedite development and regulatory review of medicines for serious conditions, as alternative mechanisms to the standard review process of medicinal products. Adapted to each regulatory framework, Regulatory Agencies also developed legislation and guiding principles to support the reduced timeframe required to bring innovative medicinal products to the market and improve accessibility of those medicines to patients, particularly ones targeting unmet medical needs.(1) Unmet medical needs demand the further development of innovative medicinal products and treatment options, including advanced therapies and regenerative medicinal products. Therefore, the regulatory landscape had to evolve and expand its scope to accommodate the newest advances in pharmaceutical science and technology. (1) In a standard review process, the evidence required in pre-marketing development studies of medicinal products includes demonstration of their quality, safety, efficacy or provision of risk-benefit data confirmatory of a positive balance, before they are granted with marketing authorization. Some of the alternative pathways that have been established may postpone the requirement of evidence demonstration of certain characteristics of the medicine candidate, turning it into post-marketing obligations, for example, or considerably decreasing the standard time for regulatory review of marketing authorization applications submitted to the Regulatory Authority. (2)

In general, the newest medicines introduced on the market globally are primarily approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). Over 2010-2019, the number of New Active Substance (NAS) approved by FDA, EMA and Pharmaceutical and Medical Devices Agency (PMDA) has generally increased. Although the number of approvals by the majority of Regulatory Agencies has flattened during the last 5 years (2015-2019), FDA has approved 230 NAS during this period, representing an increase in NAS approvals by this Regulatory Agency. (1,3) When comparing the 2010-2014 and 2015-2019 intervals, EMA has increased the number of NAS's approvals by 42%, followed by FDA which increased this number by 40%. In contrast, PMDA decreased this number by 4%, when comparing the same periods. These differences may be explained by different factors such as different submission strategies of companies to each agency, the unmet medical need existing in each market, and the review agility of each Regulatory Agency. (4) The higher number of NAS approvals creates the need to apply resources more efficiently, allowing for faster evaluation of applications for marketing approval of medicines of major interest to public health.

In addition, in 2019 FDA approved 60% of new drugs through one or more expedited programs, in comparison with only 34% in 2000. (1)

Each Regulatory Agency is settled in a regulatory framework, instituted by a set of legislation and expanded by additional regulatory initiatives which address specific needs. Since the late 1980s, FDA and EMA invested in developing multiple alternative tools, such as pathways, designations, or programs allowing for the approval of many medicinal products and therapies in the past two decades. More recently, in Japan, there was also an investment in developing similar tools and programs to expedite approval of critical medicines. (2,5) Despite recent convergence in median approval times over the last 20 years, and although Agencies are now offering expedited tools created to accelerate the review of promising NASs, differences in the median approval times across Regulatory Agencies are still observable. (3)

EMA has reinforced its commitment to contribute to human and animal health, and to support the innovation, investigation and development of new and better medicines in its Final programming document published by EMA[1]. This document describes the main initiatives and activities on the 2019-2021 horizon, with their focus being described as contributing to the improvement of Human health. Under this priority, there are two specific objectives: '*Objective 2 - ensure timely access to new beneficial and safe medicines for patients,* which includes early access to medicines as the main field of work', and '*Objective 3 - support for patient focused innovation and contribute to a vibrant life science sector in Europe',* which includes clinical trial regulation and supporting innovation as the main fields of work. In the EU regulatory framework, some provisions to foster early access to new medicines with public health relevance are included in legislation, for example, to support *accelerated assessment (introduced in 2005)*[2]*, conditional marketing authorisation (2006)*[3] or *compassionate use (2005)*[4]*.* In March 2016, EMA also launched the PRIME scheme, specially focused on

[1] "Final programming document 2019-2021", published in 2019, which describes the EMA's multiannual programming for 2019-2021. (30)

[2] Provided by recital 33 and Article 14(9) of 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. (13)

[3] Provided by 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 (20)

[4] Provided by recital 33 and Article 83 of 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. (13)

providing regulatory support to medicines targeting unmet medical needs. Since early access tools are not exclusive, they can be used in combination, according to particularities of each medicine candidate, medical condition or imminent public interest. (1,6)

FDA has created four programs intended to facilitate and accelerate review and approval of new medicinal products addressing medical needs in the treatment, prevention or diagnosis of serious or life-threatening conditions: *Fast Track designation (introduced in 1987)*, *Accelerated Approval (1992)*, *Priority Review designation (1992)*, and *Breakthrough Therapy designation (2012)*[5].(1) The main objective of these tools is to enable faster access of critical medicines to patients when available data indicates that the therapies' benefits outweighs their risks. In 1988, FDA formally published an Interim Rule[6] dedicated to this topic, being the first result of the expressed need to expedite the availability of promising new medicines. The rules outlined in subpart E recognized the relevance of accepting greater risks and unknown side effects from new treatment of life-threatening and severely incapacitating conditions than they would in other cases, and that a singular attention to earlier stages of development should be given to medicines with evidence of treating such medical conditions, relying on well-controlled phase 2 studies with relevant evidence of effectiveness. (7) FDA's approach applies subpart E regulations specifically to medicines for rare diseases, and uses the Agency's expedited programs, since it is recognized that rare diseases have certain aspects that are not applicable or easily verifiable as they are for other common diseases, and because some development challenges are even higher due to the rarity of the disease. (7) Recently, Congress amended Section 506 of the Food, Drug, and Cosmetic (FD&C) Act (21 U.S.C. 356) in December 2016 to add a section specifically dedicated to address the need to implement new regulations on expedited development and review of regenerative medicine therapies (RMATs), given the higher emerge of this type of products to address serious medical conditions without treatment options available.(8,9)

In Japan, the most significant changes in the regulatory framework were implemented after it recognized its strengths in basic research, as well as the production of many promising medicine candidates by its Academia, but also its weaknesses in finding practical application of their investigation for many years. Realizing this, the Japanese government started to invest in a strategic plan aimed at strengthening the production of innovative pharmaceutical products, from earlier stages of investigation and ahead of other countries. (10) The

[5] The expedited programs are described in the FDA's guidance document "*Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics*". (7)
[6] Codified in 21 CFR Part 312 (Subpart E) (36)

Government of Japan declared, through the “Japan Revitalization Strategy” and the “Healthcare and Medical Strategy” adopted on the 14th of June 2013, that they would promote the practical application of pharmaceuticals, medical devices, and regenerative medicines by creating front-line, innovative medical products with the potential to acquire a share of the expanding global market. (10) Following this, Japanese pharmaceutical affairs legislation was reformed the Pharmaceuticals, Medical Devices and Other Therapeutic Products Act (PMD Act) was passed in November 2014. (11) This new Act reviews Regenerative Medicine Products (RMPs) independently from conventional pharmaceuticals and medical devices, and it introduces conditional and time-limited approval for these types of therapies. (11)

In this dissertation, the aim is to describe, compare and critically discuss the expedited-approval tools and systems for medicinal products and other advanced therapies targeting unmet medical needs, available in the USA, EU and Japan; we will do so, using some practical examples of medicinal products already approved by the three Regulatory Agencies to analytically compare the outcomes of the expedited review; and support the comparison with already published analysis.

2 Methods

The information for this dissertation study was gathered based on the regulations, guidance documents and information from scientific literature published online and on the official websites of the regulatory authorities from the EU, the USA and Japan. The Regulatory Agencies chosen are some of the most important ones in the World and which already have established an extensive range of expedited approval tools and programs.
The programmes selected for this comparison were: *Fast Track Designation*, *Breakthrough Therapy Designation*, *Accelerated Approval*, *Priority Review* and *Regenerative Medicine Advanced Therapy* from US expedited programmes; *Accelerated Assessment*, Conditional MA, *Authorisation under Exceptional Circumstances*, *Compassionate use* and *PRIME scheme* from EU regulatory tools for expedited MA; *Compassionate Use*, *Priority Review System*, *Restrictive Approval System*, *Conditional Accelerated Approval System for Pharmaceuticals*, *Conditional and Time-Limited Approval for RMPs* and the Japanese *Sakigake designation* as Japanese tools for expedited MA's. The Qualified infectious disease products designation available in the USA was not selected for this comparison since there are no similar expedited programmes available in the EU or Japan.

The comparison of the three regulatory contexts was based on a segmentation of the pathways and programmes of each one. First, similarities were identified and described, according to a qualitative analysis - *Expedited approval without conditions, Conditional approval, Approval with limited patient cohort or indication and Development support programs.* The characteristics found to be the starting point for the comparison were the requirement of clinical data from pre-marketing phases or post-marketing phases, characteristics of the evaluation of post-marketing data and the development support from the Regulatory Agency. This analysis is exposed in Tables, where the comparable tools are included along with their essential characteristics and segmented by the qualitative classification.

In addition, a comparison was performed, using examples of medicinal products approved using regulatory tools for expedited MA in the EU, USA and Japan, regarding the pathways used until its final approval. The medicinal products used were Kymriah®, Keytruda® and Veklury® based on their relevant example and applicability of different tools for expedited approval. Kymriah® was the first approved gene therapy – CAR-T Therapy, Keytruda® used a combination of tools and programs to be approved, and Veklury® was a recent and impactful example of expedited approval to address a public health crisis.

3 Literature Review

3.1 EU regulatory framework

In the EU, there is a legal framework in place governing the regulation of medicinal products, namely the ones for human use, ensuring that a product introduced on the market in the Member States complies with the efficacy, safety and quality standards for its intended use. The legal framework implemented has a direct impact on the activities of the EMA and the National Competent Authorities (NCA). Quoting the European Commission (EC) official web page on the legal framework governing medicinal products for human use in the EU, it is stated that the legal framework "*sets standards to ensure a high level of public health protection and the quality, safety and efficacy of authorised medicines. In addition, it promotes the functioning of the internal market, with measures to encourage innovation. It is based on the principle that a medicinal product requires a marketing authorisation by the competent authorities before being placed on the market.*"(12) The fundamentals of regulatory legislation in the EU are settled in Directive 2001/83/EC[7], as amended, and in Regulation (EC) No 726/2004[8], complemented by subsequent Directives and Regulations which establish specific principles on topics as orphan medicinal products, clinical trials, paediatric research, Advanced Therapy Medicinal Product (ATMP's), among others. This legislation encompasses, but is not limited to, the regulatory requirements and particularities from the pre-authorization phase to marketing authorization and its maintenance once granted.

The Regulation (EC) No 726/2004 includes a number of provisions regarding patients' early access to innovative medicines addressing public health needs and that are eligible to the centralised procedure. The legal dispositions to highlight are the accelerated assessment procedure, the possibility of obtaining a conditional marketing authorisation, and the Committee for Medicinal Products for Human Use (CHMP) deliberation on compassionate use. (13) These three major tools will be further described in this review. In addition, in 2016 the PRIME scheme was launched by EMA to optimise the use of regulatory tools and other existing programs under the EU legal framework, such as scientific advice/protocol assistance, in order to support the development of medicinal products of major interest to public health. The PRIME

[7] 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 (25)

[8] 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 (13)

scheme supports eligible products from early stages of development through enhanced scientific and regulatory dialogue. (14)

If a developing entity is evaluating the best approach to the medicine's development, particularly when they are innovative medicines without sufficient guidance available on official documents, for medicines that deviate from scientific guidelines, or when there is a limited knowledge about the EU legal framework on medicines, EMA provides the opportunity to formally request, at any stage of development, scientific advice or protocol assistance, which is a specific advice for developers of designated orphan medicines for rare diseases. This is the official process for requesting EMA's guidance, feedback or endorsement, through recommendations of the EMA's Scientific Advice Working Party (SAWP) for medicinal products for human use, on the best path forward, the appropriate study designs, etc. capable of generating robust data and other determinant aspects that could be required, or highly recommended at the time of evaluation of the Marketing Authorization (MA) application. This avoids major objections raised by the Committee responsible for the review and assessment, allowing the application of more efficient methods of resource management, which can impact the extent of patients' exposure in studies that would not generate useful data for the purpose in scope, among other things. (15)

The EMA's advice is based on questions directly from the developing company. These questions can be related to quality, non-clinical, clinical and/or methodology studies, and based on the strategy and alternative development plans suggested. For instance, this might include identifying which studies may generate better data collection. Nevertheless, the advice is not legally binding to granting a MA. After the new medicine is authorised, developers may also seek advice from EMA for other post-authorisation procedures to further develop an integrated lifecycle approach, such as advice on protocols of voluntary post-authorisation safety studies (PASS), with the possibility of seeking follow-up advice. (15)

In addition to the eligibility for an expedited pathway in the EU, is it possible to combine more than one early access tool for the same candidate medicine, on the basis of not being mutually exclusive. As an example, when a medicinal product is eligible to PRIME scheme, it may benefit from a CHMP opinion on compassionate use while undergoing clinical trials, follow a shortened review procedure at the time of MA application by using the accelerated assessment pathway, and may also be granted a Conditional MA until comprehensive data are available. (6)

In the subsections below, each regulatory tool for expedited MA existing in the EU will be further characterized and detailed, according to information gathered mainly from official guiding documents published by EMA and by EU legislation.

As previously mentioned, EMA is committed to enabling early patients' access to new medicines, particularly to the ones that target an unmet medical need or are of major public health interest. The Regulatory Agency in the EU intends to support the development process of medicines from early stages and to offer regulatory mechanisms that help promising new medicines reach patients as early as possible. Companies (either big pharma or small and medium enterprises) or Academia (including academic start-ups) developing such medicines can request EMA's support in applying any of the tools or programs available, and in making use of these regulatory opportunities to expedite the review and approval of their medicine candidates with high public health interest.

3.1.1 Legal tools for expedited MA

Accelerated assessment

Based on recital 33 of Regulation (EC) No 726/2004[9], which states that "*in order to meet, in particular the legitimate expectations of patients and to take account of the increasingly rapid progress of science and therapies, accelerated assessment procedures should be set up, reserved for medicinal products of major therapeutic interest, (…)*" (13), and according to Article 14 (9) of Regulation (EC) No 726/2004[9], accelerated assessment may be granted if the new product requesting the MA is considered to be of major interest to public health and therapeutic innovation by the CHMP.(13,16) Two to three months before submitting the MA application, the developing company should submit a request for accelerated assessment as part of the letter of intent to submit the MA application, ideally after having requested a pre-submission meeting six to seven months before the target submission date. In this meeting, the applicant will be provided with guidance around accelerated assessment and the submission strategy for the MA application. Additionally, the developer has the opportunity to present the supportive data already available and the one that is foreseen, including applicable

[9] 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. (13)

timelines and the proposed Risk Management Plan (RMP). It also has the opportunity to review its request with the rapporteurs from the concerned committees - CHMP, Pharmacovigilance Risk Assessment Committee (PRAC) or Committee for Advanced Therapies (CAT). (16) It is also requested that applicants provide information about Good Manufacturing Practices (GMP) and Good Clinical Practices (GCP), incorporated in the accelerated assessment request in order to guarantee enough time for identification and possible execution of inspections by the Agency, as needed and in a timely manner. (16) Without the prejudice of the final CHMP Opinion about MA approval, the CHMP rejects or accepts the request for accelerated assessment based on the following criteria: the request, justifications presented, and the Rapporteurs' recommendations about the appropriateness of an accelerated assessment. The justification presented should include arguments supporting the importance of the candidate medicine to significantly address the unmet medical need, despite the technical innovation it could represent by itself; explain the importance and the added value of this product within medical practice; and its benefit/risk balance based on traditional outcomes of safety and efficacy endpoints or other relevant outcomes, such as number of hospitalizations, patients perspective of added value, etc. (17)

In case of acceptance, the evaluation of the MA application will follow a timetable for the accelerated assessment procedure, in accordance with Article 14(9) of Regulation (EC) No 726/2004: 150 days instead of 210 days is the standard timetable under the MA application for centralised procedures, apart from time of clock stops, which correspond to the period in which applicants provide additional data and responses to requests for supplementary information. Nevertheless, the same evidence requirements for MA as an evaluation under standard timetable are applicable despite the abbreviated timelines. If deemed appropriate by the CHMP, the committee may decide to convert the application into an assessment of standard centralised procedures, following normal timelines, but only if it's no longer justified to conduct an accelerated assessment, for instance, when major objections are identified or GMP/GCP inspection during the assessment is mandatory. (16,17)

The evident benefit of using this tool is that MA approval is granted faster than in standard conditions, when there is enough evidence to follow this alternative pathway.

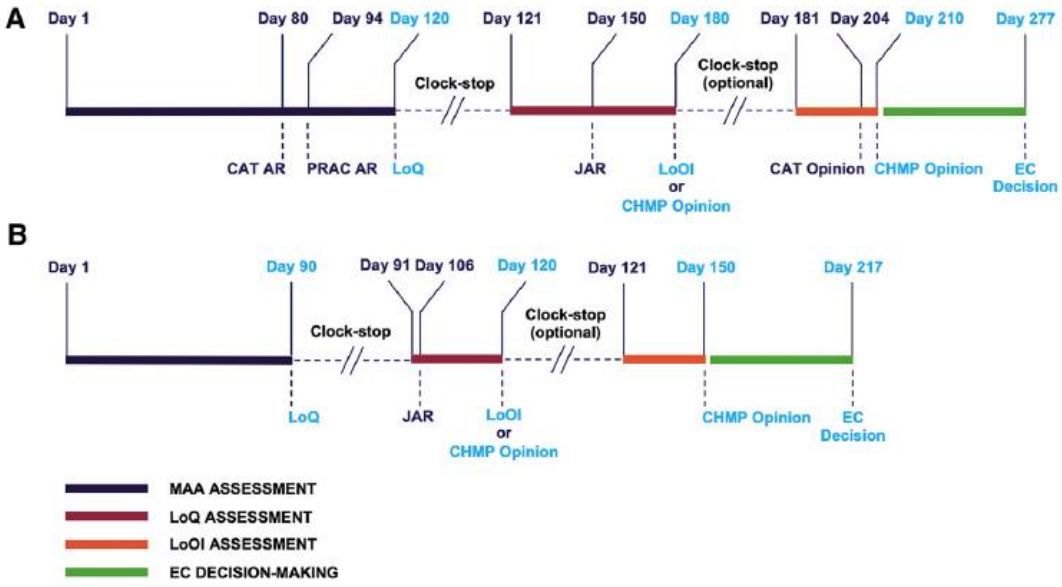

Figure 1 - Review of MA applications according to the Centralised Procedure.

In this schematic illustration, two timetables represent the standard (A) and accelerated (B) assessment for ATMPs. In A, the Assessment Report (AR) is separate from CAT ad PRAC, which are integrated in the Day 120 List of Questions (LoQ); a 90-day clock-stop is then initiated, which ends upon submission of the applicant's response, a Joint Assessment Report (JAR) is then formalized on day 180 to the applicant, which could include a list of outstanding issues (LoOI), restarting the clock after submission of responses or with oral explanation. After day 204 JAR and comments from CAT, CHMP, PRAC and EMA, a CHMP Opinion is released on day 210. An EC Decision is then hypothetically granted on day 277. In example B, is it represented the shorten periods of each stage, having also shorter clock-stops of 30-day for the applicant to respond, which globally can lead to an expected EC Decision on day 217. (18) *Figure adapted from "EU Regulatory Pathways for ATMPs: Standard, Accelerated and Adaptive Pathways to Marketing Authorisation"* (19).

Conditional marketing authorisation

The conditional MA was introduced in 2006, and its particularities are described in Regulation (EC) No 507/2006[10], also in accordance with Article 14(7) of Regulation (EC) No 726/2004[11]. In the applicable legislation, a conditional MA may be granted to medicines that address unmet medical needs in the interests of public health, in case they indicate a positive benefit/risk balance. The risk of having less comprehensive data available than in normal situations must also be considered (only applicable to clinical data related to safety and efficacy, which have

[10] 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 (20)

[11] Article 14(7) of 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. (13)

not been supplied yet, except for products intended to be used in emergency situations where higher risks related to the absence of some data may be acceptable), and based on applicable criteria. (20)

To be eligible for a conditional MA, the candidate medicine should target the treatment, prevention or diagnosis of seriously debilitating or life-threatening diseases, which covers the case of orphan medicines. Orphan medicines are indicated to treat rare diseases[12], when the medicine is unlikely to generate sufficient profit to justify research and development costs, and when there isn't any satisfactory method of diagnosis, prevention or treatment of a certain medical condition or, if such method exists, the medicinal product will be of significant benefit.(21) The candidate medicine may be intended to address an emergency situation, being accepted less comprehensive data in terms of pharmaceutical and non-clinical studies. (20) The following criteria are defined in Article 4 of Commission Regulation (EC) No. 507/2006 and should be required for this special procedure pathway: the benefit-risk balance of the product is positive, as defined in Article 1(28a) of Directive 2001/83/EC[13]; it is likely that the applicant will be able to provide comprehensive data; unmet medical needs will be fulfilled; the benefit to public health of the medicinal product's immediate availability on the market outweighs the risks inherent in the fact that additional data are still required. (20,22,23) Given the type of medical conditions to which these medicines may be targeted, it might be acceptable to conduct studies that are smaller in size and/or with a shorter duration and/or different endpoints than those normally expected for confirmatory studies, assuming that this data will sustain the benefits outweighing the risks. (22)

Six to seven months prior to target submission date, applicants should notify the Agency of their intention of submission, preferably along with the request for a conditional authorisation, if not done earlier. Ideally, applicants should liaise with EMA in early dialogue meetings (Scientific Advice or protocol assistance) to discuss their development plan and design of intended studies that will be completed before authorisation or are planned to be conducted as specific obligations following the granting of a conditional MA. There is also the possibility of liaising with other relevant stakeholders (Health Technology Assessment (HTA) bodies), providing a broad justification on the positive benefit-risk balance, ability to provide

[12] A rare disease is defined as any disease affecting not more than 5 people in 10.000 in the European Union, which translates into 246,000 people, approximately. In the EU, there is about 5,000-8,000 distinct rare diseases, affecting 6-8% of the EU population – this means that between 27 and 36 million people are affected by rare diseases in the Community. (82)

[13] 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 (25)

comprehensive data, fulfilment of the unmet medical need and benefits to public health associated with the immediate availability of the candidate medicine, besides the risks inherent to needing additional data. The request for conditional MA should be clearly justified in terms of the unmet medical need to be addressed, based on medical or epidemiologic data, and justification should also include information about the non-existence of any satisfactory method of diagnosis, prevention or treatment in the EU or a major improvement to an existing method must be described as necessary. A major therapeutic advantage refers to a meaningful improvement in terms of efficacy or clinical safety, such as improvement of morbidity or mortality of the disease. Additionally, applicants should justify their claims about benefits to public health associated with the immediate availability of the medicinal product, if possible, based on an assessment of objective and quantifiable epidemiological data and risks inherent to the fact that additional data are still required, compared to a medicinal product following a standard MA procedure.(22) Since the conditional MA is not exclusive, applicants may also request accelerated assessment, given the relevance of this type of product, and CHMP will be responsible for evaluating both requests. Applicants are even encouraged by EMA to request accelerated assessment once a product addressing an unmet medical need is considered of major interest to public health, as outlined in Recital 7 of Regulation (EC) No 507/2006. (20,22,23) It is possible to submit a conditional MA application at the conclusion of phase II studies - therefore it is considered that comprehensive clinical data are not ready yet. This is applicable to medicines targeting rare diseases because there is a small target population, which results in insufficient data at the time of submission. As a result, Orphan Designation may qualify as a medicinal product for the Conditional MA application pathway, if all conditions are met. (19)

MA approval of a medicinal product that followed a conditional MA application will mean that its benefit-risk balance is positive, pending further confirmation. This positive balance may be initially demonstrated by a surrogate clinical endpoint, such as a biomarker, instead of a direct therapeutic measure. (19)

After being granted, the conditional MA is valid for one year, with annual renewals. As a conditional MA, it will include specific obligations to be addressed by the Marketing Authorization Holder (MAH), such as delivering results from ongoing or new studies (for example, results of long-term studies, studies with direct endpoint on efficacy with higher clinical relevance, safety and efficacy results from a larger database or for longer duration, investigating the effect duration, etc.), typically including randomised clinical trials, and executing additional activities related to the collection of pharmacovigilance data, due to the need for intense monitoring in order to confirm/sustain the positive benefit/risk balance through

further comprehensive data. The imposed conditions and deadlines, which are reviewed during the assessment in annual renewals, are made public in the European Public Assessment Report (EPAR), enhancing transparency regarding the conditional nature of the authorisation granted for that specific product. Once the required comprehensive data is obtained, the conditional MA may be converted into a standard MA at the time of the renewal or assessment of the data submitted to fulfil the last condition of the MA, which means that no further specific obligations are required, and that the renewal will be quinquennial and possibly valid unlimitedly thereafter.(20,22)

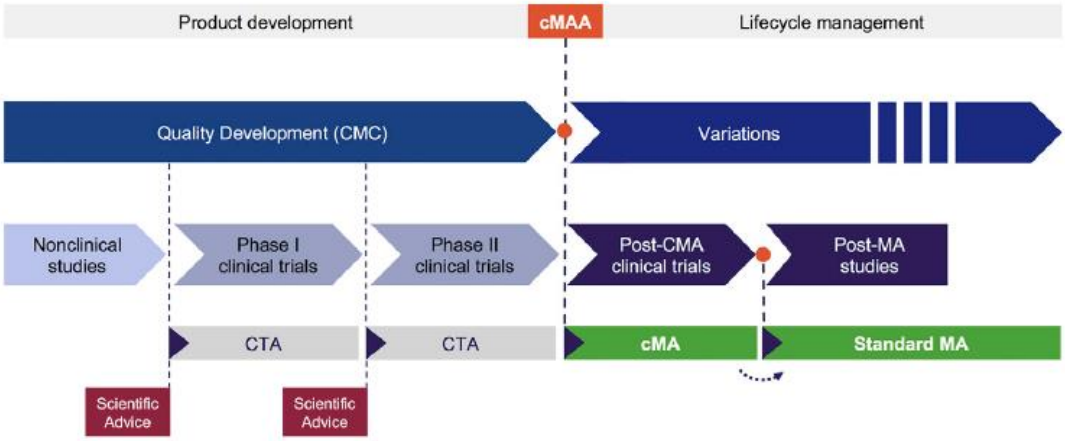

Figure 2 - Acceleration of drug development via the Conditional MA procedure.

This schematic representation envisions a conditional MA on the basis of phase II clinical trials data, evidencing that after it's granted, further studies as part of the conditions imposed are performed to confirm the positive benefit/risk balance, leading to a standard MA. Figure adapted from "EU Regulatory Pathways for ATMPs: Standard, Accelerated and Adaptive Pathways to Marketing Authorisation" (19).

Authorisation under Exceptional Circumstances

The Authorisation under Exceptional Circumstances pathway is applicable to extreme settings where a disease is so rare or a condition is so specific that a clinical endpoint is very difficult to measure for scientific and/or ethical reasons. (19) A MA may be granted in absence of comprehensive data under exceptional circumstances, in accordance with Article 14(8) of Regulation (EC) 726/2004[14], only for objective, verifiable reasons, and will be subject to a

[14] Article 14(8) of 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, states that *"(…) the authorisation may be granted subject to a requirement for the applicant to introduce specific procedures, in particular concerning the safety of the medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken. This authorisation may be granted*

requirement for the applicant to introduce specific procedures, in particular concerning the safety of the medicinal product, which will be assessed annually to guarantee the maintenance of the MA. (13,24)

In this case, the applicant provides available data from studies conducted with the candidate medicinal product in order to be granted the MA, but comprehensive data cannot be obtained after authorisation, which means that this authorisation pathway normally won't lead to a standard MA, unlike the conditional MA pathway. (19,23)

As outlined in number 6 of Annex I, Part II, of Directive 2001/83/EC[15], as amended, a MA may be granted, subject to certain specific obligations, in case the applicant is capable of demonstrating evidence that comprehensive data on the efficacy and safety aspects under normal conditions of use cannot be provided. These exceptional cases include therapeutic indications for which the candidate medicine is intended are so rare that the applicant cannot reasonably be expected to provide comprehensive evidence, or comprehensive information cannot be provided in the present state of scientific knowledge, or generally accepted principles of medical ethic could not accept to collect such information, and therefore, the product may be likely to have Orphan medicinal product designation .(25)

As mentioned above, in this particular expedited MA application, the MAH will be subject to specific procedures/obligations introduced as part of the procedure. Directive 2001/83/EC, as amended, also identifies the type of obligations that may be attached to the authorization, such as: completion of an identified programme of studies within a specific period to obtain results which shall form the basis of a reassessment of the benefit/risk profile by the competent authority (the programme shall include studies' outlines and expected milestones); supply of the medicinal product on medical prescription only and may, in certain cases, be administered under strict medical supervision only, for instance, in an hospital or by an authorised person in the case of a radio-pharmaceutical; deliver any medical information, such as package leaflet, drawing the attention of the medical practitioner to the fact that the information available about the medicinal product is still incomplete regarding certain product characteristics. In article

only for objective, verifiable reasons and must be based on one of the grounds set out in Annex I to Directive 2001/83/EC, as amended. Continuation of the authorisation shall be linked to the annual reassessment of these conditions." (13)

[15]Number 6 of Annex I, Part II, of 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. (25)

14(8) of Regulation (EC) 726/2004[16] the safety features of the medicinal product authorised under exceptional circumstances are also highlighted, particularly the notification to the competent authorities of any incident relating to its use and action to be taken, in addition to the implementation of pharmacovigilance activities and interventions proactively designed to identify, characterise and prevent or minimise risks. (13) With regards to safety, the particularities are normally provided in the RMP and they are intended to characterise risks associated with the use of the medicinal product and to ensure that the MAH is appropriately aware of any relevant safety issue that may result from its use, healthcare professionals are informed about its safety particularities and correct actions are taken if a safety issue is arises. (24)

When applying for a MA under exceptional circumstances, a justification must be included in Module 1, as part of the four essential aspects to be considered: a claim showing that comprehensive non-clinical or clinical data on the efficacy and safety under normal conditions of use is not possible to be obtained by the applicant; a listing of non-clinical or clinical efficacy or safety data that cannot be comprehensively provided; justifications on the grounds for approval under exceptional circumstances; and proposals for detailed information on the specific procedures/obligations to which the MAH will be subject. (24) In order to get support to proceed with the MA application, ideally four to six months before submission of the MA application, the developing company may request advice from EMA about the justification to apply for a MA under exceptional circumstances, about limitations associated with the rarity of the disease to which the medicinal product will be targeted, and the adequate approach to gather information on its safety and efficacy. The scientific advice will not be binding to the outcome of the CHMP assessment. (24)

The justification provided shall be based on supportable reasons, such as inability to provide comprehensive efficacy and safety data due to rarity of the indication (the justification consists of, but is not limited to, relevant epidemiological evidence of rarity of the disease, quantification of the population that might be available to participate in clinical studies or feasibility to conduct alternative studies to obtain further relevant data), inability to provide comprehensive information due to the present state of scientific knowledge (a description of what knowledge would be essential to conduct such studies and a justification of the inability to develop such knowledge) and inability to collect such information because it would be in opposition to

[16]Article 14(8) of 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. (13)

medical ethical principles (a description of relevant principles of medical ethics in scope should be made available by the applicant, focusing on internationally accepted standards or other guidelines, as well as the justification of applicability to the case in scope), typically if it concerns clinical studies or studies using human biomaterials. (24)

In case it was not previously requested by the applicant, the CHMP may propose the attribution of a MA under exceptional circumstances, including specific obligations included in the authorisation. After granting the MA, the CHMP revises annually the implementation/completion of specific obligations, in the reassessment procedure of benefit/risk balance. The authorisation will remain valid if such balance remains positive. The renewal of the product follows the same rules as for standard MA, performed according to Article 14 (1-3) of Regulation (EC) No. 726/2004[17]. The MA will be valid for five years, and for an unlimited period after that, unless suitably justifiable and supported by pharmacovigilance data gathered in the respective period of post-marketing experience. (24)

Compassionate Use

As defined in Article 83(1) of Regulation (EC) No 726/2004[18], which states that "*by way of exemption from Article 6 of Directive 2001/83/EC, MS may make a medicinal product for human use belonging to the categories referred to in Article 3(1) and 3(2) of Regulation (EC) No 726/2004 available for compassionate use*", the compassionate use is a program created to enable the use of a medicine, subject to strict conditions, which is not authorized via the Centralised Procedure[19] yet in the EU as a treatment option, but has already entered the MA application process or is undergoing clinical trials in the EU or elsewhere. Therefore, its safety profile and dosage guidelines may not be fully established at the time of the approval of compassionate use programme. (13,26)

[17] Article 14 (1-3) of 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. (13)

[18] Compassionate Use is mentioned in recital 33 and Article 83(1) of 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. (13)

[19] Without prejudice to the subsequent MA, Article 83 is applicable to unauthorised medicinal products for human use falling within the scope of articles 3(1) and 3(2) of Regulation (EC) No 726/2004 – medicines for therapeutic areas within the mandatory scope of the Centralised Procedure. (26)

The main objectives of the compassionate use programme are the expedition and improvement of access to new treatment options under development by patients in the EU; the allowance to use unauthorised new medicines under a joint approach regarding the conditions of use and distribution, and the patients targeted to benefit from the new medicine; and the promotion of transparency among different countries among Member-States, in terms of treatment availability. (26)

Through the CHMP Opinion, EMA may recommend the usage of a medicine via compassionate use, but it does not create a legal framework. Alternatively, it is a way to facilitate the availability of medicines expected to represent a new treatment option of life-threatening, long-lasting or seriously debilitating illnesses, without satisfactorily authorised medicines. In addition, regarding local implementation at the Member-States' level, each one may set their own procedures and coordinate this programme according to what's more suitable for their healthcare context. (26)

This programme may be made available to a group of patients who cannot be enrolled in clinical trials and have a disease with no satisfactorily authorised therapies. The request of CHMP opinion should be addressed by one or more Member-States when there is evidence that medicines targeting chronically or seriously debilitating disease, or a life-threatening disease, need to be available for compassionate use, via notification to the EMA. The recommendation requested to EMA may be related to the method of administration, distribution and/or which patients would benefit from the compassionate use programme. There is also the possibility of a proactive CHMP opinion on a compassionate use programme if it is noted that more than one Member-State have notified the EMA of their use of Article 83, independently but for the compassionate use of the same medicinal product. (13,26)

In order to provide an opinion based on rigorous scientific criteria, CHMP will evaluate the data available on the safety, quality and efficacy of the product. This data may have already been evaluated by a Member-State and, if so, the EMA will collect it and add other relevant information in the public domain or additional data requested directly to the developing company, to conduct an assessment and adopt a robust opinion on the compassionate use programme. The assumptions for compassionate use with regards to efficacy may be based on promising early data observed in exploratory trials (for example, uncontrolled phase II trials) or in mature randomized phase III trials, if the medicinal product has already initiated the MA application process. (26)

After MA application has received CHMP opinion for a product that has been included in a compassionate use programme, the CHMP opinion for compassionate use may be updated accordingly, taking into account the MA application opinion that was adopted by the CHMP. After MA is granted, reference is made to the EPAR, which is made available at EMA's website for transparency purposes, and updates of compassionate use recommendations are no longer needed. (13,26)

Taking into account the responsibility to ensure the availability of the medicinal product with such a high relevance to the benefit of public health, once a compassionate use programme has been set up in a Member-State, the MAH should ensure that patients taking part in the compassionate use programme have access to the medicinal product until the medicinal product is placed on the market. (26)

3.1.2 Development support tools for expedited MA

Prime Scheme

Having in mind the need to improve regulatory tools capable of supporting expedited MAs in the EU and aiming to encourage developers to focus on medicines that may have a great impact on public health, EMA has launched a project in March 2016 focused on this objective – PRIME: priority on medicines. Based on the regulatory framework and tools already available – such as, Scientific Advice for early and enhanced dialogue, Conditional Approval and Accelerated Assessment – PRIME is a voluntary scheme aimed at increasing support to developers that are investing in medicines that have the potential to address patients' unmet medical needs, and supports them by enhancing interaction in earlier stages of development and fostering better strategies to speed up the evaluation of MA applications, with the ultimate objective of making these promising therapies available to patients. (27,28)

To be eligible for PRIME, the candidate medicine should address an unmet medical need based on data from early clinical studies, i.e., it shall target diseases without a method of diagnosis, prevention or treatment considered satisfactory, or offer a significant therapeutic advantage over treatments already available. If so, it will be considered a priority by EMA. (27,28) The applicant should submit a voluntary request for PRIME eligibility, and it should be based on acceptable data justifying the potential benefits and major positive impact on public health. (29)

The recommended stage to request PRIME eligibility is during the development of the candidate substance, based on preliminary clinical evidence (proof of concept, indicating the promising activity of the candidate substance). Nevertheless, a mechanism was created to further support micro-, small and medium enterprises (SMEs) and academics - they can apply for PRIME eligibility at an earlier stage (at proof of principle stage, providing early evidence of potential activity through nonclinical data in a relevant model), being also required the results of a first-in-man study (initial clinical trial) indicating tolerability and adequate exposure for the desired pharmacotherapeutic effects.(27,28) In a two-year review report[20], EMA described that between 2016 and 2018, only eight requests were submitted at the proof of principle stage and, from these, three had been granted PRIME eligibility. Subsequently, one of them has progressed to proof of concept phase, and enabled confirmation of PRIME eligibility after submission of exploratory data. (28)

When a developer applies for a PRIME scheme and it is positively addressed, it will be given support from EMA from early stages of development, with a joint focus on optimising development plans – such as clinical trials' design, data robustness and assessment of benefits and risks, and it's expected that, at the time of submission of a MA application, the candidate medicine might also be eligible for accelerated assessment. (27) Under this scheme, it is possible to recognise that the candidate medicine might be eligible for accelerated assessment during the clinical development phase. (16) This early dialogue approach is also beneficial from a resources management perspective – resources in clinical trials are limited so it is critical to design clinical trials and development plans in an efficient way, ensuring that data generated can provide information needed to support marketing application without any waste of resources. (27)

Unlike the standard MA where the appointment of rapporteurs occurs only after MA application has been executed, in this scheme it is expected that the appointment of a rapporteur is made early in development as a key part of the PRIME mechanism of support. (16) As part of this early dialogue, the Agency will appoint a rapporteur from the CHMP, or from the CAT if the candidate medicine concerns an advanced therapy, who will act as a supportive intermediate to increase understanding of the requirements and critical information to be included in the MA application. EMA will also assign a dedicated point of contact who will be responsible for fostering communication and collaboration between the sponsor and the Agency. (27)

[20] "PRIME: a two-year overview" is a report made public on EMA's website, that includes an overview of PRIME scheme from 2016 until 2018. (28)

EMA is also accountable for organising meetings with a multidisciplinary team of experts and CHMP/CAT members, outlining guidance and inputs into the overall development plans and regulatory strategy to be adopted, and providing scientific advice at the most important stages of the medicine's development, allowing sponsors to engage directly with additional stakeholders. This includes EMA committees such as Paediatric Committee (PDCO) to discuss the paediatric investigation plan, Committee for Orphan Medicinal Products (COMP) to discuss orphan designation and its maintenance, or PRAC to plan the post-authorisation activities. Other relevant stakeholders, such as HTA bodies who will be responsible for evaluating medicines from an economic perspective and be accountable to grant access for patients nationally, and patient associations, may also be included in these meetings with multidisciplinary teams, as applicable.(27,28)

According to EMA's report "PRIME: a two-year overview", by May 2018 the Agency had organised 31 kick-off meetings, followed by 37 scientific advices, and the first meeting generally occurs two to three months after appointment of CHMP/CAT Rapporteur. Regarding scientific advices, they have been requested on quality, nonclinical and clinical aspects of the drug development, as well as on post-authorisation follow-up studies and registries. (28)

Another benefit for a candidate medicine from integrating the PRIME scheme is that, at the time of preparation to submit the MA application, the applicant may have already received confirmation about the potential for an accelerated assessment procedure and, if so, it can expect a reduced period of evaluation from CHMP. (28)

Current status of PRIME Scheme

Every month, EMA updates key figures and information on PRIME eligibility requests on its official website[21]. Until February 2021, 336 requests from developers to include their candidate substances in PRIME scheme were submitted to the Agency, with an average of eight requests per month. Of those, 88 were granted eligibility to PRIME.(27,28) Regarding the type of applicants, the highest number of requests received were submitted by micro-, small- and medium-sized-enterprises registered with the Agency's SME office, but there is also a significantly high number of requests submitted by other types of applicants. In contrast, only four requests were submitted by Academic centres and they were denied sine they didn't fulfil

[21] EMA has a section dedicated specifically to PRIME on its official website - PRIME: priority medicines – which is available at *https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines* (27)

eligibility criteria at the time of application.(27) As a priority in the 2019-2021 horizon, it is also outlined by EMA that collaboration and integration across the European medicines regulatory network (composed by the Member-States, the European Commission, and EMA) and with Academia should be continuously strengthened to facilitate translation of innovation into medicinal products, namely by involving academia at early stages of dialogue, by providing additional support of entry to PRIME, and also fee incentives.(30)

Another fact is, two years after PRIME scheme has come into effect, there were about 20 ATMP's that had integrated this scheme, and more than 40% of promising medicines that were in the scheme by that time belonged to this class of medicinal products. This could be also indicative of the increased interest in this class of products by the industry and scientific community, and also the importance of targeting unmet medical needs. (19)

Of the overall number of requests until November 2020, 73 belonged to oncology, representing the most significant therapeutic area in scope, followed by Neurology with 38 requests, the Endocrinology-Gynaecology-Fertility-Metabolism therapeutic area which represented 26 requests in total, and Haematology-Hemostaseology with 24 requests.(31) An analysis of reasons for the denial of requests indicates that 87% of cases were related to issues on robustness of presented data (e.g. trial design issues, failed study, inconsistency of results, inappropriate claim in subgroup, lack of comparator, inadequate comparison to historical data) or inconclusive or insufficient effect.(28)

The first drug candidates to be granted with PRIME eligibility, on the 26th of May 2016, were *Aducanumab* – a biological active substance targeted to treat Alzheimer's disease; *Avacopan (CCX168)* – a chemical substance included in the Immunology-Rheumatology-Transplantation therapeutic area; *Axicabtagene ciloleucel* – an advanced therapy for oncology; and *Emapalumab* – another biological substance intended to treat primary haemophagocytic lymphohistiocytosis (HLH). According to monthly updated information available at EMA's official website, each drug candidate differ by status – PRIME eligibility withdrawn by the applicant from (Aducanumab), or after submission of MA application (Avacopan (CCX168)); already approved by the EC since the 23th of August 2018 which is the case of Axicabtagene ciloleucel; and Emapalumab received negative CHMP opinion after submission of MA application. (27)

After the first four active substances were granted PRIME eligibility, others applied for the scheme – a total of 15 active substances were granted eligibility in 2016, 19 active substances in 2017, 14 in 2018, 16 in 2019, and 19 were granted PRIME eligibility in 2020, from January

to November[22].(27) Since the launch of PRIME, the rate eligible/granted indicator has remained relatively stable, at this point representing a cumulative rate of 25%, compared to a cumulative rate of 21% by May 2018. (28,31)

Additionally, according to "PRIME: a two-year overview" report published by EMA in 2018, of the 36 medicines included in PRIME scheme by that time, 30 targeted rare diseases. In the same report, it is noted that most requests for PRIME eligibility were received when candidate substances were at the proof of concept stage, supported by exploratory data, and based on phase 1 or a combination of data from phase 1 and phase 2 studies.(28) According to the last update of the list of products granted eligibility to PRIME, on the 13th of November 2020, to support their request, applicants submitted mostly two types of data from development studies – non-clinical data and either clinical exploratory data or tolerability first in man data. The most common type of data supporting requests of products, which were granted PRIME eligibility, were the combination of non-clinical and clinical exploratory data, in 79 cases, specifically. (27) By analysing the 88 active substances under the PRIME scheme umbrella, 12 have already received a positive opinion from CHMP and were then approved by the EC - Autologous CD34+ haematopoietic stem cells transduced with lentiviral vector encoding the human βA-T87Q-globin gene (Lentiglobin); Axicabtagene ciloleucel, Givosiran, Onasemnogene abeparvovec, Polatuzumab vedotin, Recombinant Vesicular Stomatitis Virus with Envelope Glycoprotein replaced by Zaire ebolavirus (Kikwit Strain) Glycoprotein, Tisagenlecleucel, Bulevirtide, Entrectinib, Imlifidase, Belantamab mafodotin and Lumasiran[23]. (27)

EMA Innovation Task Force

Since August 2014, EMA has a new multidisciplinary taskforce accountable for providing an environment for informal early dialogue with applicants, particularly SMEs and academic sponsors to proactively discuss innovative aspects in medicines development and identify scientific, technical and regulatory issues related to emerging therapies and technologies (examples of topics are nanomedicines, biomaterials, pharmacogenomics, synthetic biology, modelling and simulation, and 'mobile health'). This horizontal cross-sectorial group,

[22]For transparency purposes, EMA is publishing a monthly list of products granted eligibility in PRIME scheme, on its official website. In this list, it is possible to consult not only all products, its current stage in PRIME scheme, but also the therapeutic area they belong to, the type of data supporting their request to PRIME scheme, and the type of applicant submitting the request.

[23] In addition to the list of medicines granted eligibility on PRIME scheme, the respective EPAR of each product was consulted ate EMA's website.

composed by experts from Quality, Safety, Efficacy, Pharmacovigilance, Scientific Advice, Orphan Drugs and good practices compliance, legal and regulatory affairs fields, was created by EMA with a particular focus on Emerging Therapies and Technologies, to implement measures capable of ensuring that the medicines' evaluation system is built on a robust and solid setting that can face the challenges brought by new therapeutic environment and health technologies. (32)

The set of objectives established for this taskforce encompasses key points focused on supporting innovation of medicines in the EU, having emerging therapies and technologies, and borderline therapeutics for human and veterinary use, for which there is no established EMA scientific, legal and regulatory experience, as their scope for action. The objectives of the Innovation Task Force (ITF) can be summarised on the following topics: early identification of the need for specialised expertise; establishment of a discussion platform for early dialogue with applicants, in particular with SMEs; addressing the impact of emerging therapies and technologies in current scientific, legal and regulatory requirements with relevant EMA's Committees and Working Parties; together with the appropriate Committees for Medicinal Products, human and veterinary, and the EC, the provision of regulatory advice to applicants on the eligibility to EMA procedures; review of the regulatory and scientific implications of emerging therapies and technologies, in cooperation with EMA's Committees and Working Parties, and NCAs; and increasing EMA's awareness and learning about emerging therapies and technologies. (32)

3.1.3 Medicine development concept

Adaptive pathways

As part of EMA's efforts to improve patients access to new medicines, in a timely manner, the adaptive pathways approach is a scientific concept, which uses the existing EU regulatory framework and review tools, such as scientific advice, compassionate use, the conditional approval pathway, and patient registries and other pharmacovigilance tools, for medicine development and data generation which allows early and progressive patient access to a medicine that addresses patients' unmet medical needs.(33)

The adaptive pathways approach should not be considered a route for approval of medicines, and it doesn't change the standards for the evaluation of benefits and risks of the candidate

medicine neither the requirement to demonstrate a positive benefit-risk balance to obtain MA. It can be defined as a prospectively planned and iterative approach intended to bring promising medicines to market, also based on the experience acquired after implementing the 2012 pharmacovigilance legislation which strengthened post-marketing monitoring tools. (33,34)

The approach of adaptive pathways is based on three principles: 1 - iterative development in two pathways - approval in stages, initially targeting the development to a well-defined group of patients, then expanding to wider patient populations; or confirming the positive benefit-risk balance following a conditional approval based on surrogate endpoints considered predictive of important clinical outcomes; 2 - gathering evidence through real-life use to complement clinical trial data; 3 - involvement of patients and HTA bodies in discussions on the medicine's development from early stages. (33,34)

To be eligible for the adaptive pathways approach, the candidate medicine should correspond to some requirements, namely the use of real-world data for regulatory purposes, the need to discuss with HTA bodies during development, and the inclusion of any iterative aspect in the development plan. (33)

The iterative development plan is designed to allow for the contribution of many relevant decision-makers that can be involved during different stages of the product life-cycle, including entities responsible for patients' access to medicines in the Member States and regulators, creating the opportunity to agree upfront on a post-authorization set of studies that can generate appropriate and important data which MAH is committed to gather and deliver. (34)
EMA launched a pilot project in March 2014, ending in August 2016, to explore the adaptive pathways approach and the practical implications of this concept with drug candidates. It consisted of inviting drug developers to submit development programmes of their candidate medicines that followed pre-defined criteria: an iterative development plan, prospectively planned; the involvement of HTAs and other stakeholders, with proposals on how the requests of these stakeholders can be met; and real-world data as a complement to randomized controlled trials. Considering the 18 selected from 62 applications, seven progressed to a formal scientific advice (one) or parallel regulatory-HTA scientific advice (six) at the end of the pilot project. The experience added with this pilot allowed for the collection of key insights showing that adaptive pathways can foster multi-stakeholder dialogue, and that this approach can support medicines' development in therapeutic areas where generation of evidence is very challenging, such as infectious diseases, Alzheimer's disease, degenerative diseases, and rare cancers; amongst other key learnings that are described in the final report made public by EMA. (34)

According to EMA's plan to explore the next steps after conclusion of the pilot project, the adaptive pathway concept continued to be experienced in context of parallel scientific advice with HTA bodies, with the inclusion of additional stakeholders, and EMA is committed to go further in exploring this approach of major interest to public health. (33)

The adaptive pathway concept was developed in parallel with a similar one from the Innovative Medicines Initiative (IMI), the ADAPT-SMART, which started in September 2015 in collaboration with 32 different entities, with EMA as the scientific leader. The ADAPT-SMART project is an enabling platform funded through IMI aiming to facilitate and accelerate the availability of beneficial treatments, considered to target high unmet medical needs, for the right patient groups at the earliest appropriate time in the product life span in a sustainable way, and through collaboration among stakeholders. In the first review, it was found some outputs that can be relevant and useful to the eventual scenario that a drug/molecule is considered suitable to fulfil Medicines Adaptive Pathways to Patients (MAPPs) engagement criteria, but it was also concluded that further studies were needed to form appropriate recommendations along these bases in subsequent reviews. (35)

3.1.4 Overview of EU Expedited Programs

Table 1 - Comparative table of EU Regulatory tools for expedited MAs, by characteristics and features.

The table below provides a comparison of EMA's expedited programs, highlighting a summary of all relevant features. Adapted from "Support for early access" on EMA's Webpage (6)

	Accelerated assessment	***Conditional MA***	***Authorisation under Exceptional Circumstances***	***Compassionate Use***	***PRIME scheme***
Type of mechanism	Regulatory tool for early access	Regulatory tool for early access	Regulatory tool for early access	Regulatory tool for early access	Support scheme for medicine development
Legal basis	Recital 33 and Article 14(9) of Regulation (EC) No 726/2004	Article 14(7) of Regulation (EC) No 726/2004; Regulation (EC) No 507/2006	Article 14(8) of Regulation (EC) 726/2004; Directive 2001/83/EC	Article 83(1) of Regulation (EC) No 726/2004	Recital 33 and Article 83(1) of Regulation (EC) No 726/2004
Qualifying criteria	Medicines of a major interest from the point of view of public health and in particular from the therapeutic innovation point of view, namely targeting an unmet medical need, and with strong evidence of fulfilling that need.	Medicines for seriously debilitating or life-threatening diseases, including orphan medicines and medicines for emergency situations, satisfying the following criteria: positive benefit-risk balance; comprehensive data after authorisation is likely to be provided; fulfils unmet medical need; benefits of immediate availability outweigh the risks due to additional data still being required.	Medicines applicable to extreme settings (rare diseases or specific conditions) that comprehensive clinical data or endpoint is very difficult to measure for scientific reasons and/or because of ethical reasons.	Applicable to unauthorised medicinal products for chronically, seriously debilitating or life-threatening diseases, with no satisfactory treatment authorised in the EU; targeted at a group of patients; undergoing centralised MA applications or clinical trials; falling under the mandatory or optional scope of centralised procedure.	Medicines of a major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation, namely targeting an unmet medical need.

Application	Requested 2-3 months before submission of MA application to EMA, ideally after a pre-submission meeting 6 to 7 months before the target MA submission date; the same evidence requirements for standard MA application are applied.	Discuss as early as possible during development, through scientific advice/protocol assistance. EMA should be notified 6-7 months before submission of MA application, which can be submitted after conclusion of phase II studies. CHMP may propose it during assessment of MA application.	The applicant may request advice from EMA 4 to 6 months before submission of the MA application about applicability and justification to be included in Module 1. MA may be granted subject to a requirement for the applicant to introduce specific obligations, particularly concerning the safety of the medicinal product.	National competent authorities are responsible for requesting CHMP opinion on compassionate use. CHMP may provide a voluntary recommendation if several independent opinions are requested by Member-States.	Submission of a voluntary request for eligibility, based on preliminary clinical evidence (proof of concept). For SME's and academics, it's possible to submit at an earlier stage (proof of principle), only results of a first-in-man study (clinical trial) are required.
Features and mechanism of expedition	Assessment of MA application follows a shortened timetable: 150 days or less, instead of 210 days of standard procedures, excluding the time of clock stops needed during the review (excluding the time that applicants require for responses to the CHMP's questions)	Earlier authorisation is granted based on less complete clinical data - benefit-risk balance is positive but pending confirmation. MA includes specific obligations to be addressed by the MAH in a specific timeframe, which are made public in the EPAR.	Comprehensive data cannot be obtained after authorisation - this authorisation pathway normally won't lead to a standard MA.	CHMP provides recommendations to the requestor Member State to harmonise the conditions of use, distribution and the target population. After MA application has received positive CHMP opinion, the CHMP recommendation for compassionate use should be updated accordingly.	The development program will be supported by the Agency in early stages of development, focused on optimising investigation plans: a rapporteur is appointed earlier to act as a supportive intermediate; meetings are organized with a multidisciplinary team and relevant committees; dedicated contact person within EMA

Other Characteris-tics	The pre-submission meeting is an opportunity to meet with rapporteurs from the concerned committees; they recommend the acceptance or not of the accelerated assessment.	During pre-submission meetings, it's possible to liaise with other relevant stakeholders (e.g., HTA bodies); fewer comprehensive clinical data on safety and efficacy may be acceptable, as well as smaller studies in size and/or with a shorter duration and/or different endpoints from confirmatory studies.	Applicant should justify that comprehensive data on the efficacy and safety aspects under normal conditions of use are unable to be provided. New indications may be added through variations to the MA; however, the MA will remain under exceptional circumstances.	Compassionate use benefits seriously ill patients who cannot be treated satisfactorily with medicinal products approved or are unable to enrol in ongoing clinical trials.	It's possible to know if the medicine may be eligible for accelerated assessment, during the clinical development phase.
Post-marketing requirements	The same applied for standard MA's.	MA valid for 1 year, with annual renewals. Obligations to confirm the positive benefit/risk balance must be addressed by the MAH and they are reviewed during renewals' assessment. After obtaining comprehensive data, MA is converted into a standard MA.	The MAH is subject to specific procedures and obligations (e.g., completion of an identified programme of studies within a specific timeframe). The CHMP revises annually the implementation/compl etion of procedures/obligations . The fulfilment of obligations imposed is aimed at the provision of information on the safe and effective use of the product.	After MA is granted, reference is made to the EPAR and updates of compassionate use recommendations are no longer needed. The MAH should ensure that patients taking part in the compassionate use programme have access to the medicinal product until the medicinal product is placed on the market.	As appropriate, according to expedited pathways applicable to the medicine in scope. For example, fulfil que conditions imposed if the MA was granted as conditional.

3.2 USA Regulatory Framework

In 1988, the US FDA issued regulations on expediting the availability of promising therapies to patients with serious conditions, in 21 Code of Federal Regulations (CFR) Part 312 (Subpart E)[24]. This set of regulations represented the first official call for earlier attention to medicines promising to address the need for treatment of serious conditions, including the possibility of sponsors consulting earlier with FDA. (9,36)

Subsequently, several amendments to the FD&C Act were implemented in the following years to include new regulatory tools for expedited MA – product development programs and expedited review – including fast track designation, accelerated approval, and breakthrough therapy designation. The most recent one is the regenerative medicine therapies designation, which resulted from an amendment of regulations in late 2016.(9)

FDA has been investing in creating projects and platforms enablers of enhanced communication to foster the development of medicines which are critical to public health. In line with this objective, FDA created INTERACT meeting – Initial Targeted Engagement for Regulatory Advice on CBER producTs, an informal non-binding consultation with the CBER, allowing sponsors to obtain preliminary informal insights for innovative investigational medicines, which may have unique challenges due to the unknown safety profiles, complex manufacturing technologies, development of innovative devices, etc., at an early stage of development, namely before the pre-IND meeting phase. Therefore, this early dialogue is focused on pre-clinical trial dialogue between the FDA and medicine developers, to discuss issues that may arise at early stages related to Chemistry manufacturing and Controls (CMC) and clinical development aspects. (37)

3.2.1 Regulatory tools for expedited MA

The US FDA has created four different tools aimed at increasing a response to the need for drugs targeting to serious diseases of public relevance, namely when there isn't any treatment available or when the new drug candidate has considerable advantages over existing treatments. This condition may be simply referred to as an unmet medical need[25]. In the USA,

[24] Codified in 21 CFR Part 312 (Subpart E) (36)

[25] FDA clarifies on its guiding documents that an "unmet medical need" is a medical condition without adequate treatment or diagnosis by available therapy, and it can include an immediate need for a specific population or a long-term need for a society. (7)

the definition of drugs targeting an unmet medical need are therapies against severe or life-threatening diseases with no current therapy option. If therapies are available, the medicinal product must exhibit a considerable advantage over available therapy[26] to be eligible for any of the FDA's expedited programs.(19,38)

Despite all expedited tools being intended to decrease the time needed for review and approval of new medicines, these four different procedures - *Priority Review, Breakthrough Therapy, Accelerated Approval* and *Fast Track* – can speed up the availability of drugs trough different approaches and with different implications. It is also relevant to highlight that a drug development program may qualify for more than one of the FDA's Expedited Programs. (38)
Some important concepts, indispensable to the correct interpretation of Agency's expedited programs correctly, were clarified by FDA and they are summarised on its guiding document for industry intended to address explanations on expedited programs available - *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*. (7) When referring to a "drug intended to treat a serious condition"[27], it's implicit that the medicinal product in scope must have an effect on serious conditions or a certain aspect of a condition, such as its expression or symptoms. These drugs may encompass the following characteristics: they are intended to "*prevent a serious condition or reduce the likelihood that the condition will progress to a more serious condition or a more advanced stage of disease*"; they will avoid or decrease a "*serious adverse event associated with available therapy for a serious condition*"; they will be able to "*mitigate or prevent a serious treatment-related side effect*" or they will "*improve diagnosis or detection of a serious condition in a way that would lead to improved outcomes*" if it's a diagnostic product. (7)

Regarding the concept of "available therapy": at the time of Biologic License Application (BLA) or New Drug Application (NDA) submissions for priority review designation, available therapy will be determined by FDA once the available *standard of care (*SOC) is evolving over the time for a specific indication. When referring to a serious medical condition without any available therapy, this will undoubtedly constitute an unmet medical need.(7) If the available therapy

[26] "Available therapy" is defined by FDA as a therapy "*approved or licensed in the United States for the same indication being considered for the new drug*" and "*relevant to current U.S. standard of care (SOC) for the indication*". (7)

[27] A "serious condition" means that it is "*associated with morbidity that has substantial impact on day-to-day functioning. (…) the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.*", as outlined in the applicable section of Code of Federal Regulations in Subpart I - Expanded Access to Investigational Drugs for Treatment Use. (83)

was approved through an expedited program, and was based on a surrogate[28] or an intermediate clinical endpoint[29], meaning that clinical benefit of this new therapy hasn't been verified yet, this will also constitute a case for an unmet medical need because it is desirable to have additional treatment options if clinical benefit cannot be verified in confirmatory studies of therapies approved under such characteristics. In addition, there are cases where available therapy exists, but it will only be considered to address the medical need in scope if certain conditions[30] are applicable to that treatment. (7)

In the subsections below, each regulatory tool for expedited MA existing in the USA it will be further characterized and detailed, according to information available on official guiding documents and sources from FDA, supported by the US legislations in place.

Fast track designation

This process was designed to bring relevant new drugs to the market in an expedited way, and consequently for the patients, faster than in standard procedures, when they are intended to treat a broad range of serious clinical conditions and fulfil an unmet medical need. This designation is aimed to facilitate the development of candidate medicines and expedite the review of new drugs. (38) According to FD&C Act[31], a designation of "Fast Track Product" is given "*if it is intended, whether alone or in combination with one or more other drugs, for the*

[28] Surrogate endpoint is a "marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is thought to predict clinical benefit, but is not itself a measure of clinical benefit."(7) Examples of surrogate endpoints are listed on the FDA website, and include change in CD4 counts in AIDS patients, progression-free survival and shrinking tumor for cancer, etc.

[29] Intermediate clinical endpoint is a "*measurement of a therapeutic effect that can be measured earlier than an effect on IMM and is considered reasonably likely to predict the drug's effect on irreversible morbidity or mortality (IMM) or other clinical benefit*" (7)

[30] FDA described these conditions as: it must have an "*effect on a serious outcome of the condition that is not known to be influenced by available therapy*"; it has to demonstrate an "*improved effect on a serious outcome(s) of the condition compared with available therapy*"; it has an "*effect on a serious outcome of the condition in patients who are unable to tolerate or failed to respond to available therapy*"; in case it can be used "*effectively with other critical agents that cannot be combined with available therapy*"; if it can provide "*efficacy comparable to those of available therapy, while avoiding serious toxicity that occurs with available therapy, avoiding less serious toxicity that is common and causes discontinuation of treatment of a serious condition, or reducing the potential for harmful drug interactions*"; in case it can provide "*safety and efficacy comparable to those of available therapy but has a documented benefit, such as improved compliance, that is expected to lead to an improvement in serious outcomes*"; or it "*Addresses an emerging or anticipated public health need, such as a drug shortage*". (7)

[31] According to 506(b) - Expedited approval of drugs for serious or life-threatening diseases or conditions, of 21 U.S. Code of the FD&C Act (8)

treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition" or if it's designated as a "*qualified infectious disease product*" and this designation was created in 1998. (7,8)
The seriousness of a condition is judged based on its impact on survival, basic daily functions, or whether the chronicity of the disease will lead to severe deterioration of living conditions (e.g., Acquired immunodeficiency Syndrome (AIDS), Alzheimer's disease, heart failure and cancer, but also epilepsy, depression and diabetes). (38) The candidate medicine should therefore target one of these diseases to be considered medically relevant, by providing a treatment where there isn't any available, or be considered a potentially better treatment by providing evidence of: higher effectiveness; effect/improved effect on serious outcomes; improved safety profile avoiding more serious side effects than available therapy; reducing the toxicity of the treatment, which will reduce the number of discontinuations; improving the diagnosis of a serious condition leading to an earlier diagnose and consequently better outcomes; or its ability to address emerging or anticipated public health demands. (38)

The developing company is responsible for requesting Fast Track designation, and it is possible to submit the request at any time of the drug development process. Depending on the stage of drug development, different amounts/types of information will be required to determine the potential of the drug to address the unmet medical need – it may include theoretical rationale, mechanistic rationale (based on nonclinical data), or evidence of nonclinical activity. Within 60 days, FDA is held accountable for reviewing the request and making a decision on whether the candidate medicine can be incorporated into a Fast Track approach or not. (7,38)
After receiving Fast Track designation some features are added to the process and are projected to facilitate early drug approval and faster access by patients. This process starts with early and frequent communication between the developing company and FDA, including pre- Investigational New Drug (IND) meetings, end-of-phase 1 and end-of-phase 2 meetings, which encourage the debate around drug development aspects and the review process, such as study design, extent of safety data needed, dose-response concerns, and use of biomarkers. This represents an opportunity for both the developing company and Agency to raise questions and correct/resolve any issues as soon as they are identified. (7,38)
The main particularities of the process after Fast Track designation are the increased frequency of meetings with FDA, where the drug's development plan and appropriate studies to support drug approval are discussed; the increased frequency of written communication

about relevant topics, including the possibility of eligibility for Accelerated Approval and/or Priority Review; and the opportunity of having a Rolling Review[32].

Breakthrough Therapy Designation

When preliminary clinical results are available, suggesting that the candidate medicinal product represents clinically significant improvements over existing treatments, and is intended to treat a serious condition, the development and review processes may be expedited under Breakthrough Therapy designation. According to FD&C Act[33], a breakthrough therapy is defined as a drug alone or in combination intended to "*treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development*", and it was created in 2012. (7,8,38)

The request for a Breakthrough Therapy designation submitted by the company should ideally be addressed to FDA at or before the end-of-phase-2 meetings, and preliminary clinical evidence of a treatment effect that may represent substantial improvement over available therapies is required, although it is not sufficient yet to determine safety and effectiveness essential for MA approval. Whether a request for this type of designation is made after the submission of an original BLA or NDA or a supplement is unforeseen, since the main objective of this expedited process is to support an accelerated approval by developing evidence needed in an efficient way. (7,38) FDA advises developing companies to obtain preliminary clinical evidence in early development in comparison to available therapy, considering the SOC, or to placebo if there isn't any available therapy, indicating that new drug is expected to bring a substantial improvement over available alternative. (7,38) In some cases, other types of clinical data may also be acceptable based on comparison of single-arm studies with well-documented historical experience, but clinical evidence should be based on evident credibility. The response for Breakthrough Therapy designation request will be issued by FDA within 60 days

[32] Biologic License Application (BLA) or New Drug Application (NDA), as applicable, are normally included as part of the full application submitted to the FDA, once all the information is complete and the drug's application dossier is entirely concluded. Nevertheless, a rolling review allows the applicant to submit completed sections of BLA and NDA before completion of the entire sections of the application dossier). (38)

[33] According to Section § 506 (a)(1) - Expedited approval of drugs for serious or life-threatening diseases or conditions, of 21 U.S. Code of the FD&C Act (8)

of receipt date. In case the drug company hasn't requested Breakthrough Therapy designation, FDA may suggest the submission of the request at a later stage. This may occur if FDA considers that the drug development program is compatible with criteria for Breakthrough Therapy designation after assessing the preliminary clinical evidence and other data submitted, and if the expedited process of this designation can represent a significant benefit for the remaining development program of the drug candidate. (7,38)

To support the Breakthrough Therapy designation, the improvements over available therapies must be substantial and clinically significant, and they depend on the relevance of clinical outcomes and on the magnitude of the treatment effect, including its duration. Determination on whether an improvement may be considered "substantial" consists of a matter of judgement and it depends on the relevance of drug's effect to the serious condition or an aspect of it, and on the effect on a clinically significant endpoint. To be considered a clinically significant endpoint, it should generally measure an effect on irreversible morbidity or mortality (IMM) or an effect on symptoms that represent serious consequences of the disease, such as: an effect on an established surrogate endpoint; an effect on a surrogate endpoint or intermediate clinical endpoint considered reasonably likely to predict a clinical benefit; an effect on a pharmacodynamic biomarker that doesn't meet criteria for an acceptable surrogate endpoint, but strongly suggests the potential of a clinically meaningful effect on the underlying disease; and a considerably improved safety profile compared to available therapy with evidence of similar efficacy. (7,38)

If the new drug can demonstrate a substantial improvement over available treatments, then it may include one or more of the following approaches: new drug reveals a greater or more important response when directly compared to available therapy (studies may be conducted in treatment-naïve patients, in those whose disease failed to respond to available therapies, in comparison with the failed therapy or as a no-treatment controlled study); new drug shows a substantial and clinically significant effect on an important outcome when compared with placebo or a well-documented historical control if there's no available treatment; new drug shows a greater or more important response when it is added to available therapy (studies may be conducted in treatment-naïve patients in those whose disease failed to respond to available therapies); new drug can show a direct effect on the basic cause of the disease and preliminary evidence indicates that it has a long-term disease-modifying effect whereas available therapies only have effect on symptoms; new drug has the potential to reduce or inhibits disease progression; or if new drug has a significant improvement over available therapies with regards to the safety profile and serious adverse reactions. (7)

The benefits of being granted with Breakthrough Therapy designation for the review process and ultimately a faster approval, are the eligibility for all Fast Track designation features; the intensive orientation on a more efficient drug development program from Phase 1 studies; and the involvement of FDA senior managers and their commitment to expedite the review and approval process. Even if only preliminary clinical evidence is needed to support Breakthrough Therapy designation, full data supporting the safety and effectiveness of the drug's intended use is needed to sustain FDA's revision and approval for availability to patients. (7,38) Nevertheless, it was determined that FDA may review parts of the MA before the sponsor submits the complete application - rolling review - after evaluation of preliminary clinical data submitted and determination of Breakthrough Therapy designation. (7)

By fostering a straight collaboration and interactive communication with the developing company, FDA will be able to provide timely advice on the study design (e.g., adaptive designs, an enrichment strategy, use of historical controls, etc.) or on the use of an interim analysis by a data monitoring committee, and a more efficient drug development program (requiring less time to complete the study and potentially minimizing the number of patients exposed), helping to generate adequate data to demonstrate safety and efficacy results needed to satisfactory grant a MA. These approaches might be significantly important for rare diseases. (7)

Additionally, if supported by clinical evidence at the time of BLA, NDA, or efficacy supplement submission, the product with breakthrough designation could be also eligible for priority review. The involvement of senior leadership members, including experienced staff in regulatory project management, is also fundamental to expediting the review process, especially in a collaborative and multi-disciplinary programme. (7,38)

However, it is relevant to highlight that Breakthrough Therapy designation may be rescinded by FDA if substantial improvement over available therapies isn't supported by subsequent data compared to preliminary clinical evidence available at the time of designation. (7,38)

Accelerated Approval

In response to the need to expedite the review process of MA application, when an extended period is needed to measure the outcomes of a drug intended to treat serious conditions and target unmet medical need, in 1992 FDA put forth a set of regulations that created the Accelerated Approval pathway. For these exceptional conditions, the Accelerated Approval

regulation allowed for faster approval based on a surrogate endpoint. Twenty years later, Congress approved the Food and Drug Administration Safety Innovations Act (FDASIA)[34] in which section 901[35] amends section 506 (c) of Federal FD&C Act, increasing the authority of FDA to consider appropriate measures to approve drugs targeting serious conditions that fill an unmet medical need based on its effect, either on a surrogate or an intermediate clinical endpoint, as a basis for the accelerated approval, since they can save valuable time and represent a major interest to public health. (38,39)

Although they are not measures of a clinical benefit themselves, surrogate or intermediate clinical endpoints are indicators that can be used to support accelerated approval process, as established in 21 CFR part 314, subpart H and 21 CFR part 601, subpart E (8,38,40,41) This pathway has been used in some chronic diseases and contexts in which an extended period is needed to collect sufficient data and evaluate the results to assess the expected clinical benefit of the medicinal product. In the case of human immunodeficiency virus (HIV) disease and a variety of cancers, accelerated approval has been used in the approval of medicines based on an effect that can be quickly assessed, such as tumour growth or viral load. Nevertheless, for these types of diseases, a longer period, and larger trials to evaluate the real effect on survival or morbidity, is required. On the other hand, Accelerated Approval pathway can also be useful in an acute disease setting where an effect on a surrogate endpoint could be demonstrated in a small number of patients. Typically, in these cases, the intended clinical benefit, such as survival, can only be demonstrated in a large study due to the nature of the disease. If the frequency of the clinical benefit occurs rarely, then a long and large study is needed. (7)

FDA is responsible for deciding which endpoint will be accepted for each case. The developing company should provide FDA with all scientific support regarding the endpoint to consider – whether to consider the proposed surrogate or intermediate clinical endpoint – to facilitate this decision, when needed. To accommodate this approach, the FD&C Act provides that for such a study demonstrating the drug's effect on a surrogate or intermediate clinical endpoint must

[34] The FDASIA was signed into law on July 9, 2012 and intended to expand the FDA's authorities and strengthens the agency's ability to safeguard and advance public health by several means, which include promotion of innovation to accelerate patient access to safe and effective medicinal products and increase stakeholder involvement in FDA processes. Under this act, Breakthrough Therapy designation has come into effect. (39)

[35] Section 901 *Enhancement of Accelerated Patient Access to new Medical Treatments, is* under TITLE IX—*Drug Approval and Patient Access,* and refers the establishment of enhanced "*authority of the FDA to consider appropriate scientific data, methods, and tools, and to expedite development and access to novel treatments for patients with a broad range of serious or life-threatening diseases or conditions.*" (39)

be “adequate and well controlled”. (38) To improve process efficiency, FDA encourages developing companies to engage in early development phases concerning the potential eligibility for this pathway, and to communicate with the Agency around proposed surrogate endpoints, or intermediate clinical endpoints; study designs, and the planning and conduct of confirmatory trials; and increasing readiness to the requests raised by FDA, also in other aspects such as manufacturing or development of companion diagnostic. (7)

The benefits of using these adjusted endpoints are mainly related to a faster review and approval process, but the developing company will still need to perform additional studies such as phase 4 confirmatory clinical trials, to confirm the clinical benefit predicted by the evidence of surrogate or intermediate clinical endpoints. These studies conducted at a later stage of development are commitments of the company to FDA, which will normally close that obligation if the results of confirmatory studies have verified the assumptions pre-established and clinical benefits are finally confirmed. Otherwise, if confirmatory studies cannot demonstrate a positive benefit-risk balance or clinical benefits cannot be verified, FDA may revoke the authorisation previously granted or change the therapeutic indication labelled. (38)

Priority Review

In 1992, FDA created a two-tiered system of review times – Standard Review and Priority Review – under the Prescription Drug User Act (PDUFA)[36]. With this approach, FDA adopts the review designation for each application, and this adopted strategy is enabling a reduced drug review period prior to approval in the USA. In a standard review, the assessment process takes 10 months to complete, whereas in a Priority Review designation, FDA intends to review a MA application within 6 months. Therefore, distinctive attention and resources are focused on the evaluation of the candidate medicine. (38)

The Priority Review designation is granted with the assumption that approval of that medicinal product will bring a significant beneficial impact in the safety profile or effectiveness of the treatment, diagnosis, or prevention of serious conditions. (38) When the results of studies conducted with the candidate medicine demonstrate evidence of increased effectiveness in

[36] PDUFA was created by Congress in 1992. Under this act, FDA is authorized to collect fees from companies that produce human drug and biological products. PDUFA must be reauthorized every five years, and PDUFA VI is now into effect through September 2022. This will provide for the continued timely review of NDA and BLA since user fees have been playing an important role in expediting the drug approval process. (84)

treatment, prevention, or diagnosis of a certain condition; of a better safety profile by eliminating or substantially reducing a treatment-limiting drug reaction; of enhancement of patient compliance leading to an improvement in critical outcomes; and of safety and effectiveness in a new subpopulation, then a significant improvement is considered applicable to this new drug. (38)

The applicant may proactively request Priority Review and, within 60 days of the receipt of the original BLA, NDA, or efficacy supplement, FDA will provide notification around the decision of assigning Priority Review designation. Nevertheless, this decision will not affect the extent of the clinical trial period nor the scientific/medical criteria to perform the application's assessment, the quality of evidence required or the final decision on the approval. (38)

Regenerative Medicine Advanced Therapy

Regenerative medicine therapies are defined in section 506(g)(8) of the FD&C Act, and the term includes cell therapy, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products. (8) Based on FDA's interpretation of section 506(g), human gene therapies, including genetically modified cells, that lead to a sustained effect on cells or tissues, may meet the definition of a regenerative medicine therapy, but microorganisms (e.g., viruses, bacteria, fungi) that are not genetically modified do not meet the criteria to be included in this definition. In addition, a combination product[37] can also be eligible when the biological product component is a regenerative medicine therapy and provides the greatest contribution to the overall intended therapeutic effects. (8,9)

According to the same Act, in Section 506 (g)(1), the sponsor is accountable for requesting the designation and FDA should facilitate an efficient development program for, and expedite review of, such drug, if conditions to be qualified as regenerative advanced therapy are met. (8,9)

To be eligible for Regenerative Medicine Advanced Therapy designation, an investigational medicine should meet the definition, as described above, to be intend to treat, modify, reverse,

[37] Combination product is a biologic-device, biologic-drug, or biologic-device-drug product, which the primary mode of action means the single mode of action of a combination product expected to make the greatest contribution to the overall intended therapeutic effects of the combination product. (85)

or cure a serious condition; and have the potential to address unmet medical needs for the serious condition based on its preliminary clinical evidence. (8,9) This evidence is expected to be obtained from clinical investigations specifically conducted to evaluate the effects of the therapy on the serious condition in scope, and Center for Biologics Evaluation and Research (CBER) intends to consider factors, including but not limited to: the rigor of data collection; the consistency and persuasiveness of the outcomes; the number of patients and sites contributing to the data; and the severity, rarity, or prevalence of the condition, to determine whether the preliminary clinical evidence is sufficient to support designation. (9) CBER will notify the sponsor, in 60 days after receipt of the designation request, as to whether it is acceptable or not. (8)

In contrast to Breakthrough Therapy designation, the regenerative medicine advanced therapy designation is granted regardless of whether the drug indicates a substantial improvement over available therapy or not, and it does not change the regulatory standards for the extension of demonstration of the safety and effectiveness evidence needed in order to be granted MA. (9)

The advantages of being granted with regenerative medicine advanced therapy designation include all the benefits of breakthrough therapy and fast track designations. Early interactions with FDA are also a benefit of this designation and they may be used to discuss potential surrogate or intermediate endpoints to support accelerated approval. (8,9)
Regenerative medicine therapies designation is, therefore, compatible with the simultaneous eligibility for fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation, if conditions for each program are met. However, sponsors should apply for each designation separately. (9)

Compassionate Use programs

FDA has four main mechanisms of expanded access programs for drugs, which are the “Emergency Use (IND/protocol)”, the “Individual Patients (IND/protocol)”, the “Intermediate-Size Patient Populations (IND/protocol)”, and “Treatment (IND/protocol)”. Each one is applied according to the urgency of use of the medicinal product, the number of patients that need to use it, when it can be used, and also the need to use the new therapy before FDA approval, due to its criticality. (42) The USA regulation applicable to all programmes of expanded access is 21 CFR 312.305. More specifically to Emergency use and Individual Patients, it is applicable

21 CFR 312.310; for Intermediate-Size Patient Populations it is applicable 21 CFR 312.310; and for treatment, the regulation applicable is established on 21 CFR 312.320 part. (42)
All these mechanisms are applicable to an individual or to many patients with a serious or immediately life-threatening disease without comparable or satisfactory alternative therapy, when the benefit/risk balance is positive and potential risks are acceptable in the clinical context in scope. It should also be noted that the request for expended access under one of these mechanisms will not interfere with the initiation, conduct, or completion of clinical studies. (42)

From the four mechanisms, the one applicable in more extreme conditions is the emergency use programme, which can even be authorized by FDA via telephone after the physician determines the indispensable use of the unapproved medicine, before written submission to FDA. (42)

Qualified infectious disease products

In line with its aim of creating a legal and regulatory framework supportive of the development of medicines targeting unmet medical needs, in 2012FDA also created a mechanism of incentives for the development of antibiotics in response to the increasing threat of antibiotic resistance and the lack of investment by pharmaceutical companies in this type of medicinal product. It is integrated in the *Food and Drug Administration Safety and Innovation Act* of 2012 (FDASIA), as part of Title VIII: *Generating Antibiotic Incentives Now*, section 801, referred to as the GAIN act, which provisions are under section 505E of the 34 Federal FD&C Act. (39,43)
In this act, it was conceded an extended exclusivity period of five years for qualified infectious disease products, legally defined in Section 505E(g) of the FD&C Act, as an incentive to develop these medicinal products considered of major interest to the society.(44)

Given the importance of this topic, it was defined by Public Law 112–144—July 9, 2012 that, if the Secretary designates a new antibiotic as a qualified infectious disease product, then priority review to any application submitted for approval for such a drug will be granted by FDA. (39) There is also opportunity to request fast track designation for Qualified Infectious Disease Product (QIDP), if it's of the sponsor's interest, but it can only be requested on or after submission of an IND, whereas QIDP designation may be requested prior to submission of an IND. (8,43)

3.2.2 Overview of FDA's Expedited Programs

Table 2- Comparative table of FDA's Regulatory tools for expedited programs for serious conditions, by characteristics and features.

The table below provides a comparison of FDA's expedited programs, highlighting a summary of all relevant features. Adapted from official guiding documents available at FDA's Webpage (7,9)

	Fast Track	***Breakthrough Therapy***	***Accelerated Approval***	***Priority Review***	***Regenerative Medicine Advanced Therapy***
Type of mechanism	Designation	Designation	Approval Pathway	Designation	Designation
Legal basis	Section 506(b) of the FD&C Act, as added by section 112 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) and amended by section 901 of the FDASIA of 2012	Section 506(a) of the FD&C Act, as added by section 902 of FDASIA	Section 506(c) of the FD&C Act, as amended by section 901 of FDASIA; 21 CFR part 314 subpart H 21 CFR part 601, subpart E	Prescription Drug User Fee Act of 1992	Section 506(g) of the FD&C Act, as added by section 3033 of the 21st Century Cures Act (Cures Act)
Qualifying criteria	A drug intended to treat a serious condition, with nonclinical or clinical data available to demonstrate the potential to address unmet medical need. May also be drug that has been designated as a QIDP designation.	A drug intended to treat a serious condition, with preliminary clinical evidence indicating that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies	A drug that treats a serious condition, generally providing a meaningful advantage over available therapies. It should demonstrate an effect on a surrogate endpoint reasonably likely to predict clinical benefit or on an	An application (original or efficacy supplement) for a drug that treats a serious condition and would provide a significant improvement in safety or effectiveness if approved; any supplement that proposes a labelling change pursuant to a	A drug that is a regenerative medicine therapy, and is intended to treat, modify, reverse, or cure a serious condition; preliminary clinical evidence must indicate that the drug has the potential to address unmet medical needs for

			intermediate clinical endpoint.	report on a paediatric study; an application for a drug with QIDP designation; Any application or supplement for a drug submitted with a priority review voucher	such disease or condition.
Application	It is possible to submit the request at any time of the drug development process, ideally, no later than the pre-BLA or pre-NDA meeting; response is provided within 60 calendar days of receipt of the request.	With IND or after; ideally, no later than the end-of-phase 2 meetings; response is provided within 60 calendar days of receipt of the request	The possibility of accelerated approval should be discussed with the review division during development, supporting, for example, the use of the planned endpoint, and discussing the confirmatory trials which should be underway at the time of approval.	With original BLA, NDA, or efficacy supplement Response is provided within 60 calendar days of receipt of original BLA, NDA, or efficacy supplement.	With the IND or after and, ideally, no later than the end-of-phase 2 meeting. Response is provided within 60 calendar days of receipt of the request
Features and mechanism of expedition	Increased frequency of communication with FDA, including pre-IND meetings, end-of-phase 1 and end-of-phase 2 meetings; mechanisms to expedite development and review; possibility of rolling review	Organizational commitment of FDA senior management; Intensive guidance on efficient drug development is provided; possibly of early interactions to discuss any potential surrogate or intermediate endpoints; possibility of rolling review and to take other	Expedite the approval, which may be based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit	Shorter clock for review of MA application: eight months (six months plus 60 filing days) while standard review is 12 months (10 months plus 60 filing days). Shorter clock for review of efficacy supplement: six months (Standard review: 10 months).	All benefits of the fast track and breakthrough therapy designation programs, including early interactions to discuss any potential surrogate or intermediate endpoints;

		actions to expedite review and faster approval.			
Other Characteris-tics	Designation may be rescinded if it no longer meets the qualifying criteria for fast track.	Full data supporting safety and effectiveness for drug's intended use is needed to sustain FDA's approval; designation may be rescinded if it no longer meets the qualifying criteria.	-	Designation will be assigned at the time of original BLA, NDA, or efficacy supplement filing; full data supporting safety and effectiveness for drug's intended use is needed to sustain FDA's approval.	Legal basis addresses potential ways to support accelerated approval and satisfy post-approval requirements; full data supporting safety and effectiveness for drug's intended use is needed to sustain FDA's approval. Designation may be rescinded if the product no longer meets the designation-specific qualifying criteria.
Post-marketing requirements	The same applied for standard MA's.	The same applied for standard MA's.	Confirmatory trials to verify and describe the anticipated effect on IMM or other clinical benefit, e.g., phase 4 confirmatory clinical trials.	The same applied for standard MA's.	The same applied for standard MA's.

3.3 Japan Regulatory Framework

In Japan, pharmaceutical legislation consists of several laws and regulations, namely the *Pharmaceutical and Medical Device Act*, *Law Concerning the Establishment for Pharmaceuticals and Medical Devices Organization*, *Law Concerning Securing Stable Supply of Blood*, among others related to additional products that can be used for medicinal purposes. With regards to the *Pharmaceutical and Medical Device Act (PMD Act)*, its objectives are "*to improve public health through regulations required to assure quality, efficacy, and safety of drugs, quasi-drugs, cosmetics, medical devices, and regenerative medicine products and to prevent hazard and expansion of hazard in public health*", also promoting the research and development of drugs, medical devices and regenerative medicine products. (45)

To allow marketing of medicinal products in Japan, formal approval is required from the competent authority, as it is required in the US and EU markets. In Japan, the competent authority is the Ministry of Health, Labour and Welfare (MHLW). Approval may be requested by submitting data in a set of documents supporting product quality, efficacy, and safety, which are subject to experts' review, namely from evaluation from the Pharmaceutical and Medical Devices Agency[38] (PMDA).(45)

Aligned with the development plan of the '*Japan Revitalization Strategy*' and the '*Healthcare and Medical Strategy'*, the Japanese Government reformed its pharmaceutical affairs regulations, effective on the 25th of November 2014, consisting of 17 chapters and 91 articles. This renewed legislation regulates all pharmaceutical products and medical devices in Japan, and it's called the *Pharmaceuticals, Medical Devices and Other Therapeutic Products Act* (PMD Act). (10,46) The elements of the renewed Act include the enhancement of safety measures related to pharmaceuticals, medical devices, etc.; the classification of regenerative medicine products[39] under a different category from conventional pharmaceuticals and medical devices; and the establishment of regulations based on the characteristics of medical devices, among others. (47)

[38] Pharmaceutical and Medical Devices Agency (PMDA) is the independent administrative organization, established in April 2004 in Japan, responsible for providing consultations concerning the clinical trials of new drugs and medical devices, and to conduct approval reviews and surveys of the reliability of application data. (45)

[39] Under PMD Act, regenerative medicine products are defined as processed human cells that are intended to be used for the reconstruction, repair or formation of structures or functions of the human body or the treatment or prevention of human diseases, or for gene therapy.(11)

3.3.1 Regulatory tools for expedited MA

Specifically referring to regenerative medicine products, this new Act introduced a conditional and time-limited approval for these products, which led to the possibility of approving a regenerative medicine product based on the potential benefit demonstrated by pilot clinical trial data.(5) In this Act, the greater focus on safety measures based on risk-benefit evaluation methods during the development of innovative products became more evident when the importance of establishing an environment that facilitates the development of new therapies and their global market expansion, was recognized. Achieving qualitative enhancements in safety measures over the entire lifecycle of the product, from the development stage to the post-marketing phase, was seen as a priority by the MHLW in Japan. (10)

Based on the above-mentioned and on the goal of promoting research and development in Japan at early practical application for innovative pharmaceutical products, medical devices, and regenerative medicines, the Strategy of Sakigake created the “Sakigake Designation System”, in addition to the scheme for rapid authorization of unapproved drugs which aimed to accelerate the practical application of unapproved/off-label use of drugs for serious and life-threatening diseases. This strategy included a plan to promote stronger research and development of medicinal products through Health and Labour Sciences Research Grants[40] and the partnership between the PMDA and the Network for Drug Discovery, such as Drug Discovery Support Network[41] and The iD3 Booster[42], which are support strategies created for promising compounds developed by the academia. The strategy also includes the establishment of quick and accurate evaluation methods based on the latest scientific technologies in collaboration with research and medical institutions such as universities and the National Institute of Health Sciences (NIHS), and a plan to promote the development of regulatory science to guide practical application of innovative technologies for researchers, pharmaceutical companies and venture enterprises developing regenerative medicine. (10)

In addition to the expedited programs created to accelerate medicines’ review and approval, a tool was created to provide effective support to sponsors and developers - *Priority interview*

[40] The Health Science and Labor Research Grants (HSLRG) program was created to promote scientific research addressing Japan’s needs on health, medical and welfare field. (86)

[41] Drug Discovery Support Network is Japan’s first drug discovery support system, integrated in the Japan Agency for Medical Research and Development (AMED) and intended for drug discovery molecules generated at the universities. (87)

[42] The iD3 Booster is an approach coordinated by the Department of Innovative Drug Discovery and Development of AMED for accelerating the translation of promising basic researches into innovative new medicines. (88)

advice. Aiming to obtain specific advice regarding indications, the development plan of a product and the steps forward to obtain faster review and approval, it is possible that certain candidate medicines obtain priority interview advice privileges. Orphan drugs[43] and the ones included in the Sakigake Designation System are eligible for this tool, and it can also be used by drug developers to obtain advice about potential eligibility for the Conditional Accelerated Approval System for Pharmaceuticals. (45)

Compassionate Use

In 2016, a program was introduced through Notification No. 0122-(7) of the Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau (PSEHB). Patients who are ineligible for clinical trials of drugs not approved yet, or drugs of off-label use with high medical need, would receive enhanced access. It is applicable to investigational medicinal products intended to be used for serious life-threatening diseases without appropriate treatment available.

This program is a trial conducted from a compassionate point of view or expanded trial. This is in parallel with the ongoing development and approval process, that should occur after a trial or while a trial is ongoing after the enrolment phase has ended, at the final development phase (pivotal trial). In this phase, it is considered, and in fact has already been demonstrated, that patients will greatly benefit from the unapproved medicine or off-label drugs. (45)

Priority Review System

The Priority Review System was created with the objective of reviewing specific applications for drugs that should be subject to prioritized evaluation when compared to other applications received, based on the decision taken from the Pharmaceutical Evaluation Division[44]. Normally, applications for drug approval are processed by reception order of the application forms. Under this Priority Review System, candidate medicines with orphan drug designation,

[43] In Japan, an orphan drug is targeted to treat a disease affecting less than 50.000 patients. (89)

[44] Pharmaceutical Evaluation Division is a Division integrated in the Pharmaceutical Safety and Environmental Health Bureau (PSEHB), which is one of the 11 bureaus of the MHLW. One of its main activities is to provide technical guidance and supervision concerning the production of drugs, quasi-drugs, cosmetics, and medical devices, to designate orphan drugs and to work closely with the Pharmaceutical and Medical Devices Agency (PMDA).

the ones covered by the Sakigake Designation System, and others with particular importance to public health point of view (for example, new drugs to treat serious diseases), will be processed with an expedited approach, prioritized at each stage of the review process, after an evaluation is performed and a decision is made in terms of the seriousness of the disease targeted by the medicine and the clinical usefulness, according to Article 14-(7) of the Pharmaceutical Affairs Law. (45) During the evaluation of the seriousness of the disease, important effects on the patient's survival will be taken into consideration, including if it's a progressive and irreversible disease with high impact on patients' daily life, or other relevant cases. From the therapeutic usefulness perspective, alternative methods of treatment, prophylaxis, or diagnosis, and the characteristics of the existing treatments in terms of their efficacy, safety and physical and mental burden on the patient, will be taken into consideration. PMDA is responsible for compiling opinions of experts and promptly providing them to the MHLW. Subsequently, the Pharmaceutical Evaluation Division will evaluate the experts' report and decide whether priority review is applicable or not. (45)

To proceed with the review for approval, the Pharmaceutical Evaluation Division notifies this application with priority review rights, to be evaluated in the next meeting of the committee concerned with the Pharmaceutical Affairs and Food Sanitation Council (PAFSC)[45], and their approval is obtained. (45)

Special Approval for Emergency

This restrictive approval system was created to respond more effectively in emergency situations, namely with regards to medicinal products used to prevent the spread of diseases that constitute a major threat to public health, or when the candidate medicine is intended to be used against a disease for which there is no other method of treatment, and when it is marketed in other countries. The conditions for this approval are outlined in Article 14-3 of PMD Act and its foreseen that, in emergency situations, unapproved medicines to prevent damage to public health, when there are no appropriate options available, and when such medicines are legally available in a country with a regulatory system equivalent to the one in Japan, then the medicinal product may be approved. (46,48) The application is submitted to the PMDA once designated by the Cabinet Order and proceed to the evaluation phase with urgency. After proper consultation with the PAFSC experts, and if they recommend approval

[45] PAFSC is the advisory body to the MHLW, accountable for discussing and review important pharmaceutical and food sanitation-related matters. (45)

of the product in scope, then the Minister of the MHLW may grant official approval of such products under certain restricted conditions, without going through ordinary review process for approval. The MAH may be requested to implement specific safety monitoring programs and other measures, as appropriate. If conditions to approve the medicinal product under this special pathway are no longer observed or when the benefit of the approved medicine doesn't overweight it's risk anymore, then the Minister can withdraw the approval to prevent damage to public health. (45,48)

Conditional Accelerated Approval System for Pharmaceuticals

The Conditional Accelerated Approval pathway was created to address a specific need regarding diseases with rare occurrence in humans, and to address the lack of investment in drug investigation and development by pharmaceutical companies. In addition, it is recognized that the particularities of such diseases require studies with significantly longer implementation periods, or it's not at all possible to conduct studies in humans. Therefore, this system is intended to be used in the review and approval process of drugs indicated to treat serious diseases which occur in a small number of individuals and don´t have an effective treatment, or the existing treatment is considered limited. Another benefit of this tool was the improvement in consistency and predictability of interactions between regulatory bodies and entities applying for drug's approval, and to facilitate patient access to new pharmaceutical products. The Conditional Accelerated Approval system, the particularities of which are outlined in the PSEHB/PED Notification No. 1020-1[46], allows the approval of such innovative medicines without submission of the results of confirmatory clinical trials at the time of approval. Rather it requires that the necessary post-marketing surveys, etc. are conducted as a condition for granting the MA. (45,49)

To be eligible for this exceptional review system, the candidate medicine must meet all of the following requirements cumulatively: the drug is indicated for a serious medical condition based on a comprehensive review, which takes into consideration the life-threatening characteristics of the disease, its irreversibility and possibility of representing a significant limitation on daily activities, or other applicable factor; the clinical usefulness for the planned therapeutic indication is high, based on a comprehensive review of the existence of treatments,

[46] Notification No. 1020-1 outlines the procedures for the "*Implementation of a Conditional Early Approval System for Pharmaceutical Products*" and was made effective as of October 20, 2017. This notification was emitted by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW. (49)

prophylactic measures, or diagnostics for that specific condition, or a review of the superiority over existing options in terms of efficacy, safety and physical/psychological burden on patients; confirmatory clinical trials are impracticable or difficult to conduct due to difficulties such as a small population; and the results of clinical studies other than confirmatory clinical trials suggest a certain level of efficacy and safety. (45,49)

After eligibility is confirmed and approved by the MHLW, consultations with PMDA will be prioritized, since this system intends to facilitate faster access to medicinal products that may represent high clinical relevance to severe diseases. (45,49) In addition to the Conditional Accelerated Approval, the candidate drug will also be eligible for priority review. (45)
After approval of the MA application, all the conditions of approval outlined in the Report on the Deliberation Results must be executed and reported to the Japanese Regulatory Agency, as applicable.

For example, post-marketing surveys or other studies required for confirmation of the efficacy and safety data may represent a condition for approval, and medical information databases, such as MID-NET[47] (Medical Information Database Network), and patient registries may be used to collect relevant data for these surveys, as necessary. As a condition of approval, appropriate instructions or requirements to ensure the correct use of the approved medicinal product from medical institutions need to be implemented. (45)

Conditional and Time-Limited Approval for RMPs

In Japan, medicinal products manufactured from human cells, genes, or tissues were firstly regulated by the previously established Pharmaceutical Affairs Law[48] (PAL) and, since November 2014, were regulated under the PMD Act, creating a new regulatory pathway for ATMP, generically mentioned as Regenerative Medicine Products (RMPs) in the legislation. (19,46)

[47] Medical Information Database Network (MID-NET) is a Japanese project initiated by MHLW and PMDA to establish the medical information database infrastructure, using electronic healthcare data for drug safety. This project is based on Article 15, Paragraph 1, Item 5 (c) of the Pharmaceuticals and Medical Devices Agency Act (Act No. 192 of December 20, 2002) and was created to improve the safety features for pharmaceutical products. Medical institutions are cooperating by using an electronic system as a database for medical information, comprehensively collecting information from 10 million people in Japan. (90,91)
[48] Law No. 84, November 27, 2013 (47)

They are defined as "*items intended for use in human or animal healthcare which are obtained after culturing or other processes using human or animal cells: a) reconstruction, repairing or formation of the structure or function of the bodies of humans or animals; b) treatment or prevention of disease in humans or animals; and items intended for use in the treatment of disease in humans or animals which are introduced into cells of humans or animals and contain genes to be expressed in their bodies*" in the PMD Act. (46)

In this legislation, a new expedited pathway, distinct from the standard review process, was introduced to expedite approval of RMPs on the basis of the safety profile demonstrated in humans and its predicted efficacy, determined in early-stage clinical trials - Conditional and Time-Limited Approval. (19,46) For RMPs, before initiation of clinical trials, a regulatory science strategy consultation for quality and safety with PMDA should occur.(45,46)

This MA granted in a conditional pathway is limited to a maximum of seven years, a period intended to allow the MAH to provide additional data required by the imposed conditions, intended to confirm and further explore the appropriate use of the medicine (e.g., perform the later-stage trials that will be required for subsequent full MA). Nevertheless, the MA may be withdrawn either because data from additional studies was considered inadequate to support full MA or because trials agreed in conditions for granting the MA were not performed in due time. (19,46)

HeartSheet, a human somatic stem cell-processed product (an autologous skeletal myoblast preparation using cell sheet technology) authorized in September 2015 to Terumo, the first RMPs to be approved using the conditional/time-limited approval pathway. Later, in 2018, two additional RMPs were approved through the conditional/time-limited approval pathway - STEMIRAC Inj., developed by Nipro Corporation; and Collategene Intramuscular Injection 4 mg, developed by AnGes, Inc. (19,50)

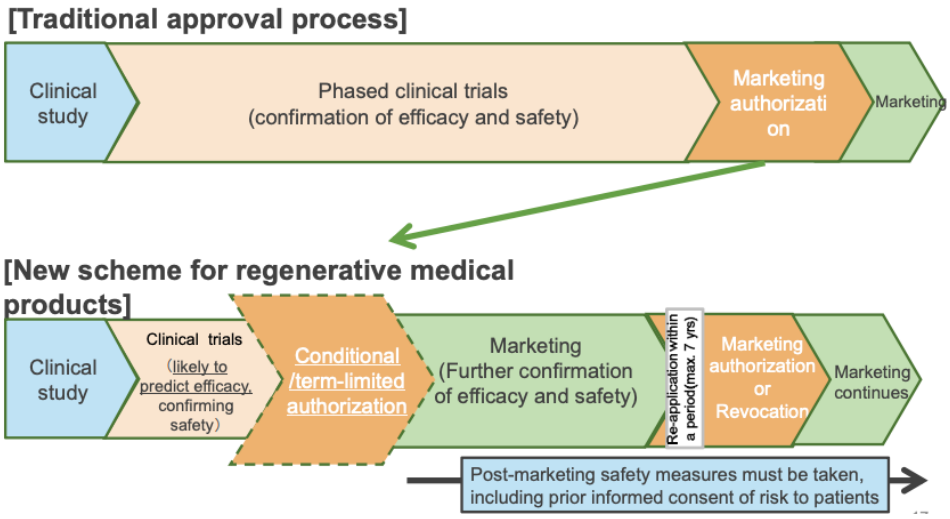

Figure 3 - Scheme evidencing the Traditional approval process and expedited approval system under PMD Act.

The new scheme for RMPs allows a conditional/time limited approval after verification of clinical data predicting efficacy but confirming a positive safety profile. After 7 years, if confirmatory trials support initial data, the MA will be converted in a standard MA. Adapted from: https://www.pmda.go.jp/files/000204615.pdf (51)

Sakigake designation

In November 2014, PMDA introduced its priority review system for innovative therapies targeting unmet medical needs - the Sakigake designation. The strategy of Sakigake included several actions to implement the plan defined by the Japanese MHLW. Aiming to eliminate delays in drug development, MHLW decided to invest in strengthening the consultation system provided by PMDA through the delivery of advice to pharmaceutical companies and academia on the development roadmap and planning of study protocols of confirmatory studies, through enhancement of Pharmaceutical Affairs Consultation on Research and Development Strategies[49]. In addition, this reduction of review period was also planned in alignment with an enhancement of its quality by strengthening the existing structure and improving the quality of PMDA review and safety measures. To enable enhanced quality revision, PMDA strongly invested in electronic capabilities, advanced analytic and predictive evaluation methods, such as modelling and simulation, to streamline the drug development process and deliver with higher quality standards. (10)

[49] Launched in July 2011 by PMDA, the Pharmaceutical Affairs Consultation on R&D Strategy provides advice mainly for universities, research institutions, and venture companies that are developing promising medicines and technologies on the early product development stage and clinical trials. (92)

In 2015, the Sakigake Designation from PMDA came into effect, being its priority review support system for innovative therapies targeting unmet medical needs. In Japanese, “Sakigake” means “pioneer” and it is similar in principle to the EMA’s PRIME scheme and the FDA’s Breakthrough designation because its objective is to expedite the authorization of new medicines which intent is very well defined in terms of benefit to public health. (2)

This approach mainly focused on making Japan the world’s leader in the application of innovative medicinal products, covering strategic fields from basic research to clinical trials, approval review process, and ultimately the global expansion, among other focus areas. One of the measures related to the approval review process was the strategy of “Review system for designated world-first products”, intended to designate drugs expected to represent a major benefit to public health, and which are predicted to be highly effective against life-threatening and serious diseases using a mechanism of action different from the ones of already approved drugs. (45)

This exceptional designation system includes several benefits for the development pathway of the candidate medicine, which can be summarized as follows: 1 - consultation with PMDA is prioritized through meetings occurring 1 month after the submission of the briefing documents, instead of 2 months; 2 - consultation with PMDA is allowed to start early in development once the Sakigake designation is granted, during phase 1/2 clinical trials, which means that consultation may be extensive prior to submission of the MA application; 3 - granting accelerated review of the MA application, with target review within 6 months, rather than standard 12 months, enabling submission of phase 3 study data after submission of the MA application; 4 - assignment of a PMDA review partner who acts as a communication facilitator to establish an efficient development program and MA application process; and; 5 - implementation of specific post-authorisation safety measures, including extended follow-up (over 10 years) and global information dissemination. (19)

To be eligible for Sakigake designation, the investigational pharmaceutical products, devices, and regenerative medicines should be targeting a disease or condition with urgent need of an innovative therapeutic drug[50]. In early stages of development, namely in phase 1/2 clinical trials, the innovative therapy must also demonstrate high efficacy and substantial improvement over conventional therapies to be eligible for this designation and accelerate the prompt

[50] The definition of innovative therapeutic drug is applicable to drugs acting with a new mechanism of action, to drugs developed to have a new therapeutic indication although they use the same mechanism of action of others, and to drugs with an innovative drug delivery system. (45)

practical application. (10,19) The candidate therapy has to meet four specific requirements cumulatively: innovativeness of the product being developed, seriousness of the disease targeted, considerably high efficacy on the target disease, and intention/system of world's leading early development and application in Japan. (45)

Regarding the requirement of the seriousness of the disease, the therapeutic indications encompassed are the ones related to life-threatening and serious diseases, and diseases presenting persistent symptoms and without radical treatment. Regarding the efficacy requirement, the candidate drug shouldn't have a competitor approved for the same therapeutic indication or, if it does, it has to demonstrate an expected considerably higher efficacy, or improved safety, than the one attributed to conventional therapeutic drugs/therapies. The last pre-requisite to consider is the developing company's intent of to apply for approval in Japan before any other country, or simultaneously in multiple regions including Japan, emphasizing the importance of initiating the development in Japan. It is desirable that steadily advanced development in Japan is demonstrable, by First in Human (FIH) and Proof of Concept (POC) studies conducted in the Japanese territory. (45)

With this strategy, a review coordinator is assigned by PMDA to act as a manager of the process of accelerated development and as liaison between relevant divisions of the MHLW and PMDA, and the developing company. The strong focus on requests for consultations for innovative drugs targeting unmet medical need allows early revision of data submitted from the initial development stages, being admitted on rolling assessment during pre-application consultation. This comprehensive assessment of quality, non-clinical and clinical data, reliability, and also GMP, GCP, and Quality Management System (QMS) are fields covered by the Sakigake Designation System on its consultation. (10,45) In addition to the "*Review system for designated world-first products*" measure, the Sakigake Designation includes another relating to the approval review process - "*Scheme for prompt practical use of unapproved drugs*". This scheme includes drugs that satisfy a high medical need and are not approved in the West, targeting to serious or life-threatening disease, in the scope for review from the Special Committee on Unapproved Drugs and Drugs Off-label Use Urgently Required for Healthcare[51].

[51] The Special Committee on Unapproved Drugs and Drugs Off-label Use Urgently Required for Healthcare was created in February 2010 as a result of the reorganization of two separate committees into a single one – the Special Committee on Unapproved Drugs, initially founded in December 2004, and the Special Committee on Pediatric Drug Treatment, established in March 2006. The merged committee started wide-ranging discussions on off-label medicines, including the ones unapproved and for pediatric use. (45)

The main objective of this scheme is to provide extensive support to the research and development and prepare the ideal environment in which companies can readily initiate the development of the drug candidate. (45)

3.3.2 Overview of PMDA's Expedited Programs

Table 3 - Comparative table of PMDA's Regulatory tools for expedited programs for serious conditions, by characteristics and features.

The table below provides a comparison of PMDA's expedited programs, highlighting a summary of all relevant features.

	Priority Review System	***Special Approval for Emergency***	***Conditional Accelerated Approval System for Pharmaceuticals***	***Conditional and Time-Limited Approval for RMPs***	***Sakigake Designation***
Type of mechanism	Regulatory tool for early access	Approval Pathway	Approval Pathway	Approval Pathway	Programme for medicine development
Legal basis	PMD Act	Article 14-3 of PMD Act	PSEHB/PED Notification No. 1020-1	PMD Act	PMD Act
Qualifying criteria	Medicines with orphan drug designation, covered by the Sakigake Designation System, and others with particular importance from the public health point of view in terms of the seriousness of the disease. No standard existing therapy or superior clinical usefulness as compared with the existing products in terms of quality of life	Used in emergency situations, namely with regards to medicinal products used to prevent the spread of diseases that constitute a major threat to public health; or when there is no other method of treatment available for a condition.	Used to drugs indicated for a serious medical condition with rare occurrence in Humans; confirmatory clinical trials are impracticable or difficult to conduct due to difficulties such as a small population; results of clinical studies suggest a certain level of efficacy and safety	Only for regenerative medical products, qualified on the basis of the safety profile demonstrated in humans and its predicted efficacy, determined in early-stage clinical trials	Innovativeness of the product being developed, seriousness of the disease targeted, considerably high efficacy on the target disease, and intention/system of World's leading early development and application in Japan.

	of patients, efficacy, or safety				
Application	MA applications will not be processed by reception order, but with an expedited approach.	MA application is submitted to the PMDA once designated by the Cabinet Order and proceed to the evaluation phase with urgency.	It is submitted without the results of confirmatory clinical trials.	MA application may be submitted based on surrogate endpoint(s).	MA application is submitted through a rolling review scheme.
Features and mechanism of expedition	Prioritized at each stage of the review process; Target total review time reduced from 9 to 6 months	Approval may be granted under certain restricted conditions, without going through ordinary review process for approval, after proper consultation with the PAFSC experts.	Approval of innovative medicines without submission of results of confirmatory clinical trials at the time of approval	MA granted in a conditional pathway is limited in time for a maximum of seven years.	Consultation with PMDA is prioritized (1 month after submission of the briefing documents); consultation with PMDA is allowed to start early in development; accelerated review of the MA application (6 months rather than 12); assignment of a PMDA review partner.
Other Characteris-tics	May be used as part of other expedited pathways/programs.	-	Consultations with PMDA are prioritized and more consistent and predictable.	Regulatory science strategy consultation with PMDA may occur before initiation of clinical trials.	Delivery of PMDA advice on the development roadmap and planning of study protocols of confirmatory studies. Enabling submission of phase 3 study data after submission of the MA application.

Post-marketing requirements	The same applied for standard MA's.	The MAH may be requested to implement specific safety monitoring programs and other measures, as appropriate.	Post-MA surveys, confirmatory efficacy and safety studies, etc. are conducted as a condition for granting the MA; also eligible for priority review	MAH to provide additional data required by the imposed conditions, intended to confirm and further explore the appropriate use of the medicine.	Implementation of specific post-authorisation safety measures over 10 years and global information dissemination.

4 Results and Discussion

4.1 Comparison between available regulatory tools in the EU, FDA and Japan for expedited MA

The expedited tools for early approval described in the introduction section, were distributed among four groups, which aggregates a set of similar characteristics - *expedited approval without conditions*, *expedited conditional approval*, *approval with limited patient cohort or indication* and development support programs.

The characteristics defining the first group - *expedited approval without conditions* - are the inclusion of mechanisms supporting a faster approval in terms of duration of agency review and the extent of data needed for the submission of MA application. The second group - *expedited conditional approval* – which expedite the approval of MA applications, includes programs based on incomplete clinical data, since the one collected is reasonably likely to predict the drug's clinical benefit and safety, when a positive benefit-risk balance is verified. In this case, the MA is subject to conditions and the MAH is responsible to address those requirements to confirm the maintenance of the MA. The third group - *approval with limited patient cohort or indication* – combines expedited pathways targeting specific medical conditions that will have a significant benefit if the new medicinal product is available earlier than in normal conditions and/or it's not realistic to obtain further comprehensive data due to the type of disease. The last group - *development support programs* – represents the supporting programs created to combine several means intended to assist the process for the development of promising medicines, creating an advanced connection between the sponsor and the Regulatory Agency.

In the subsections below, each pathway from USA, EMA and PMDA is grouped, by its specific characteristics and similarities.

4.1.1 Expedited approval without conditions

Expedited programs included in this group are typically characterized by a shortened period to review the MA application, compare to the standard review process. In addition, full data is required to support the MA approval and it's not expected that incomplete clinical development studies are acceptable, unless a combination with another expedited approval pathway is applicable. Since complete data is required at the time of MA submission, then it's not expected that the MAH is required to conduct specific additional studies or comply with additional requirements beyond the ones for a standard MA procedure. The expedited pathways included in this group are Accelerated Assessment (EMA), Fast Track (FDA), Priority Review (FDA) and Priority Review System (PMDA). Characteristics of each of them outlined in the table below.

Table 4 – Comparative table of USA, EU and Japan expedited approval pathways with no conditions for granting the MA. (2,3,7)

	Description	**Qualifying criteria**	**Features**	**Timings**
Accelerated assessment (EMA)	Pathway designed to expedite approval of products of major interest to public health and in terms of therapeutic innovation.	Medicines of major interest to public health, namely targeting an unmet medical need, and with the same evidence requirements as for standard MA application.	Opportunity to meet with rapporteurs from the concerned committees; they recommend the acceptance or not of the accelerated assessment.	CHMP opinion reduced from 210 days to 150 days, excluding the time of clock stops
Fast track (FDA)	Designation intended to facilitate the development and expedited review of MA application of drugs intended to treat a serious condition.	Targeting a serious or life-threatening condition; fulfil an unmet medical need. Availability of non-clinical or clinical data demonstrating the potential to address the unmet medical need is required to grant designation.	Opportunity to meet with FDA experts to discuss the development plan; increase in frequency of communication about the design of clinical trials; eligibility for priority review	Mechanisms to expedite development and review; possibility of rolling review, which will expedite the approval.
Priority Review (FDA)	Designation that allows evaluation of NDA/BLA or efficacy supplements' application of a drug that treats a serious condition and will provide a significant improvement in safety or effectiveness if approved.	Targeting a serious condition; significant improvement in safety or effectiveness; elimination or reduction of a treatment-limiting drug reaction; demonstration of enhanced patient compliance with treatment or demonstration of safety and effectiveness in a new subpopulation.	Designation will be assigned at the time of original BLA, NDA, or efficacy supplement filing; full data supporting safety and effectiveness for drug's intended use is needed to sustain approval.	Target total review time reduced from 12 (10 months plus 60 filing days) to 8 months (six months plus 60 filing days); reduced from 10 to 6 months in efficacy supplement.

	Description	Qualifying criteria	Features	Timings
Priority Review System (PMDA)	A designation that provides faster access to new products targeting high medical needs; includes HIV and orphan designation medicines, and the ones covered by the Sakigake Designation System	Medicines with particular importance from the public health point of view in terms of the seriousness of the disease; no standard existing therapy or superior clinical usefulness as compared with the existing products in terms of quality of life of patients, efficacy, or safety.	Review from PMDA is prioritized at each stage of the review process.	Target total review time reduced from 9 to 6 months.

The description and qualifying criteria of each expedited pathway are all quite similar – that is to say, they are only applicable to products with a high interest to public health, or which target unmet medical needs. The main difference to highlight here is that, although the Accelerated Assessment (EMA), Priority Review (FDA) and Priority Review System (PMDA) are related to the review of a MA application or an efficacy supplement submission, expediting this review time, Fast Track (FDA) Designation is intended to provide a specific support, combining additional meetings with FDA experts and an opportunity to raise questions and correct/resolve any issues as soon as they are identified, but it refers to the pre-MA submission phase. The Fast Track designation will indeed represent a significant benefit to the development program, ending with an overall shortened review period. Regarding the expected review time of MA application, except for the Fast Track designation, the decrease each one represents is clearly defined – from 210 days (6,9 months, approximately) to 150 days (4,9 months, approximately) in Accelerated Assessment (EMA), from 12 to 8 months in the Priority Review (FDA) and from 9 to 6 months in Priority Review System (PMDA). That represents a decrease of 2, 4 and 3 months, respectively. The greater decrease in review time is seen in Priority Review from FDA, although the shortest one is from the EMA since the Accelerated Approval is expected to last 4,9 months, approximately. Nevertheless, this review period is based on the assumption that no questions are raised during the review process, which is very unlikely to occur. Since the estimated review time excludes clock-stops for the applicant to respond, the review period is normally longer, resulting in the addition of several months to the review process. Additional details on the review time for approval are added further into this dissertation.

Another difference to highlight is the applicability of the expedited pathways to efficacy supplements. Only the Priority Review (FDA) is referred to as applicable to efficacy supplements, which might be an advantage because not only the original MA application is subject to a faster review.

FDA developed an additional mechanism using the benefit of Priority Review, through vouchers that can be provided to sponsors in specific circumstances. An example of this approach is to use a voucher system to incentivize the development of medicines for rare paediatric diseases, that may be attributed to the medicine's developers when Rare Paediatric Disease Designation (RPDD) is granted to a medicine. Once the RPDD is granted, the voucher may then be converted into the possibility of applying for priority review of a MA application submitted later for a different product. It is also possible to legally trade the voucher between companies, for hundreds of millions of dollars. (19)

4.1.2 Expedited conditional approval

Expedited programs included in this group are mainly characterized by the possibility of approving promising medicines for serious conditions, that fulfil unmet medical needs, based on an intermediate or surrogate endpoint, with further confirmatory studies to support clinical benefit being completed in post-approval phase, as imposed conditions to maintain the MA. EMA's Conditional Marketing Authorization is similar in principle to the FDA's Accelerated Approval and, more recently, PMDA also created a correspondent mechanism of expedited approval but applicable to Regenerative medicinal products.

PMDA's Restrictive Approval System was created to allow an expedited review process in emergency situations, for example, when there´s the need to use a medicinal product to prevent the spreading of diseases that constitute a major threat to public health. In such cases, less comprehensive data is acceptable once the benefits overweighting the risks are confirmed. Characteristics of each are outlined in the table below.

Table 5 – Comparative table of USA, EU and Japan expedited approval pathways with imposed conditions for granting the MA. (2,3,7)

	Description	**Qualifying criteria**	**Features**	**Timings**	**Post-marketing requirements**
Conditional MA (EMA)	Regulatory tool for medicines fulfilling an unmet medical need for seriously debilitating or	Positive benefit-risk balance; when comprehensive data after authorisation is likely to be provided; fulfils unmet medical need; benefits of	MA includes specific obligations to be addressed by the MAH in a specific timeframe. During pre-submission meetings, it's possible to liaise	Earlier authorisation is granted based on less complete clinical data - benefit-risk balance is	Conditional MA is valid for 1 year only, on a renewable basis when a positive benefit/risk balance is maintained;

	Description	Qualifying criteria	Features	Timings	Post-marketing requirements
	life-threatening diseases, including orphan medicines or those for emergency use.	immediate availability outweigh the risks.	with other relevant stakeholders. Smaller studies in size and/or with a shorter duration and/or different endpoints from confirmatory studies are acceptable.	positive but pending confirmation.	once pending confirmatory studies are completed, it can become a "standard" MA
Accelerated approval (FDA)	Pathway allowing approval of medicines for serious conditions which provide a meaningful benefit over available therapies, fulfilling an unmet medical need.	Candidate medicine demonstrates an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict drug's clinical benefit; to apply for this approval pathway, results from phase 1 or 2 are required.	Discussion during the development phase with FDA experts, about design of clinical trials and post-marketing planning; the FDA doesn't provide timelines for responses to questions raised.	MA is expedited based on results of surrogate endpoint(s) or an intermediate clinical endpoint from phase 2 trials or interim phase 3 data.	Confirmatory studies, which are post-approval commitments, with hard clinical endpoints are required to demonstrate benefit, e.g., phase 4 confirmatory clinical trials.
Conditional and Time-Limited Approval for RMPs (PMDA)	System created to accelerate the availability and practical use of highly useful and effective Regenerative Medicine	Applicable to products based on its safety profile demonstrated in humans and predicted efficacy, determined in early-stage clinical trials.	Consultations with PMDA are prioritized; regulatory science strategy consultation may occur before initiation of clinical trials; submission of MA application is allowed once a certain degree of efficacy and safety is confirmed.	Approval without submission of results of confirmatory clinical trials at the time of approval; MA is limited in time for a maximum of 7 years.	The developing company must conduct post-marketing clinical studies[52] to confirm preliminary efficacy and safety results; application for regular approval must be resubmitted within a predetermined period.
***Special Approval for Emergency* (PMDA)**	Approval pathway used in emergency situations	Medicinal products used to prevent the spread of diseases that constitute a major threat to public health and when there is no other method of treatment available; it's legally available in a country with a regulatory system	Approval may be granted under certain restricted conditions, without going through ordinary review process for approval, after proper consultation with the PAFSC experts.	MA application is submitted once designated by the Cabinet Order; evaluation phase is processed with urgency; review	The post-MA requirements may vary, as applicable. MAH may be requested to implement specific safety monitoring programs and other measures.

[52]Examples indicate that post-marketing randomized comparative studies are not necessary and post-marketing comparative clinical studies are acceptable if they have an external control group.(2)

	Description	Qualifying criteria	Features	Timings	Post-marketing requirements
		equivalent to the one in Japan.		timelines may vary.	

As highlighted before, the common characteristic of all conditional pathways available in the EU, USA and Japan is the need to provide additional comprehensive data to confirm efficacy and safety profile of the conditionally approved medicine. The type of studies, their duration, endpoints and other characteristics are defined as applicable to each case, according to the extent of data needed to confirm clinical and safety data.

Regardless the particularities of clinical data generated to support a positive benefit-risk balance of a medicinal product, which may be dependent on further studies or confirmatory trials, when it comes to CMC considerations in expedited programmes in the EU, the quality development must be advanced satisfactorily to allow commercial supply of the medicinal product. Therefore, the manufacturing process must be demonstrated as robust, reproducible, validated, and controlled to enable ongoing supply of the commercial demands of patient treatment. To ensure that, CMC development activities must be adequately planned and executed to keep pace with clinical development. (19) The same principle is expected to be applied to the expedited pathways available in the USA and Japan because quality standards of the medicinal product should always be verified regardless of the extent of clinical and safety data available at the time of submission.

All of these pathways are applicable to original MA applications only, therefore efficacy supplement applications are out of scope, and there's a higher level of uncertainty about confirmatory results, clinical benefit and unidentified risks related to exposure to the medicines. In all cases, a clear justification needs to be included at the time of application for the expedited conditional pathway because they are only applicable to products that meet pre-defined criteria. If not verified, then the review process will follow a standard procedure, with typical requirements applicable. The Conditional and Time- Limited Approval from PMDA is even more restrictive in terms of applicability criteria because it is valid for Regenerative medicine only.

In all cases, MA may be withdrawn by the Regulatory Agency if confirmatory results do not meet the required criteria as expected to endorse the positive benefit/risk for the indicated use.

Regarding use in emergency situations, only EMA and PMDA, through the Conditional MA and Special Approval for Emergency pathways, have an explicit mechanism of drug approval in such critical circumstances (e.g., pandemic situations). Nevertheless, FDA has a mechanism that does not constitute an approval pathway in the statutory meaning but authorizes and facilitates the availability of the unapproved product in critical situations with similar criteria – the Emergency Use Authorization.

The Conditional and Time- Limited Approval from PMDA has an additional characteristic that may be seen as an imposed restriction – it is valid for no more than seven years. This means that, if studies with longer duration are required to demonstrate clinical benefit of the regenerative medicine, then it's not possible to consider this pathway because required data will not be obtained in the mandatory timeframe. Continuous improvement is necessary to solve previously addressed issues within the expedited-approval pathways and programmes. In addition, it is necessary to ensure that innovative medical products are not only rigorously screened, but also readily available to patients in need. The time limitation of conditional approval could be a potential solution to some of these problems.

4.1.3 Approval with limited patient cohort or indication

Expedited programs included in this group are MA under exceptional circumstances (EMA) and Conditional Accelerated Approval System for Pharmaceuticals (PMDA) and they are essentially characterized by the possibility of approving promising medicines for serious conditions with rare occurrence in Humans and associated with an inherent difficulty in collecting comprehensive efficacy and safety data. To support the MA approval, sponsors should demonstrate, with the most practicable level of evidence, that the candidate medicine has an acceptable level of risk, both identified and unidentified risk. But they should also demonstrate major clinical benefit to the patients in need through data available from studies conducted. Characteristics of the two pathways mentioned above are outlined in the table below.

Table 6 – Comparative table of EU and Japan expedited approval pathways for cases when limited patient cohort or indication is in scope. (2,3,7)

	Description	**Qualifying criteria**	**Features**	**Post-marketing requirements**
MA under exceptional circumstances (EMA)	Pathway allowing approval of medicines that fulfil unmet medical needs for serious, life-threatening or rare diseases without comprehensive efficacy and safety data.	Applicable to life-threatening or serious diseases; due to the rarity of the disease, it's not possible to provide comprehensive clinical data, or endpoint is very difficult to measure for scientific reasons and/or because of ethical reasons.	MA may be granted subject to a requirement for the applicant to introduce specific obligations. Comprehensive data cannot be obtained after authorisation - this authorisation pathway normally won't lead to a standard MA.	It is not required that applicants submit comprehensive data to convert MA to a standard MA, but it's required that data concerning safety of the medicinal product is provided. The CHMP annually revises the implementation/completion of procedures and obligations.
***Conditional Accelerated Approval System for Pharmaceuticals* (PMDA)**	Pathway used to expedite the approval of drugs indicated for a serious medical condition with rare occurrence in Humans.	Applicable to serious diseases and rare diseases; confirmatory clinical trials are impracticable or difficult to conduct due to difficulties such as a small population; results of clinical studies suggest a certain level of efficacy and safety.	Approval of innovative medicines without submission of results of confirmatory clinical trials at the time of approval; consultations with PMDA are prioritized; also eligible for priority review.	Applicant must conduct surveillance activities and/or clinical studies[53]; post-MA surveys, confirmatory efficacy and safety studies, etc., conducted as conditions for granting the MA.

These two expedited pathways play an important role in granting availability of innovative and promising medicinal products to patients in need. Otherwise, it would be much more difficult to grant authorization to use such therapeutic alternatives that cannot demonstrate their added value as others for non-rare diseases can. This is also an incentive to companies and academia to invest in drug research and development for conditions that are unlikely to generate significant profit but are highly needed to treat patients without a satisfactory response to their medical need.

In both cases, specific safety monitoring programs/activities must be implemented by the MAH in order to closely supervise, flag any safety concern, report it to the Regulatory Agency in a close communication setting, and activate risk mitigation activities, as appropriate. Regarding the EMA's expedited program, the MA is not expected to be

[53] Examples indicate that post-marketing surveillance is acceptable and post-marketing comparative studies are not necessary.

converted into a standard MA, and the same interpretation may be applicable to the equivalent pathway in Japan, because it is recognized that it is too difficult, or that it would take an extended period of time to conduct a confirmatory study, or it's even impracticable to conduct further studies for ethical reasons.

Although FDA doesn't have an expedited pathway with an equivalent description and qualifying criteria, i.e., a program to allow the availability of medicinal products for rare diseases, these cases are also considered in another program available. FDA recognizes the great challenge that rare diseases represent and that drug development for common diseases is different from that of rare disease because certain aspects of the development programs are not feasible. Recognizing this, FDA applies a more flexible approach and considers accelerated approval for these critical medicines. Breakthrough therapy designation may also be applicable as a useful mechanism of supporting faster approval of such medicinal products.

4.1.4 Development support programs

Expedited programs or systems included in the development support programs group are characterized by a supporting plan to assist with the development of promising medicines with high medical interest to public health. Using expedited pathways and designations already foreseen by regulations in place and associated with close communications and a supporting program held by agency experts and other relevant stakeholders, it is possible to provide targeted guidance to enhance and expedite product development steps. In this group, the expedited programs included were Adaptive pathways and PRIME Scheme from EMA, Breakthrough Therapy Designation and Regenerative Medicine Advanced Therapy from FDA and Sakigake Designation from PMDA, since all of them have the abovementioned characteristic in common.
Characteristics of each program are included in the table below.

Table 7 – Comparative table of USA, EU and Japan development support programs. (2,3,7)

	Description	**Qualifying criteria**	**Features**	**Timings**
Adaptive pathways (EMA)	Scientific concept of development and data generation, which uses the existing EU regulatory	Medicines that address patients' unmet medical needs.	Approval in stages; gathers evidence through real-life use to complementary clinical trial data; involvement of patients and HTA	According to expedited pathways applicable to the medicine in scope.

	Description	Qualifying criteria	Features	Timings
	framework and review tools in place to expedite approval of promising medicines; prospectively planned and iterative approach.		bodies in discussions on the medicine's development from early stages; further studies may be required as conditions for MA.	
PRIME Scheme (EMA)	Voluntary scheme to improve support for the development of medicines that target unmet medical needs. It comprises early dialogue with EMA experts, enhanced interaction supporting optimization of development and accelerated evaluation.	Medicinal products under development in the EU to be registered through the centralized procedure; medicines of major interest to public health and from the viewpoint of therapeutic innovation, namely targeting an unmet medical need, based on data from early clinical studies.	Early dialogue with appointed rapporteur from CHMP or CAT to provide continuous support from early stages of development; kick-off meeting with the rapporteurs and experts; scientific advice involving additional stakeholders; dedicated point of contact from EMA.	Possible to include Accelerated Assessment (CHMP opinion reduced to 150 days); post-MA requirements might be imposed, according to expedited pathways applicable to the medicine in scope.
Break-through therapy Designa-tion (FDA)	A designation designed to expedite the development and review of medicines that demonstrate significant improvement over available therapy/therapies.	A drug intended to treat a serious condition with preliminary clinical evidence, such as demonstration of substantial improvement in effectiveness or safety over available therapies on clinically significant endpoints.	All Fast-Track designation features; FDA's intensive guidance on efficient drug development program from phase I studies; initial comprehensive multidisciplinary meeting; organizational commitment with senior managers; possible to include priority review and rolling review; full data supporting safety and effectiveness for drug's intended use is needed to sustain FDA's approval.	Application may be submitted simultaneously or after submission of IND, and it's recommended on or before the end of phase II studies; if priority review is granted, FDA finishes its review at least 1 month earlier than with standard revision; this designation result in a faster approval due to increased efficiency.
Regenera-tive Medicine Advanced Therapy (FDA)	Designation to expedite review of regenerative medicine therapy intended to treat, modify, reverse, or cure a serious condition; without requirement to demonstrate significant improvement in safety or effectiveness over available therapies.	Preliminary clinical evidence must indicate that the medicinal product has the potential to address unmet medical needs for such disease or condition; full data supporting safety and effectiveness for drug's intended use is needed.	All benefits of the fast track and breakthrough therapy designation programs, including early interactions to discuss any potential surrogate or intermediate endpoints Legal basis addresses potential ways to support accelerated approval and satisfy post-approval requirements.	All benefits of the fast track include mechanisms to expedite development and review; possibility of rolling review, which will expedite the approval.

	Description	Qualifying criteria	Features	Timings
Sakigake Designa-tion (PMDA)	Programme for development of medicines to accelerate approval and practical use of highly useful and effective medicines targeting serious diseases.	Innovativeness of the product being developed; seriousness of the disease targeted by the medicine; considerably high efficacy on the target disease, and intention/system of World's leading early development and application in Japan.	Consultation with the Agency is prioritized, and pre-application is substantial discussed; review of application is expedited; a PMDA concierge is assigned; it is allowed an extended re-examination period; enables submission of phase 3 study data after submission of the MA application.	Includes all features from Priority Review; target total review time is 6 months for drugs, devices, and in-vitro diagnostics (IVDs), and a designated priority review; for regenerative medical products, total review time is not established; it is required to implement post-marketing safety measures as extended follow-up over 10 years and global information dissemination.

As highlighted before, the three Regulatory Agencies have their own programs available to support the development of promising medicinal products, increasing the efficiency of the development plan established and expediting its availability on the market, and this principle is common to all of them. The main difference between these programs, when compared with the previous groups of pathways and designations, is the provision of a development program sustained by the Regulatory Agency inputs and support, whose experts are committed to providing additional assistance to the developing company or academia, instead of just accelerating the review process or approving on the basis of certain specific conditions.

Regarding PRIME scheme, Breakthrough Designation and Sakigake Designation, FDA was the first Regulatory Agency to implement its supporting program in 2012, followed by PMDA in 2015 and more recently the EMA in 2016. Although these three schemes from the EU, USA and Japan are equivalent in principle, they are distinct in the way they are being implemented by the respective Regulatory Agencies. One example of this is that all of them require data from early stages of development, namely phase 1 or 2 studies, evidencing the potential clinical benefit of the medicinal product, but PRIME scheme differentiates the data requirements when application is made by a SME or Academia, being more flexible in accepting clinical data from earlier stage studies as a mechanism for incentivizing those to invest in drug development and increasing their chance of success since increased support will be given from earlier stages. Another difference to underline is that Sakigake Designation is the only development support program that benefits drug candidates which endorse the PMDA vision of becoming the World's leader in the application of innovative medicinal products. This is made possible

as the developing company is required to submit MA application in Japan first, or simultaneously in multiple regions including Japan, and by the demonstration of FIH and POC studies conducted in their territory. Further, with regard to meetings with experts from Regulatory Agencies, namely with multidisciplinary teams during the drug development assistance process, it is expected that different experts provide input on the development strategy, depending on the type and characteristics of the medicinal product. Nevertheless, only PRIME scheme mentions that other stakeholders, such as HTA bodies, may also be included in those meetings, which may be very helpful to expedite real access of the newly approved medicinal product to patients. Breakthrough designation and Sakigake designation features do not include this possibility, which may be seen as a disadvantage. However, the lack of inclusion of HTA bodies may also be related to a different setting in the USA and Japan from that of EU Member States, with regards access to medicines.

Adaptive pathways are a scientific concept of development and data generation and not a new pathway for granting MA. It might seem similar to PRIME scheme, but it is an even less formal regulatory concept, with a higher level of involvement from EMA and other stakeholders, and which allows the optimization of the product development plan according to the increased use of data generated along the pathways chosen, using EMA regulatory tools and processes available, e.g., start using the promising medicinal product in a well-defined subpopulation and expand, or have a Conditional MA, supported by surrogate endpoints and then confirm the positive benefit/risk balance, or both.

On the subject of Regenerative Medicine Advanced Therapy Designation, from FDA, it is specifically concerning to expedite the review of regenerative medicine therapy (cellular and gene therapy products) intended to treat, modify, reverse, or cure a serious condition, and it doesn't need to demonstrate significant improvement in safety or effectiveness over available therapies. This is a major difference from other pathways and development programs because, typically, the candidate medicinal product should demonstrate a clinical or safety advantage over existing SOC, if any exists, i.e., potentially in the absence of available therapies. In this case, if the investigational product demonstrates that it has the potential to address an unmet medical need, then it may benefit from the advantages of fast track, breakthrough therapy designation or accelerated approval. Nevertheless, PMDA and MHLW first developed conditional and term-limited approval for regenerative medical products in Japan and then the FDA adopted the RMAT designation in the US. Conditional and Time-Limited Approval for

RMPs from PMDA is also a regulatory tool for the same type of medicinal products, but the concept itself is not equivalent since the one from FDA will benefit from early interactions with FDA as part of the breakthrough therapy designation, which is included as an advantage, but a similar approach is not applicable to the PMDA program for RMAT. In addition to an early interaction with the FDA to discuss the trial design and possible options to include surrogate or intermediate endpoints, RMAT designation also provides support for potential accelerated approval. In January 2018, EMA also updated its procedural advice on the evaluation of ATMPs, aiming to clarify the evaluation procedure of this type of products. This procedural guidance is related to the initial evaluation of new ATMPs, but it also applies to post-authorization procedures, since it strengthens timely and effective interactions between the applicants, EMA and its committees involved (CAT, CHMP and PRAC), detailing its roles and responsibilities; it streamlines the processes for adopting the lists of questions and issues by the committees and which situations need oral explanations; and it allows for longer clock-stops to developers to respond to questions raised by the Committees). (52) Although this is not a specific pathway created to expedite the review of ATMP in the EU, this procedural guidance reveals the EMA's enhanced investment, providing support for the development of such type of medicines and recognizing its importance as promising therapies for unmet medical needs.

4.2 The example of Keytruda®

Keytruda® (pembrolizumab) is a biologic medicinal product (a humanized monoclonal antibody of the IgG4/kappa isotype) developed by Merck Sharp & Dohme Corp., intended to address a medical need in some types of cancer. Its mechanism of action is based on the inhibition of interaction between the programmed cell death-1 receptor (PD-1) and its ligands, programmed death ligand 1 and 2 (PD-L1 and PD-L2). The interaction of PD-L1 and PD-L2 with PD-1 receptor of T-cells inhibits proliferation of T-cells and its cytokine production. By using pembrolizumab as a PD-1 checkpoint inhibitor, it will block ligand binding and activation, resulting in an immune response against the tumour cells. (53)

The first therapeutic indication of Keytruda was a serious life-threatening disease and no satisfactory alternative treatment – melanoma in patients with progressive disease following ipilimumab and with BRAF V600E mutation-positive melanoma, progressive disease following a BRAF tyrosine kinase inhibitor. (54)

The first steps for approval were taken in the USA. After submission of IND for investigation of pembrolizumab, in 2009, “End of phase 1” meeting was held in 2012 to discuss the submission of data from the phase 1 study to support a request for accelerated approval. Later in 2012, orphan designation was also granted, specifically for the treatment of Stage IIB-IV malignant melanoma and, in early 2013, a pre-phase 3 meeting was held to discuss several topics, including the potential for accelerated approval, and Breakthrough Therapy designation was then granted for the treatment of unresectable or metastatic melanoma refractory to ipilimumab or who have not received prior ipilimumab. Additional meetings with FDA were held in 2013 to discuss topics such as CMC, initial pediatric study plan and nonclinical, clinical pharmacology and clinical development programs. As FDA suggested in the pre-BLA meeting, a rolling submission of data to allow an efficient review of the proposed BLA. The first module was submitted in November 2013 and the final one was submitted in February 2014, completing the BLA. After this submission, other components were also submitted within the rolling submission context, such as the Risk Management Plan and the 120-Day safety update report, and other meetings were held with FDA to discuss the path forward. (54)

Primarily, the MA application was submitted to the US FDA, on the 27th of February 2014, and the applicant requested accelerated approval under 21 CFR 601 Subpart E. This request was addressed based on the demonstration of durable objective responses of satisfactory magnitude, and the ability to predict clinical benefit in patients for the requested indication - treatment of unresectable or metastatic melanoma in patients who have been previously treated with ipilimumab (SOC for the indicated disease). During the review cycle, although there were no concerns raised related to significant risk to public health, other issues were identified, namely the need for a Medication Guide[54] as part of the Risk Management strategy, the need to add a Boxed Warning in physician labelling, and responses to all issued raised required from the sponsor. In addition, it was also recognized that the Keytruda MA application should be approved earlier than the FDA was expected to deliver their decision (PDUFA date) due to the seriousness of the unmet medical need for the melanoma patient population who have failed standard therapies. (54) The benefit/risk assessment showed that, for the patient population of the therapeutic indication with an estimated 5-year survival rate of 16% due to their serious

[54] A Medication Guide is a FDA-approved patient medication information considered necessary to patient’s safe and effective use of the drug products that should be distributed when certain drugs and biological products are determined by FDA to pose a serious and significant public health concern. (93)

and life-threatening condition and with no satisfactory treatment, pembrolizumab demonstrated a clinically objective response rate of 24% and was likely to predict a true clinical benefit to patients. Therefore, evidence from data gathered supported the approval and the final decision was made on the 4th of September 2014, ahead of the expected date (28th of October 2014). Specifically, FDA reviewed in 189 days, from the submission date until final approval. The approval was granted under the provisions of 21 CFR 601 subpart E. (54)

Recommendations for Post-marketing risk evaluation and mitigation strategies (REMS) were not required, but at FDA's request, a Medication Guide was submitted to provide patients with access to information regarding risks and mitigation strategies of potentially serious autoimmune adverse drug reactions. (54) Regarding other post-marketing requirements and commitments, the requirements under accelerated approval were to conduct and submit results of a multicentre, randomized trial or trials establishing the superiority of pembrolizumab over standard treatments in the approved indication. And the ones under Fast-Track designation were to conduct an animal study that would measure the effect of PD-L1 inhibition on the magnitude of the primary and recall antibody responses to antigen challenge to evaluate the effect of PD-1 inhibition on the primary immune response once steady state plasma levels have been achieved and reassess the magnitude of the recall response after a suitable period in the presence or absence of continued dosing. Other post-marketing commitments were considered such as the development and validation of a process-specific host cell protein (HCP) assay with improved sensitivity, re-evaluation of drug substance and drug product lot release and stability specifications after commercial scale manufacture of 30 batches, and the assessment of the endotoxin recovery at various time-points from three drug product batches spiked with control standard endotoxin (7.5 EU/mL and 10 EU/mL) in vials using the kinetic turbidometric assay. (54)

While application was being reviewed by FDA, the sponsor also submitted the MA application for Keytruda to EMA, on the 4th of June 2014 through the centralised procedure, for the treatment of unresectable or metastatic melanoma in adults. As mentioned in the EPAR, which is publicly available, Scientific Advice pertained to non-clinical and clinical aspects of the dossier was provided by CHMP on the 13th of December 2013. After submission of the MA application, the procedure started on the 25th of June 2014, and the first Assessment Report by Rapporteur and Co-Rapporteur was circulated to all CHMP members on 12th of September 2014, followed by the PRAC RMP Advice and assessment overview, which was adopted by PRAC on the 9th of October 2014. Following these assessments, two clock-stops

were used to allow the sponsor to respond to questions raised (List of Outstanding Issues). And finally, during the meeting on the 21st of May 2015, the CHMP issued a positive opinion for granting the MA to Keytruda, considering by consensus that the benefit-risk balance was favourable based on the overall data submitted, the scientific discussion within the Committee, and the safety and tolerability of pembrolizumab which had been described appropriately and was acceptable. Nevertheless, the MA was granted subject to specific conditions (conditional MA). Conditions imposed were the submission of the first periodic safety update report for Keytruda within 6 months following authorisation, the conduction of required pharmacovigilance activities and interventions outlined in the agreed RMP, the implementation of additional risk minimisation measures (educational programme aimed at increasing the awareness about the potential immune-mediated adverse events and infusion related reactions, and how to manage them), the creation of an educational package of physician and patient educational materials, and the completion of post-authorisation measures (Post-authorization efficacy study (PAES) and an additional study to evaluate the value of biomarkers to predict the efficacy of pembrolizumab). (53) Further to the CHMP positive opinion, the European Commission granted the MA for Keytruda on the 17th of June 2015, which represented a total of 408 days from the submission date of MA application. (55) Regarding Japan, Keytruda was grated orphan designation as well, and MA application for Keytruda was submitted on the 22nd of December 2015. The Second Committee on New Drugs concluded, on the 9th of September 2016 meeting, that the product may be approved with a re-examination period of 10 years, and that such recommendation should be presented to the MHLW, through the Pharmaceutical Affairs Department of the PAFSC. In total, 281 days represent the period between the submission and approval dates. (56) This MA was approved and indicated to subjects with unresectable malignant melanoma as PMDA concluded the product's efficacy in the therapeutic indication and acceptable safety in view of its benefits. The MA for Keytruda was also subject to specific conditions namely the need to implement a risk management plan, the requisite of conducting a drug use-results survey involving all Japanese patients until obtaining satisfactory data to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

When analysing the information above, which is available on the assessment reports made public by FDA, EMA and PMDA, it is possible to underline some key differences between the steps taken until the MA is granted, such as the ones presented in the table below.

Table 8 – Comparative table of USA, EU and Japan steps and characteristics of MA application of Keytruda until its final approval. (53,54,56)

	FDA	EMA	PMDA
Approval lead-time	189 days	408 days	281 days
Expedited pathways	Breakthrough Therapy Designation; Accelerated approval; Priority Review; Orphan designation	Conditional MA	Conditional early approval; orphan designation
Additional features	Rolling review	Scientific Advice	Re-examination period of 10 years
Post-MA Conditions	Medication Guide; study to stablish superiority; animal study to measure the effect of PD-L1 inhibition; development and validation of a process-specific Host Cell Protein assay; re-evaluation of drug substance and drug product lot release and stability specifications; assessment of the endotoxin recovery at various time-points	First PSUR within 6 months; conduction of required pharmacovigilance activities and interventions; implementation of an educational programme aimed at increasing the awareness; creation of an educational package of physician and patient educational materials; completion of post-authorisation measures (PAES); study to evaluate the value of biomarkers to predict efficacy.	implement a risk management plan; conduct a drug use-results survey involving all Japanese patients until obtaining satisfactory data to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

4.3 The example of Veklury®

As of 11th of March 2020, a pandemic was declared by the World Health Organization because of the COVID-19 outbreak, caused by infection from Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). This outbreak has caused 109 594 835 confirmed cases of COVID-19, including 2 424 060 deaths, reported to WHO as of 18th of February 2021. (57,58) Expedited access and compassionate use programs are extremely useful in case of use needed in emergency cases, such as pandemics like the one from SARS-CoV-2. In scope of such crises, the EU, USA and Japan have options to allow the emergency use authorization, outlined in Article 5.2 of Directive 2001/83/EC, US Project Bioshield Act, and Article 23.2.8 Japanese Pharmaceutical Affairs Act, respectively. (42) In response to the fast evolution of the SARS-Cov-2 pandemic, Regulatory Agencies agreed to allow for the flexibility of regulatory processes and align resources to expedite regulatory approvals as soon as evidence needed was available, supporting efficacy of treatments and vaccines. (59) In just a few months, it was possible to gather robust data from clinical trials conducted in a record period. The first treatment

approved as a result of these studies was Veklury® (Remdesivir). It is a direct acting antiviral drug that inhibits viral RNA synthesis developed by Gilead to treat patients with COVID-19 disease. This is still a critical medicine since no other options targeting SARS-Cov-2 are currently available, although other medicines are used at the time of hospital admission. (60)

On the 1st of May 2020, FDA issued an Emergency Use Authorization (EUA) for emergency use of Veklury for the treatment of hospitalized patients with severe COVID-19 disease. (61) Under such EUA, remdesivir could be used in US hospitals, although it was not approved by FDA at that time, but have demonstrated, based on available evidence, that it could be effective, and its benefits outweighed the potential risks. Before that date, on the 6th of April 2020, FDA accepted Gilead's proposal to allow for a rolling review and under this process, Gilead could submit partial data and FDA reviewed sections of NDA application as they arrived. On the 10th of August 2020, Gilead finally submitted the NDA application and on the 22nd of October 2020, FDA approved NDA 214787 for remdesivir, which is indicated for adults and paediatric patients (12 years and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization. (61) The MA application was granted with Fast Track and Priority Review designations, and also a Material Threat Medical Countermeasure Priority Review Voucher[55], benefiting from all features associated with these designations. The expedited tools used allowed the approval by the FDA in 76 days, after receiving NDA for Veklury, and in 199 days after rolling review allowance. The conditions of approval include a list of post-marketing requirements to be addressed by the MAH, such as the conduct of clinical trials in pediatric patients and in patients with renal or hepatic impairment, the conduct of a drug-drug interaction trial with rifampin and a dedicated QT trial and a post marketing commitment was issued for a clinical trial to collect pharmacokinetic and safety data in pregnant patients, among others. (62,63)

At the same time, MA application was submitted to the EMA on the 5th of June 2020. Application for MA through the Centralised Procedure was officially submitted after rolling review started on the 30th of April 2020, based on preliminary results from the NIAID-sponsored study CO-US-540-5776 (ACTT1). On the 15th of May 2020, the applicant was invited to submit an application for Conditional MA, after adopting an interim opinion on the rolling review. After circulation of Assessment Reports to all CHMP

[55] FDA provides additional incentives for certain medical products intended to treat or prevent harm from specific chemical, biological, radiological and nuclear threats.(94)

members, and an extraordinary CHMP meeting held on the 19th of June 2020, the CHMP issued a positive opinion for granting a Conditional MA to Veklury on the 25th of June 2020 based on the overall data submitted, followed by the EU Commission Decision on the 3rd of July 2020. This represents that Veklury was approved in the EU in only 28 days, from the MA application submission date to the EU Commission Decision date, and 64 days after the beginning of rolling review. The approved therapeutic indication is "Veklury is indicated for the treatment of coronavirus disease 2019 (COVID 19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen (see section 5.1)" and the authorization is subject to specific obligations to be completed by the MAH in the specified timeframe. The number of conditions to satisfy is quite significant, but that is justifiable by the emergency of this context, and they should be completed by the 30th of June 2021, in line with the agreed plan for development of CMC dossier. (64)

Although the European Union doesn't have a formal emergency use authorization, comparable to the EUA in the USA or to the Special Approval for Emergency in Japan, it has other tools to allow the use of critical medicines in the event of an outbreak or an emerging threat to public health. The compassionate use opinion covers these special cases and may be granted in the same conditions as the ones in the USA and Japan. On the 3rd of April 2020, the EMA issued a CHMP scientific opinion on compassionate use of remdesivir, based on efficacy in animal models only. This recommendation was later revised, on the 11th of May 2020, to widen the scope of indication, allowing the inclusion of patients with SpO2 ≤ 94% or requiring supplemental oxygen. (65)

In Japan, an expedited tool was used to grant access to patients, allowing the potential treatment of COVID-19 disease - MHLW granted the Special Approval for Emergency for treatment of COVI-19 on the 7th of May 2020. As a result of the EUA granted by FDA, since a Special Approval for Emergency may be granted when a product is legally available in a country with a regulatory system similar to the one in Japan, and on the basis of the application submitted by Gilead on the 4th of May 2020, PMDA issued a report regarding available information, approval conditions, labelling of remdesivir, etc. The results outlined in the report were then discussed by the PAFSC of the MHLW on the 7th of May 2020, and remdesivir was therefore recommended for the Special Approval for Emergency, as defined in article 14–3 of the Pharmaceuticals and Medical Devices Act, for the treatment of patients with COVID-19. This approval was granted with the following conditions: getting a written informed consent prior to administration, implementation of a risk management plan; submission of results of additional clinical

trials at earliest convenience, within 9 months; and maintaining a registry of all patients who took remdesivir during the designated period. (48,66)

Table 9 – Comparative table of USA, EU and Japan steps and characteristics of MA application of Veklury until its final approval. (61,64,66)

	FDA	EMA	PMDA
Approval lead-time	76 days	28 days	3 days
Expedited pathways	Fast Track and Priority Review designations.	Conditional MA	Special Approval for Emergency, referencing the EUA of remdesivir in the US.
Additional features	Rolling review; Material Threat Medical Countermeasure Priority Review Voucher	Rolling review	The re-examination period is 8 years.
Post-MA Conditions	Conditions about Gilead and authorized distributors; conditions about hospitals and other healthcare facilities to whom Veklury is distributed and healthcare providers administering Veklury; and conditions related to printed matter, advertising and promotion.	Conditions regarding quality of the active substance, the finished product; conditions regarding clinicals aspects, namely efficacy and safety data	Getting a written informed consent prior to administration, implementation of a risk management plan; submission of results of additional clinical trials at earliest convenience, within 9 months; and maintaining a registry of all patients who took remdesivir during the designated period.

4.4 ATMP's – an example across regions

During the 90's breakthrough in the development of therapies based on human genes and/or cells was observed, such as gene-based therapies for severe combined immunodeficiencies (adenosine deaminase [ADA]-SCID and X-linked [X]-SCID) and haemophilia and cell-based therapies for cornea and cartilage repair. (67)

In the EU, the term used to identify cell- and gene-based therapies developed for commercial use is ATMP. In other countries such as the USA, Canada, Australia, Japan, and Korea a regulatory framework for cell- and gene-based therapies is also established, which has been further developed in the recent years across the International Council for Harmonisation (ICH) regions.(19)

It is expected that the number of authorized ATMPs will increase over the next few years, particularly because the development of cell and gene therapy is also gathering more importance in different regions worldwide. For instance, by December 2020, there were 18 Cellular and Gene Therapy Products approved by the US FDA, 10 ATMPs approved in the EU, and 8 Regenerative Medical Products approved in Japan. (19,68–70)

In the USA, cell and gene therapies are a particular subset of biological medicinal products, subject to biologics license application (BLA). In contrast, human cells, tissues, or cellular or tissue-based products (HCT/Ps) are considered to be minimally manipulated products intended for homologous use only, and some are regulated by 21 C.F.R. Part 1271, or both by this and by the communicable disease authority of Section 361 of the Public Health Service (PHS) and FDA's traditional premarket and post-market regulation of medical devices and drugs under the Federal FD&C Act. (71–73) In addition, the introduction of the FDA's 21st Century Cures Act, enacted on the 13th of December 2016, admits granting a RMAT designation to some cellular and gene therapy products, if certain circumstances are verified. The benefit of this designation is the qualification for a special FDA support, also applicable to fast track and breakthrough therapy designations. (19)

Regarding the EU, since these investigational medicines were included in the definition of medicinal products, the EC wanted to ensure that they met the efficacy, safety and quality standards for its intended clinical use and, to do so, the cell- and gene-based therapies term was introduced as a new category of biological medicinal products, named ATMP, in the European Legislation through Directive 2003/63/EC, amending Directive 2001/83/EC, in June 2003. (19,74) Following this legislative update, in 2008, a new European Regulation was created which was fully implemented in the subsequent year, amending both Directive 2001/83/EC and Regulation (EC) No 726/2004, which defined ATMPs as three specific types of medicinal products. According to Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007, on Advanced Therapy Medicinal Products, an Advanced Therapy Medicinal Product (ATMP) is "a gene therapy medicinal product" (GTMPs) as defined in Part IV of Annex I of Directive 2001/83/EC, a "somatic cell therapy medicinal product" (SCTMPs) as defined in Part IV of Annex I of Directive 2001/83/EC, or a "tissue engineered product" (TEPs) that "contains or consists of engineered cells or tissues and is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue". (75) In accordance with Regulation (EC) No 1394/2007 on ATMPs, an expert committee was established in 2009 within the

EMA, the Committee for Advanced Therapies (CAT), in charge of providing scientific recommendations on the classification of ATMP, performing the primary evaluation of ATMP MA applications, contributing to other ATMP-specific activities, and following scientific developments of this field, providing also scientific expertise and advice for any Community initiative. (76)

Comparing to other medicinal products for human use, and despite being classified as an ATMP, the candidate medicine must undergo clinical trials to demonstrate safety and efficacy before submission of MA application, unless it is intended to be used on an occasional basis within a hospital and can be included in the hospital exemption scheme.(75) The innovative medicine may be approved and reach the European market through three types of authorisation via centralised procedure, depending on the extent of clinical data obtained during development and/or whether the medicine targets an unmet medical need: standard MA (when comprehensive clinical data is provided at the time of MA), conditional MA (when it is expected to obtain comprehensive clinical data in the future, after granting MA - adaptive licensing route), or MA under exceptional circumstances (when it's expected that comprehensive clinical data will never be obtained). In addition, if the ATMP is considered a priority medicine or if it addresses an urgent unmet need, then the Accelerated Assessment may be applied, expediting the review of this new therapy in comparison with a typical timetable in a standard MA application.(19) PRIME scheme is also a voluntary development support program that can be applicable to ATMPs and there are 29 advanced therapies that were granted PRIME eligibility in addition to 4 that were already approved in the EU, as of December 2020. (27)

The Sakigake Designation is also applicable to ATMPs and, so far, 2 RMP were approved benefiting from the designation features. (68)

It should be considered that the number of MAs approved for ATMP products is low in the EU and Japan compared with FDA and also compared with other types of medicinal products, although the number of approvals of such types if medicines are expected to increase in the next few years. This increase might be mainly driven by innovative therapies being developed in the gene therapy field, already reaching advanced development stages such as clinical trials, in addition to the ones already reaching the market. Additionally, Regulatory Agencies will be willing to provide enhanced support to the development of this type of medicines, mainly if they will address unmet medical needs.

4.4.1 The example of Kymriah®

Kymriah, developed by Novartis Pharma, was the first gene therapy – CAR-T Therapy, to be approved by the FDA. The active substance tisagenlecleucel consists of genetically modified white blood cells - autologous T cells transduced with recombinant lentiviral vector containing a transgene encoding chimeric antigen receptor that specifically recognizes CD19. (77) Together with Yescarta®, developed by Kite (a Gilead Company) and Luxturna®, developed by Spark Therapeutics', they are the first three gene therapies to receive a BLA in the USA, in late 2017, and are considered to represent the coming age of the gene therapy technology.(19)

The FDA received the BLA for Kymriah on the 2nd of February 2017 and approved the application on the same day. In addition, the FDA granted Kymriah Priority Review and Breakthrough Therapy designations, and MA application was reviewed using a coordinated, cross-agency approach. On the 30th of August 2017, FDA issued the final BLA approval letter, which represents a review time of 209 days. As conditions for approval, Novartis was required to conduct a post-marketing observational study involving patients treated with Kymriah to further evaluate the long-term safety, besides other specific obligations. (78,79)

Regarding the EMA, Kymriah received orphan designation on the 29th of April 2014 and was granted eligibility to PRIME on the 23rd of June 2016 in the following indication: treatment of paediatric patients with relapsed or refractory B cell acute lymphoblastic leukaemia. The evidence supported the product's potential to significantly address the unmet medical need and the EMA considered that there were benefits of supporting the development in preparation for an accelerated assessment. On the 23rd of Novartis submitted the MA application on the 2nd of November 2017 through the Centralised Procedure and approval was granted after 293 days, on the 22nd of August 2018. Some post-authorization measures were required by the EMA, namely implementation of an educational programme for patients and healthcare professionals and the conduct of Post-authorisation efficacy study (PAES) and one Post-authorisation safety study (PASS). (80)

In Japan, Novartis submitted the MA application for Kymriah on the 23rd of April 2018, proposing to use the therapy to treat relapsed or refractory CD19-positive diseases – B-cell acute lymphoblastic leukemia and diffuse large B-cell lymphoma. In 2016, Kymriah

had received designation of orphan regenerative medicinal product. Regarding approval time, PMDA took 337 days to review the MA application, following a regular approval pathway which ended on the 26th of March 2019. This MA approval didn't include any specific condition, besides the regular post-marketing surveillance. (2,81)

The information outlined above may be representative of the first example of using regulatory tools to expedite MA approval in the ATMPs field. In Japan, a regular pathway was adopted, and the approval took the more time to be completed. On the other hand, the FDA and the EMA applied regulatory tools to support the development program and expedite the approval and that resulted in a shorter period from MA application to final approval, and a faster access to patients in need.

Table 10 - Comparative table of USA, EU and Japan steps and characteristics of MA application of Kymriah until its final approval.

	FDA	EMA	PMDA
Approval lead-time	209 days	293 days	337 days
Expedited pathways	Priority Review and Breakthrough Therapy designations.	Accelerated Assessment, features of PRIME scheme.	Orphan regenerative medicinal product designation.
Additional features	MA application was reviewed using a coordinated, cross-agency approach	-	Followed a regular approval review pathway.
Post-MA Conditions	Post-marketing observational study involving patients treated with Kymriah to further evaluate the long-term safety, besides other specific obligations.	Implementation of an educational program for patients and healthcare professionals; conduct PAES one PASS, besides other specific obligations.	Regular post-marketing surveillance only.

4.5 Other facts to compare expedited pathways

The last report from the Centre for Innovation in Regulatory Science (CIRS)[56] – which outlines the results from the annual analysis of New Active Substance (NAS) approvals by the six major Regulatory Agencies: the EMA, the US FDA, the Japanese PMDA, Health Canada, Swissmedic and the Australian Therapeutic Goods Administration (TGA)

[56] The Centre for Innovation in Regulatory Science (CIRS) is a neutral and independent, international member-based organization headquartered in the United Kingdom, and it is part of the Clarivate Analytics group. (4)

– evaluates results from 2019 in comparison with the 2010-2019 period and shows the conclusions regarding median approval times, focused on facilitated regulatory pathways, among other indicators of Agency performance.

Based on this report, it is possible to conclude that FDA has been the Agency with the shortest median approval time since 2017 (243 days), but also one of the Agencies with the shortest median approval time since 2010.(3) In addition, between 2015-2019, the development lead-time from IND to submission of MA application reduced due to the benefit of being granted with Breakthrough Therapy designation. (3) This scenario may be due to the use of expedited regulatory pathways for a long time and the experience acquired, and also be due to the importance of those approved products in addressing unmet medical needs. Regarding EMA, a median approval time of 423 days is observed in the 2010-2019 interval, including the EU Commission Decision time, being the second Agency with the longest median approval period since 2011 when comparing the Regulatory Agencies in scope. The results from PMDA, in the 2010-2012 interval, show the greater reduction in median review time and, since then, it has been one of the Regulatory Agencies with lowest median approval time (304 days).(3) This decrease may be the result of the efforts made by the Japanese Government to increase access to medicinal products and implement expedited programs for regulatory review in exceptional circumstances, as defined in their legislation.

During 2019, FDA (both Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER)), approved 47 NAS, of which 8 (17%) were personalized medicines reviewed in a median approval time of 221 days, and all of them benefiting from priority review. In addition to priority review, other facilitated regulatory pathways were adopted in the review of these personalized medicines. 4 of them were approved via accelerated approval pathway, 5 received Fast Track designation and 5 also received Breakthrough Therapy designation. Some of these pathways were applied cumulatively and one of the NAS approved was granted the three designations, in addition to the priority review.(3) This is suggestive of the approved NAS being of importance to public health, as it was classified as promising medicinal products and addressing unmet medical needs. In the same period, FDA reviewed and approved 15 Breakthrough Therapy designation NASs, 7 of them also using the Accelerated Approval pathway, which indicates that a surrogate endpoint was used to grant the approval. (3)

Considering the last five years, the EMA median time for review of NAS applications has been quite stable - between 239 and 247 days, as the median time per year. Nevertheless, over 2018 and 2019, total median time has increased about one month considering the increase in the number of days that companies needed to provide a response to questions raised by the Agency during the assessment, leading to extended time of clock-stops. (3) This extension may be due to more than one factor, but reasons may include the difficulty faced by companies in providing satisfactory responses due to the lack of experience of non-top companies, which were responsible for 57% of NAS approvals in that period.

Regarding PMDA, their scheme is to review and approve medicines four times per fiscal year, starting in April. This practice results in a more fluctuated scheme of approvals throughout the year. Between 2015 and 2018, the number of approvals had decreased, from 39 NAS approved in 2015 to 31 in 2018. The median submission gap[57] in 2019 was 248 days, which represents an increase in the median time of 67 days when compared with 2018, and this might be the result of the companies' adjustment of strategy for submitting MA applications in Japan. In addition, between 2017 and 2019, of the 87 NAS approved by the PMDA, 3 have benefited from the Sakigake designation, representing a limited number of NAS when compared with EMA or FDA in the same period, for a comparable review process. These 3 NASs approved through Sakigake designation were also approved by FDA, and one of them was approved in the EU. Regarding median times for review and approval, for the three Sakigake designation NASs, the median approval time was 181 days, representing a reduction of 135 days from the non-Sakigake approvals, and no submission gap was observed in those three NAS. (3)

Furthermore, between 2015 and 2019, the top 5 therapeutic areas with NAS approved were anti-cancer and immunomodulators (46%), alimentary and metabolism, blood and blood forming organs, anti-infective, and nervous system (by WHO Anatomical Therapeutic Chemical (ATC) codes) representing 78% (796/1026) of all approvals in the abovementioned period. When comparing the median approval time of NAS between 2015-2019, from the date of submission to the date of Agency approval, including company and Agency time, and also the EU Commission Decision time in case of approval in the EU, PMDA and FDA have consistently had median approval times below the overall median approval time (between 327 and 376 days for all therapeutic areas). This also considers other Regulatory Agencies such as Swissmedic, Health Canada and

[57] Submission gap is the time from date of submission at the first regulatory agency to the date of regulatory submission to the target agency.(3)

TGA. However, EMA has been showing a higher number of days from the submission of the MA application to its final approval. (3)

In 2019, in the EU, 27 NAS's were approved. From these, 11 were Biologic NASs and their median approval time was 440 days; 16 were chemical NASs with a median approval time of 418 days. 2 of the 27 NAS approved in 2019 followed an expedited pathway through Accelerated Assessment, leading to a median approval time of 270 days - about 163 days faster than using the standard pathway applied for the other 25 molecules approved by the Agency. (3) It is important to note that median approval time in the EU also includes the EU Commission time to grant the approval through EU Commission Decision, in addition to the EMA review and final Positive Opinion.

Regarding FDA, the total number of NASs approved in 2019 was 47, and the median approval time was 243 days. From the total number of approvals, 12 were biologic NASs and 35 were chemical NASs, with a median approval time of 239 and 243 days, respectively; 32 NASs were approved after having followed an expedited pathway (Priority Review), with a median approval time of 238 days, representing 127 days less than standard approval of NASs in the same period. (3) Typically, FDA has a higher number of NAS approved and that could be due to its extensive experience in using expedited tools, or because some of the medicines developed by smaller companies and approved in the USA may not be expanded to other markets. (3)

Regarding Japan, PMDA granted approval to 33 NASs in 2019, with a median approval time of 304 days, which represents a higher timeframe than the one observed in EMA and FDA, in the same period. From the 33 NASs approved, 11 were biologics with a median approval time of 288 days and 23 were chemical NASs with a higher median approval time – 304 days. Regarding the use of expedited pathways, 14 used the expedited approach, namely Priority Review scheme of PMDA. The use of this regulatory tool resulted in a decrease in median approval time when compared with the standard pathway – 256 days in the expedited pathway, and 332 in the standard approval. (3) In addition, the proportion of new active substances (NAS) approved in 2019 using one or more facilitated regulatory pathways was 26% by EMA, 70% by FDA, and 42% by PMDA. (3) The table below has some key figures from 2019 regarding approval of NAS by EMA, FDA and PMDA.

Table 11 - Facilitated regulatory pathway (FRP) timelines for EMA, FDA and PMDA in 2019.[#]

	NAS by approval type	2019 NAS approvals, number	2019 NASs, %	Expedited*, % of 2019 approvals	2019 median approval time, days
EMA	***Overall approvals***	***27***	**-**	**-**	***423***
	Accelerated Assessment	2	7%		270
	Conditional Approval	6	22%	17%	481
	Exceptional Circumstances	0	N/A	N/A	N/A
	PRIME Scheme	1	4%	100%	281
FDA	***Overall approvals***	***47***	**-**	**-**	***243***
	Priority	32	68%		238
	Accelerated Approval	9	19%	100%	173
	Breakthrough Therapy Designation	15	32%	100%	182
	Fast Track	19	40%	95%	243
PMDA	***Overall approvals***	***33***	**-**	**-**	***304***
	Priority	14	42%		256
	Sakigake	1	3%	100%	181
	Conditional Early Approval	0	N/A	N/A	N/A

[#] Adapted from "R&D Briefing 77: New drug approvals in six major authorities 2010–2019: Focus on Facilitated Regulatory Pathways and Internationalisation" (3)

* Expedited corresponds to Accelerated Assessment to EMA, and Priority Review to FDA and priority Review System to PMDA. (3)

From the data above, it is noted that, in the case of EMA, the median approval time for medicines with Accelerated Assessment took approximately half the time of products following the standard review process, as well as the ones included in PRIME scheme. These results emphasize the importance of using such tools for expedited MA approval to accelerate the availability of products on the market. The same rationale is applicable to FDA and PMDA since Accelerated Approval and Breakthrough Therapy designation represented a shorter review time, as well as Sakigake designation.

Regarding the ratio of expedited and standard reviews, in 2019, FDA had the highest percentage of expedited pathways (68%), followed by PMDA (42%). In contrast, EMA had a lower ratio (7%).

FDA has consistently increased the proportion of expedited approvals from 47% in the 2010-2014 period to 65% in the 2015-2019 period. In Japan, the proportion of expedited approval was almost 50% in 2015, and after a decrease until 2018, it has increased for

more than 40% in 2019. Regarding EMA, the number of expedited approvals has been decreasing since 2015, and it was below 10% in 2019. This could be partially explained by the fact that the review can be converted into a standard review if timelines cannot be met by the sponsor – it happened in 4 NAS initially designated for expedited review by EMA. In addition, FDA was also the Agency that approved the highest percentage of NAS through at least one facilitated regulatory pathway (70%). (3)

The difference in median approval time between the Agencies evaluated has been attributed to product-specific and company strategy reasons, but also to agency specificities, such as: legal frameworks that impose certain timelines; processes prior to submission or rolling submission; existence of expedited regulatory pathways; work-sharing between Agencies, in which the agencies review different parts of the dossier; or the possibility of post-scientific assessment. (3) Nevertheless, the difference between the median approval time is narrower when comparing the median time from submission of MA application to the end of Agency's scientific assessment, which suggests that the overall approval time is longer for EMA and PMDA also due to the additional activities following the end of scientific assessment – EU Commission and MHLW final approval. In fact, the difference in the number of days between FDA and EMA is 59, and between FDA and PMDA is 31, when considering median approval time from submission of MA application and the end of scientific assessment. (3)

The comparison with the highest relevance to the evaluation of the performance of Regulatory Agencies is the one that derives from examining medicines approved by the three Regulatory Agencies in scope. In the 2020 report from CIRS, where a comparison was carried out for two-time cohorts (2010-2014 and 2015-2019), it is stated that the number of products approved by EMA, FDA and PMDA, but also TGA, Swissmedic and Health Canada, increased by 36% from the first 5 years to the last ones. And it suggests that the overall time for approval, from the date of submission for the first time to a Regulatory Agency, until the date of approval, which translates the time for registration by the six Agencies, may be impacted by several potential factors – for example, the company strategy, the use of expedited pathways in some Regulatory Agencies, etc. (3) Nevertheless, it also suggests that the waves of submission to the Agencies has been stable, with EMA and FDA being the preferred ones by the companies to submit the MA application first, occurring almost simultaneously, and PMDA is chosen for a subsequent wave of submission. (3) This choice may occur for several reasons – not only because approval may be granted faster, using well-established regulatory pathways in a robust regulatory context, but also because the USA and the EU are considered important

markets when starting the commercialization of a product, and approving a medicine in these regions will mean that the medicine may be available to a vast number of patients in need.

In both cohorts, FDA had the fastest time to registration, and the overall time for approval by the EMA decreased from one cohort to another, suggesting that more expedited pathways are being used by this Agency. When comparing the 2010-2014 and 2015-2019 timeframes, the PMDA submission gap[58] was reduced by over 100 days, representing a significant decrease.(3) This achievement may be related to the implementation of the governmental measures above mentioned.

In terms of total time from the date of submission in the first Regulatory Agency to approval, EMA and PMDA have decreased the duration of this interval.(3) This is also suggestive of a greater investment in improving the regulatory timeframes and in implementing measures to increase overall performance in this area.

Additionally, 30% of the NASs approved by EMA in 2019 were approved first in the EU or within one month after approval by the first Regulatory Agency, taking into consideration the FDA, PMDA, but also Health Canada, Swissmedic or TGA. Of the other 70%, the median submission gap from the submission to the first Agency and EMA was 249 days. In contrast, about 85% of the NASs approved by FDA in the same period were the first ones approved or just one month after the first approval by a different Agency.(3) The results above suggest that an increasingly higher relevance is being attributed to expedited approval pathways and that time for approval of promising medicines in the USA, EU and Japanese markets are being significantly reduced. In addition, and although the three Agencies are showing improvements in the key performance indicators such as median review times for approval, FDA is the Agency that shows consistent results and the most positive ones in the last decade, while it has been the one that has been applying expedited pathways more frequently and has been showing a significant decrease in review time to the final approval of medicines of high medical need.

[58] Submission gap is the time from date of submission at the first regulatory agency to the date of regulatory submission to the target agency.(3)

5 Conclusion

Expedited regulatory review and approval initiatives have started being implemented and developed in the USA, in the EU, and more recently in Japan, predominantly in the last decade. In this dissertation, expedited pathways were first described and then a deeper comparative analysis was made between them.

The first expedited review tools created were the Accelerated Approval pathway and the Priority Review designation, both created in 1992 in the USA, and they represented the beginning of an evolving regulatory context with a clear focus on enhancing the availability of critical medicines to patients, responding more efficiently to public health needs. Following the USA, in the beginning of the XXI Century, EMA has also invested in resources and in its scientific experts' board to implement strategies and create regulatory programs with the same objective. Lately, Japan has also invested in a strategy focused on improving public health standards, scientific development of medicinal products available to patients and in their healthcare system, which has come into effect in November 2014, compiling several measures including investment in updating its pharmaceutical affairs legislation.

Regarding development support programs, each Regulatory Agency has established and developed initiatives, grounded by their own original regulatory framework. The pioneer Agency was the FDA when, in 2012, it created the Breakthrough Therapy Designation, a program gathering a set of features capable of supporting applicants on their development programs. PMDA was the next Regulatory Agency to implement a similar program in 2015, the Sakigake designation system, aiming to eliminate delays in drug development and invest in the development of medicines, turning Japan into one of the World's leaders in medicines' innovation. In 2016, EMA also launched its development support system, the PRIME scheme, aligned with the same principles of Japan and the USA, and it is already showing encouraging results that support its benefits to the public health of the EU citizens. PRIME scheme is an example of how the European regulatory landscape is being developed and adapted to new trends in the EU, trying to ensure timely forethought and action to expedite the availability of innovative medicines to patients. As observed in the multiplicity of regulatory guiding and legislative documents, the EU regulatory framework has not been a static environment but a

constantly evolving framework for the benefit of patients in the region and the developers of medicines, such as pharmaceutical companies, SME and Academia.

Although the development support programs from FDA, EMA and PMDA are very similar in their objectives and main practical characteristics, such as the enhanced support from the regulatory agencies and ultimately a faster and more efficient drug development and approval process, they differ in some particularities. Expedited approval pathways in the USA and in the EU provide similar qualification criteria, such as severity of target disease; however, such criteria are not specified in the corresponding pathway in Japan. Only the Japanese pathway stipulates a time limitation on exceptional approval, requiring post-marketing studies for conditional and time-limited approval. In addition, the original ground of the Sakigake designation, which means “pioneer”, is linked to the objective of attracting innovative medicines to Japan, as it is required that the product is first developed in their territory. On the other hand, PRIME scheme is more focused on supporting the development of promising medicines by Academia or small/medium-sized sponsors.

All expedited pathways have their own set of features and qualifying criteria, but some of them may also be quite redundant in terms of the benefits each one is providing to the sponsors. As an example, in the USA, the Breakthrough Therapy designation, RMAT designation, and Fast Track have redundant regulatory procedures, although their main purpose is different. Nevertheless, in the USA, EU and Japan, sponsors may benefit from the combination of more than one expedited pathway since they are not mutually exclusive, and this is clearly an advantage that allows the maximization of all benefits that could be applicable to each case.

The main difference to highlight between expedited review tools and the development support programmes concept, is the intensive guidance and communication between the Agencies and sponsors. Although it is possible to request formal guidance to the Agency during drug development in a separated procedure (e.g., through scientific advice procedure of EMA) when applying to a standard procedure or even before using an expedited tool, development support programmes include the opportunity to benefit from experts’ advice and support, and from a great involvement between parties in the development program from early stages.

Additionally, the three Regulatory Agencies have their own pathway with the main benefit of reducing the review time needed for approval. Accelerated Assessment of EMA reduces the review time by 2 months, Priority Review of FDA by 4 months and Priority

Review System of PMDA by 3 months. The greater decrease in review time is for Priority Review, although the shortest overall period is for the EMA tool. Nevertheless, the time for applicants to respond to questions from the Agency is not included in this review period, so it actually may take more time than the other Agencies to reach final approval. In addition, formal approval is only effective after EU Commission Decision is made, then the gap between the submission and approval date may be about 2 months longer than it would be if final approval was reached at the end of CHMP Opinion. In Japan, a similar approach is seen, since MHLW approval is required at the end of PMDA review.

Regarding ATMP, the cell and gene therapy field has started to grow, and an interesting number of promising new medicines has already reached some markets globally. The ATMP field is supported by improved and evolving regulatory tools and schemes focused on their tailored and expedited development. For these therapies, the ATMP regulation in the EU was the first effective step to develop a regulatory basis in this respect, followed by Directive 2009/120/EC which describes the technical requirements expected from ATMPs being developed for commercialization in a risk-based approach. In the EU, PRIME scheme is the main tool by which support is provided to expedite the development of this type of innovative medicine targeting unmet medical needs. Until December 2020, PRIME scheme has allowed the expedited development of 6 ATMPD and 4 are already approved. An encouraging sign of the possibility of increasing the rate of ATMP authorisations in the upcoming years is that almost 50% of the medicines currently elected to PRIME scheme are ATMPs.

In the past years, the USA regulatory landscape has also significantly evolved around cellular and gene therapy products. For example, this has been the case with the introduction of RMAT designation, in addition to other expedited tools, and with the publication of new guiding documents such as some guidance on both CMC and clinical development of cellular and gene therapy products. INTERACT programme will also foster pre-clinical trials communication and engagement between the FDA and developers to focus on CMC and clinical development at early stages, increasing efficiency of the pathway to approval. In the US context, the Regulatory Agency is also supporting schemes to expedite these innovative products through Breakthrough designation and RMAT designation, and in Japan, Sakigake Designation and a regulatory tool (Conditional and Time-Limited Approval for RMPs) were implemented, also allowing the expedite review and approval of these products. Such schemes are dynamically contributing to the approval of ATMP therapies in these territories and

regulatory science has been evolving to keep up with the trend of the development of innovative therapies.

Authorization of Keytruda and Kymriah by the FDA, EMA and PMDA is an example of how beneficial it could be to apply expedited tools to accelerate review and approval of medicines critical to public health, in addition to the recent example of Veklury.

The existence and effective application of expedited pathways are crucial in addressing areas of unmet need and other public health emergencies such as the COVID-19 pandemic. The diligent use of regulatory tools for expedited MA and early access in such an adverse context was the most remarkable example of how critical they are to address an unmet need of society in emergency situations. Each Regulatory Agency has its own tools for early access, and although they are different in the way the provisions are implemented, their intent is basically the same. These different means of emergency access are capable of recognising the potential impact of investigational new drugs to face life-threatening illnesses, allowing broad access to these medicines, while acknowledging the uncertain risks inherent to their novelty. With regards to regulatory approval, the COVID-19 pandemic was a remarkable setting in which Regulatory Agencies integrated their resources to incredibly shorten timelines and avoid delays, while retaining quality standards of their scientific assessment as a priority. Veklury was the first critical medicine approved in the USA, EU and Japan in the COVID-19 pandemic context, and application of expedited review processes was critical to allow extended access to patients in need and faster approval by the Regulatory Agencies. This adverse environment also led to increased transparency of Regulators across regions, specifically regarding the discussions taking place with the developers. In the near future, it is expected that some measures extraordinarily adopted during this period may become part of regular practices and of a renewed approach in major interest to public health.

6 References

1. Hwang TJ, Ross JS, Vokinger KN, Kesselheim AS. Association between FDA and EMA expedited approval programs and therapeutic value of new medicines: retrospective cohort study. BMJ [Internet]. 2020 [cited 2020 Nov 26]; Available from: https://doi.org/10.1136/bmj.m3434
2. Nagai S. Flexible and expedited regulatory review processes for innovative medicines and regenerative medical products in the US, the EU, and Japan. Int J Mol Sci [Internet]. 2019;20(15). Available from: https://www.mdpi.com/509162
3. Centre for Innovation in Regulatory Science. R&D Briefing 77: New drug approvals in six major authorities 2010–2019: Focus on Facilitated Regulatory Pathways and Internationalisation. [Internet]. London, UK; 2020 [cited 2020 Aug 15]. Available from: https://cirsci.org/wp-content/uploads/2020/06/CIRS-RD-Briefing-77-6-agencies.pdf
4. CIRS. CIRS – Centre for Innovation in Regulatory Science [Internet]. 2020 [cited 2020 Aug 15]. Available from: https://www.cirsci.org/
5. Jokura Y, Yano K, Yamato M. Comparison of the new Japanese legislation for expedited approval of regenerative medicine products with the existing systems in the USA and European Union. J Tissue Eng Regen Med [Internet]. 2018 Feb 1 [cited 2020 Jun 10];12(2):e1056–62. Available from: http://doi.wiley.com/10.1002/term.2428
6. European Medicines Agency. Support for early access [Internet]. Science Medicines Health. 2016 [cited 2019 Sep 12]. Available from: https://www.ema.europa.eu/en/human-regulatory/overview/support-early-access
7. U.S. Department of Health and Human Services, 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]. FDA; 2014 [cited 2019 Oct 29]. Available from: https://www.fda.gov/media/86377/download
8. Food and Drug Administration. FD&C Act - 21 U.S. Code § 356 - Expedited approval of drugs for serious or life-threatening diseases or conditions [Internet]. USA; 2019 p. 278–80. Available from: https://www.law.cornell.edu/uscode/text/21/356
9. FDA Center for Biologics Evaluation and Research. Expedited Programs for Regenerative Medicine Therapies for Serious Conditions - Guidance for Industry. Food and Drug Administration; 2019.
10. Ministry of Health Labour and Welfare. Strategy of SAKIGAKE - Leading the world in the practical application of innovative medical products and devices [Internet]. 2014 [cited 2020 Jun 13]. Available from: https://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/dl/140729-01-01.pdf
11. Hara A, Sato D, Sahara Y. New Governmental Regulatory System for Stem Cell–Based Therapies in Japan. Ther Innov Regul Sci [Internet]. 2014 Nov 19 [cited 2020 Nov 28];48(6):681–8. Available from: https://pubmed.ncbi.nlm.nih.gov/30227468/

12. European Commission. Legal framework governing medicinal products for human use in the EU | Public Health [Internet]. 2020 [cited 2020 Apr 2]. Available from: https://ec.europa.eu/health/human-use/legal-framework_en
13. European Parliament, Council of the European Union. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 [Internet]. 726/2004 European Union: Official Journal of the European Union; 2004. Available from: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:en:PDF
14. European Medicines Agency - Human Medicines Research and Development Support Division. Development support and regulatory tools for early access to medicines [Internet]. London; 2016 [cited 2020 Jul 19]. Available from: www.ema.europa.eu/contact
15. European Medicines Agency. Scientific advice and protocol assistance | European Medicines Agency [Internet]. 2020 [cited 2020 Apr 4]. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance
16. European Medicines Agency. Accelerated assessment [Internet]. [cited 2019 Sep 13]. Available from: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/accelerated-assessment
17. 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]. London: European Medicines Agency; 2016 [cited 2019 Sep 25]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-scientific-application-practical-arrangements-necessary-implement-procedure-accelerated/2004_en.pdf
18. European Medicines Agency. Procedural advice on the evaluation of advanced therapy medicinal product in accordance with Article 8 of Regulation (EC) No 1394/2007. London, UK: European Medicines Agency; 2018.
19. Detela G, Lodge A. EU Regulatory Pathways for ATMPs: Standard, Accelerated and Adaptive Pathways to Marketing Authorisation. Mol Ther - Methods Clin Dev [Internet]. 2019;12-June(Molecular Therapy-Methods & Clinical Development). Available from: https://reader.elsevier.com/reader/sd/pii/S2329050119300130?token=A6A4A39E0ECCCF47D7B19BD25BBDD0DC7AE0C1BA9C747E49ED873106B8EADD1B1747A1CEB5064E4099BF11FE6EE20744
20. Commission of the European Communities. Commission Regulation (EC) No 507/2006 of 29 March 2006 [Internet]. 507/2006 European Union: Official Journal of the European Union; 2006. Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2006_507/reg_2006_507_en.pdf
21. European Parliament, Council of the European Union. Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products [Internet]. 141/2000 European Union: Official Journal of the European Communities; 2000. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32000R0141&from=EN
22. Committee for Medicinal Products for Human Use Guideline. 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 Regulation (EC [Internet]. London: European Medicines Agency; 2016 [cited 2019 Sep 15]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-scientific-application-practical-arrangements-necessary-implement-commission-regulation-ec/2006-conditional-marketing-authorisation-medicinal-products-human-use-falling_en.pdf

23. European Medicines Agency. Conditional marketing authorisation [Internet]. [cited 2019 Sep 13]. Available from: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation
24. European Medicines Agency. Guideline on procedures for the granting of a Marketing Authorisation under exceptional circumstances, pursuant to Article 14 (8) of regulation (EC) no 726/2004 [Internet]. London: European Medicines Agency; 2005 [cited 2019 Sep 29]. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-procedures-granting-marketing-authorisation-under-exceptional-circumstances-pursuant/2004_en.pdf
25. European Parliament, Council of the European Union. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 [Internet]. 2001/83/EC European Union: Official Journal of the European Communities; 2001. Available from: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:311:0067:0128:en:PDF
26. Committee for Medicinal Products for Human Use. Guideline on Compassionate use of Medicinal Products, pursuant to Article 83 of Regulation (EC) No 726/2004 [Internet]. London: European Medicines Agency; 2007 [cited 2020 Dec 1]. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-compassionate-use-medicinal-products-pursuant-article-83-regulation-ec-no-726/2004_en.pdf
27. European Medicines Agency. PRIME: priority medicines [Internet]. 2019 [cited 2020 Dec 1]. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines
28. European Medicines Agency. PRIME: a two-year overview [Internet]. London; 2018 [cited 2019 Aug 9]. Available from: https://www.ema.europa.eu/en/documents/report/prime-two-year-overview_en.pdf
29. Human Medicines Research and Development Support Division. European Medicines Agency Guidance for applicants seeking access to PRIME scheme [Internet]. London: European Medicines Agency; 2018 [cited 2019 Aug 12]. Available from: https://www.ema.europa.eu/en/documents/other/european-medicines-agency-guidance-applicants-seeking-access-prime-scheme_en.pdf
30. European Medicines Agency. Final programming document 2019-2021 [Internet]. London, UK; 2019 [cited 2019 Aug 25]. Available from: https://www.ema.europa.eu/en/documents/report/final-programming-document-2019-2021_en.pdf
31. European Medicines Agency. Recommendations on eligibility to PRIME scheme [Internet]. Amsterdam; 2020 [cited 2020 Dec 1]. Available from:

https://www.ema.europa.eu/en/documents/report/recommendations-eligibility-prime-scheme-adopted-chmp-meeting-9-12-november-2020_en.pdf
32. European Medicines Agency - Human Medicines Research and Development Support Division. Mandate of the EMA Innovation Task Force (ITF) [Internet]. London; 2014 [cited 2020 Jul 20]. Available from: https://www.ema.europa.eu/en/documents/other/mandate-european-medcines-agency-innovation-task-force-itf_en.pdf
33. European Medicines Agency. Adaptive pathways [Internet]. [cited 2020 Jul 18]. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/adaptive-pathways
34. European Medicines Agency. Final report on the adaptive pathways pilot [Internet]. London; 2016 [cited 2020 Jul 19]. Available from: www.ema.europa.eu/contact
35. ADAPT-SMART consortium. Review Report on IMI Projects [Internet]. 2017 [cited 2020 Jul 19]. Available from: www.adaptsmart.eu.
36. Food and Drug Administration. Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended to Treat Life-Threatening and Severely Debilitating Illnesses [Internet]. USA: Federal Register; 1988. Available from: https://www.fda.gov/media/71861/download
37. Food and Drug Administration. INTERACT Meetings [Internet]. 2020 [cited 2020 Dec 3]. Available from: https://www.fda.gov/vaccines-blood-biologics/industry-biologics/interact-meetings
38. The Food and Drug Administration. Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review [Internet]. 2018 [cited 2019 Oct 10]. Available from: https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review
39. 112th Congress. PUBLIC LAW 112–144—JULY 9, 2012: Food and Drug Administration Safety and Innovation Act [Internet]. USA; 2012. Available from: https://www.congress.gov/112/plaws/publ144/PLAW-112publ144.pdf
40. eCFR — Code of Federal Regulations - §601.41 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity. [Internet]. USA: Electronic Code of Federal Regulations; Available from: https://www.ecfr.gov/cgi-bin/text-idx?SID=ca4f83ca6aff4e7db644ee7e67b4c995&mc=true&node=se21.7.601_141&rgn=div8
41. eCFR — Code of Federal Regulations - §314.510 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity [Internet]. USA: Electronic Code of Federal Regulations; Available from: https://www.ecfr.gov/cgi-bin/text-idx?SID=b0d2e7452975d01a05b9e1597312ca4a&mc=true&node=se21.5.314_1510&rgn=div8
42. Tsuyuki K, Yano K, Watanabe N, Aruga A, Yamato M. Compassionate use of drugs and medical devices in the United States, the European Union and Japan. Regen Ther [Internet]. 2016 Jun 1 [cited 2020 Dec 13];4:18–26. Available from: file:///Users/Regina/Downloads/Compassionate_use_of_drugs_and_medical_devices_in_.pdf

43. Services USD of H and H, Administration F and D, (CDER) C for DE and R. Qualified Infectious Disease Product Designation - Questions and Answers - Guidance for Industry [DRAFT GUIDANCE] [Internet]. USA; 2018 [cited 2019 Nov 1]. Available from: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
44. TITLE 21-FOOD AND DRUGS - Sec. 355f - Extension of exclusivity period for new qualified infectious disease products [Internet]. 126 Stat. 1077, 1079 USA: United States Code, 2012 Edition, Supplement 1, Title 21 - FOOD AND DRUGS; 2013. Available from: https://www.govinfo.gov/content/pkg/USCODE-2013-title21/pdf/USCODE-2013-title21-chap9-subchapV-partA-sec355f.pdf
45. Japan Pharmaceutical Manufacturers Association - Regulatory Information Task Force. Pharmaceutical Administration and Regulations in Japan [Internet]. 2019 [cited 2020 Aug 1]. Available from: http://www.jpma.or.jp/english/parj/whole.html
46. Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices [Internet]. Amendment of Act No. 50 of 2015 Japan: Japanese Law Translation; 2015. Available from: http://www.japaneselawtranslation.go.jp/law/detail/?ft=1&re=02&dn=1&x=33&y=13&co=01&ia=03&ja=04&ky=pharmaceuticals+and+medical+devices+act&page=11&id=3213&lvm=01
47. Ministry of Health Labour and Welfare. Outline of the Law for Partial Revision of the Pharmaceutical Affairs Law [Internet]. [cited 2020 Jun 12]. Available from: https://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/dl/150407-01.pdf
48. Yasuhiro F. Special Approval for Emergency on Remdesivir for COVID-19 [Internet]. 2020 [cited 2020 Dec 27]. Available from: https://www.pmda.go.jp/english/int-activities/0004.pdf
49. Pharmaceutical Evaluation Division - PSEHB. Notification No. 1020-1 of Pharmaceutical Evaluation Division, PSEHB on “Implementation of conditional accelerated approval system for pharmaceuticals”, dated October 20, 2017 [Internet]. Pharmaceutical and Medical Devices Agency; 2017 [cited 2020 Aug 9]. Available from: https://www.pmda.go.jp/files/000227089.pdf
50. Pharmaceuticals and Medical Devices Agency. List of Approved Products [Internet]. 2020 [cited 2020 Dec 10]. Available from: https://www.pmda.go.jp/english/review-services/reviews/approved-information/0002.html
51. Hojo T. New Regulation in Japan and Future Direction of PMDA [Internet]. Paris: PMDA; 2015 [cited 2020 Nov 2]. Available from: https://www.pmda.go.jp/files/000204615.pdf
52. European Medicines Agency. Marketing-authorisation procedures for advanced-therapy medicinal products [Internet]. European Medicines Agency. [cited 2020 Dec 27]. Available from: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/advanced-therapies/marketing-authorisation-procedures-advanced-therapy-medicinal-products
53. Committee for Medicinal Products for Human Use (CHMP). Assessment report - Keytruda [Internet]. London, UK; 2015 [cited 2020 Dec 4]. Available from:

https://www.ema.europa.eu/en/documents/assessment-report/keytruda-epar-public-assessment-report_en.pdf
54. Center for Drug Evaluation and Research. Summary Review - application number 125514Orig1s000 [Internet]. 2014 [cited 2020 Dec 2]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125514Orig1s000SumR.pdf
55. The European Commission. Commission Implementing Decision of 17.7.2015 granting marketing authorisation under Regulatorion (EC) No 726/2004 of the European Parliament and of the Council for "KEYTRUDA - pembrolizumab", a medicinal product for human use [Internet]. Brussels: EUROPEAN COMMISSION; 2015 [cited 2020 Dec 4]. Available from: https://ec.europa.eu/health/documents/community-register/2015/20150717132284/dec_132284_en.pdf
56. Pharmaceuticals and Medical Devices Agency. Report on the Deliberation Results - Keytruda [Internet]. 2016 [cited 2020 Dec 4]. Available from: https://www.pmda.go.jp/files/000226881.pdf
57. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic [Internet]. Vol. 91, Acta Biomedica. Mattioli 1885; 2020 [cited 2020 Dec 30]. p. 157–60. Available from: https://pubmed.ncbi.nlm.nih.gov/32191675/
58. World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard [Internet]. World Health Organization. 2020 [cited 2020 Dec 29]. Available from: https://covid19.who.int/
59. International Coalition of Medicines Regulatory Authorities (ICMRA). ICMRA statement on COVID-19 [Internet]. 2020 [cited 2021 Feb 8]. Available from: http://www.icmra.info/drupal/news/statement_on_COVID-19
60. Malin JJ, Suárez I, Priesner V, Fätkenheuer G, Rybniker J. Remdesivir against COVID-19 and Other Viral Diseases [Internet]. 2020 [cited 2021 Feb 18]. Available from: https://doi.org/10
61. Hinton DM. Veklury (remdesivir) EUA Letter of Approval, reissued 10/22/2020 [Internet]. 2020 [cited 2020 Dec 28]. Available from: https://www.fda.gov/media/137564/download
62. U.S. Food and Drug Administration. Frequently Asked Questions for Veklury (remdesivir) [Internet]. 2021 [cited 2021 Feb 24]. Available from: https://www.gilead.com/news-and-press/press-room/press-
63. Center for Drug Evaluation and Research. Summary Review - application number 214787Orig1s000 [Internet]. 2020 [cited 2021 Feb 26]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/214787Orig1s000Sumr.pdf
64. Committee for Medicinal Products for Human Use. Assessment report - Veklury [Internet]. Amsterdam; 2020 [cited 2020 Dec 28]. Available from: https://www.ema.europa.eu/en/documents/assessment-report/veklury-epar-public-assessment-report_en.pdf
65. Saint-Raymond A, Sato J, Kishioka Y, Teixeira T, Hasslboeck C, Kweder S. Remdesivir emergency approvals: a comparison of the U.S., Japanese, and EU systems. Expert Rev Clin Pharmacol [Internet]. 2020 [cited 2021 Feb 18];13(10):1095–101. Available from: https://doi.org/10.1080/17512433.2020.1821650

66. Pharmaceuticals and Medical Devices Agency. Report on the Deliberation Results - Veklury [Internet]. 2020 [cited 2021 Feb 25]. Available from: https://www.pmda.go.jp/files/000235590.pdf
67. Boudes PF. Gene therapy as a new treatment option for inherited monogenic diseases. Eur J Intern Med [Internet]. 2014 [cited 2020 Dec 29];25:31–6. Available from: http://dx.doi.org/10.1016/j.ejim.2013.09.009
68. Pharmaceuticals and Medical Devices Agency. List of Approved Products - New Regenerative Medical Products [Internet]. Pharmaceuticals and Medical Devices Agency. 2020 [cited 2020 Dec 28]. Available from: https://www.pmda.go.jp/english/review-services/reviews/approved-information/0002.html
69. U.S. Food and Drug Administration. Approved Cellular and Gene Therapy Products [Internet]. U.S. Food and Drug Administration. 2020 [cited 2020 Dec 28]. Available from: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products
70. European Medicines Agency. Human medicines highlights 2019 [Internet]. Amsterdam; 2020 [cited 2020 Dec 28]. Available from: https://www.ema.europa.eu/en/documents/report/human-medicines-highlights-2019_en.pdf
71. Shapiro JRK, Wesoloski BJ. FDA's Regulatory Scheme for Human Tissue A Brief Overview [Internet]. 2007 [cited 2020 May 3]. Available from: www.fdli.org
72. U.S.C. Title 42 - § 264. Regulations to control communicable diseases [Internet]. U.S. Government Publishing Office, 264 U.S. Government Publishing Office, www.gpo.gov; 2011. Available from: https://www.govinfo.gov/content/pkg/USCODE-2011-title42/html/USCODE-2011-title42-chap6A-subchapII-partG.htm
73. eCFR — Code of Federal Regulations Title 21 C.F.R. § 1271. Human Cells, Tissues, and Cellular and Tissue-Based Products [Internet]. 21 C.F.R. § 1271 Electronic Code of Federal Regulations; p. 21 C.F.R. § 1271.3(d). Available from: https://www.ecfr.gov/cgi-bin/text-idx?SID=0864d350ff39652d376b1993771acc09&mc=true&node=pt21.8.1271&rgn=div5
74. Commission of the European Communities. Commission Directive 2003/63/EC of 25 June 2003 [Internet]. Official Journal of the European Union, 2003/63/EC eur-lex.europa.eu; Jun 25, 2003. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32003L0063&from=en
75. The European Parliament, The Council of the European Union. 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 [Internet]. Official Journal of the European Union, 1394/2007 Nov 13, 2007. Available from: https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf
76. European Medicines Agency. Committee for Advanced Therapies (CAT) [Internet]. 2020 [cited 2020 Apr 5]. Available from: https://www.ema.europa.eu/en/committees/committee-advanced-therapies-cat#role-of-the-cat-section

77. CHMP. Kymriah - EPAR - Product Information [Internet]. EMA; 2018 [cited 2019 Aug 8]. Available from: https://www.ema.europa.eu/en/documents/product-information/kymriah-epar-product-information_en.pdf
78. U.S. Food and Drug Administration. FDA approval brings first gene therapy to the United States [Internet]. 2017 [cited 2021 Feb 24]. Available from: https://www.fda.gov/news-events/press-announcements/fda-approval-brings-first-gene-therapy-united-states
79. Bryan WW (Center for BE and R. Approval Letter - KYMRIAH [Internet]. 2017 [cited 2021 Feb 24]. Available from: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/
80. Committee for Medicinal Products for Human Use (CHMP). Assessment report - Kymriah [Internet]. 2018 [cited 2021 Feb 26]. Available from: www.ema.europa.eu/contact
81. Pharmaceuticals and Medical Devices Agency. Report on the Deliberation Results - Kymriah [Internet]. 2019 [cited 2021 Jan 22]. Available from: https://www.pmda.go.jp/files/000231651.pdf
82. European Commission. Rare diseases [Internet]. 2020 [cited 2020 Nov 30]. Available from: https://ec.europa.eu/health/non_communicable_diseases/rare_diseases_pt
83. eCFR - Code of Federal Regulations - Subpart I - Expanded Access to Investigational Drugs for Treatment Use - §312.300 General [Internet]. USA: Electronic Code of Federal Regulations; 2019. Available from: https://www.ecfr.gov/cgi-bin/text-idx?SID=775b3a4fa521e2be2de494a6685a1270&mc=true&node=pt21.5.312&rgn=div5#se21.5.312_17
84. Food and Drug Administration. PDUFA Legislation and Background [Internet]. 2015 [cited 2020 Dec 2]. Available from: https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-legislation-and-background
85. 21 U.S. Code § 353 - Exemptions and consideration for certain drugs, devices, and biological products [Internet]. 353 USA; 2011. Available from: https://www.govinfo.gov/content/pkg/USCODE-2010-title21/pdf/USCODE-2010-title21-chap9-subchapV-partA-sec353.pdf
86. NAGATA R, ASAMI M, TAKAGAI E, NAKATANI H. Health and Labour Sciences Research Grants (HLSRG): Reports of Researches Supported by HLSRG(Scientific communication in science and technology). J Inf Sci Technol Assoc. 2004 Jun 1;54(6):289–93.
87. Japan Agency for Medical Research and Development. Drug Discovery Support Network (DDSN) [Internet]. 2017 [cited 2020 Dec 1]. Available from: https://www.amed.go.jp/en/program/list/11/network.html
88. Japan Agency for Medical Research and Development. The iD3 Booster [Internet]. 2017 [cited 2020 Dec 1]. Available from: https://www.amed.go.jp/en/program/list/11/02/001_01-01.html
89. Pacific Bridge Medical. Japan Drug Regulatory Overview [Internet]. 2014 [cited 2020 Dec 17]. Available from: https://www.pacificbridgemedical.com/wp-content/uploads/2015/04/Japan-Drug-Regulatory-Overview-2014.pdf

90. Pharmaceuticals and Medical Devices Agency. About Medical Information Database Infrastructure Development Project [Internet]. [cited 2020 Dec 2]. Available from: https://www.pmda.go.jp/safety/surveillance-analysis/0018.html
91. Ohe K. Mid-NET: Medical information database network project to utilize electronic healthcare data for drug safety. Trans Japanese Soc Med Biol Eng [Internet]. 2017 Aug 10 [cited 2020 Dec 2];55(4):159–64. Available from: https://www.jstage.jst.go.jp/article/jsmbe/55/4/55_159/_article/-char/en
92. Pharmaceuticals and Medical Devices Agency. Consultations | Pharmaceutical Affairs Consultation on R&D Strategy [Internet]. 2020 [cited 2020 Dec 3]. Available from: https://www.pmda.go.jp/english/review-services/consultations/0002.html
93. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), (CBER) C for BE and R. Guidance Medication Guides-Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS) [Internet]. 2011 [cited 2020 Dec 19]. Available from: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htmand/orhttp://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
94. U.S. Food and Drug Administration. FDA Approves First Treatment for COVID-19 [Internet]. 2020 [cited 2020 Dec 28]. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19