Incorporating Patient Perspective into Benefit-Risk Assessments of a Medicinal Product - An Inventory of the Regulatory Approaches established in the European Union and the United States

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Marleen Lipinski

aus Rathenow

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Betreuerin and 1. Referentin: Dr. Birka Lehmann

2. Referentin: Dr. Ingrid Klingmann

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Abbreviation

21st CC Act	21st Century Cure Act
AHEG	Ad-Hoc Expert Group
BLA	Biologics License Applications
BRA	Benefit-Risk Assessment
B/R	Benefit-Risk
CAT	Committee for Advanced Therapies
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CHMP	Committee for Medicinal Products for Human Use
COMP	Committee for Orphan Medicinal Products
CTTI	Clinical Trials Transformation Initiative
DIA	Drug Information Association
EC	European Commission
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EPAR	European Public Assessment Report
EU	European Union
EUPATI	European Patients' Academy on Therapeutic Innovation
EURORDIS	Rare Diseases Europe
FD&C	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
FDARA	Food and Drug Administration Reauthorization Act
FDASIA	Food and Drug Administration Safety and Innovation Act
FY	Fiscal Year
HTA	Health Technology Assessment
IAP	International Association for Public Participation
NDA	New Drug Applications
NORD	National Organization for Rare Disorders
MA	Marketing Authorisation
MDIC	Medical Device Innovation Consortium
MDUFA	Medical Device User Fee Amendments
MOU	Memorandum of Understanding
OHCA	Office of Health and Constituent Affairs
OPH	Open Public Hearings
PAS	Patient Affairs Staff
PCWP	Patients' and Consumers' Working Party
PDCO	Paediatric Committee
PDUFA	Prescription Drug User Fee Act

PEAC	Patient Engagement Advisory Committee
PEC	Patient Engagement Collaborative
PED	Patient Experience Data
PFDD	Patient-Focused Drug Development
PRAC	Pharmacovigilance and Risk Assessment Committee
PRP	Patient Representative Program
R&D	Research and Development
SAG	Scientific Advice Group
US	United States

General remarks:

In the interests of readability, the term “regulators” and “agency” is used throughout this document to refer to EMA and FDA.

1 Introduction

In many circumstances, engaging with the public has gained an increased importance during the past decades. Public bodies recognized the necessity to establish standards for the interaction with the public and for the incorporation of public´s voice into their decision-making. One key driver in the healthcare arena incorporated public participation as a *right of the public* in ground-breaking consensus paper.

The World Health Organization declared in the Alma Ata in 1978:

> *"The people have a **right** and **duty** to participate individually and collectively in the planning and implementation of their health care."*

The concept of public participation enables the public to actively take part in policy decision-making and gives the public the opportunity to the public to shape the environment that affects public live in different areas in our society.
In the last few years, the role of the patients in the healthcare setting changed from patients being passive recipient towards patients being a partner actively involved in health care and treatment decision making (Tegenge, Moncur, Sololic, Forshee, & Irony, 2017). When patients are actively involved in aspects that affects their lives, it was found that this has a positive impact on treatment outcomes and adherence to treatment plans (Mühlbacher, Juhnke, Beyer, & Garner, 2016).

Various stakeholders involved in drug development and regulatory decision making i.e. industry, regulators or Health Technology Assessment bodies (HTA) have realized the value of patient´s input and set themselves the commitments to partner with individual patients, patient organisations or patient advocates (i.e. caregivers) to learn more about different aspects like the burden of the disease, disease management, patient´s needs and preferences also to increase transparency and acceptance of regulatory decisions ((FDA, 2016; Johnson & Zhou, 2016; Mühlbacher, Juhnke, Beyer, & Garner, 2016; Haerry, et al., 2018; Janssens, et al., 2019)

Before a medical product enters the market, it needs to be approved by a regulatory body. The approval is given based on a careful benefit-risk-assessment (BRA) by the regulators evaluating quality, safety, and efficacy data justifying the regulatory decision (FDA, 2020). In this context, regulators consider it increasingly important to include the patient perspective in the benefit-risk assessment to inform regulatory decision-making processes (Hoos, et al., 2015). Mainly, it is acknowledged that patients suffering from

a disease could weigh risks differently than a regulator who takes a decision only based on the scientific data provided by the applicant (EMA, 2013; Mühlbacher, Juhnke, Beyer, & Garner, 2016; Ho, et al., 2015).

Nearly two decades ago, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) laid their foundation for interacting with patients. The EMA and the FDA have implemented various programs and initiatives with the aim to enhance the interaction with patients and to incorporate patient's perspectives and preferences into regulatory decision-making process (EMA, 2014) (FDA, 2016). In 2016, the EMA and EMA established a cross-agency program to foster knowledge sharing about patient involvement in regulatory decision-making across both agencies (FDA, 2018).

At present, there are no requirements set by the EMA or the FDA to include patient preference data into the marketing authorization application documents to inform benefit-risk evaluation of a medicinal product. Patient preference data can be provided on a voluntary basis by the Applicant. Both agencies consider patient preference data if submitted by the Applicant, but they also consult with patients during benefit-risk assessment when the agencies consider it valuable to obtain meaningful patients view especially for those medicinal products addressing areas with significant unmet need. The agencies set themselves actions to continuously work on the implementation of their commitments and they define new goals to further enhance the interactions with patients with the aim to develop methods to gain meaningful patient input (FDA, 2018) (EMA, 2020).

The present master thesis will focus on how patient perspectives is incorporated in the BRA process of a medicinal product at the EMA and the FDA. The objective of this master thesis is to evaluate how patient perspective is considered by the agencies and at which level the agencies consult with patients to obtain patients perspectives during the BRA of a medicinal product. This thesis includes a theoretical model for public participation which is presented with the attempt to establish an interconnection between patient participation and regulatory decision-making processes. A summary of potential challenges associated with patient perspectives in BRA is also presented, please refer to chapter 2. In Chapter 3 and 4, the regulatory framework and current initiatives of including patient perspective into BRA of a medicinal product at the EMA and FDA are described. In Chapter 5, an evaluation is provided (1) assess the type of

methods which are used by both agencies to involve patients in benefit-risk assessment process. Furthermore, it will be investigated for (2) which type of medicinal products the EMA and FDA primarily consider the involvement of patients. The next step is to examine (3) how transparent patient involvement has been documented in regulatory assessment reports which are publicly available. In chapter 6 the results of the evaluation are discussed.

2 General Aspects of Patient Participation in Regulatory Decision-Making

In the available literature, different terms are used to describe the consideration of the patient's view such as "*Patient Engagement*", "*Patient Involvement*", "*Patient Perspective",* "*Patient Input",* "*Patient Voice*", "*Patient-focused*", "*Patient Centricity*", "*Patient Preference*" (du Plessis D, Morgan, Georgieva, & Bertelsen, 2017; Falchetto, 2020; Geissler, Ryll, di Priolo, & Uhlenhopp, 2017; Lowe, et al., 2016; MDIC, 2015; Tegenge, Moncur, Sololic, Forshee, & Irony, 2017; FDA, CDER Patient-Focused Drug Development, 2020; EMA, 2017; Benz, Saha, & Tarver, 2020). Sometimes the impression could arise that the terms are often used interchangeably. However, concepts may be different in terms of the level of participation and the level of influence by the patients in decision-making processes (IAP, 2018). In the next subsection, the theoretical concept of public participation is presented to embed the regulators' interaction with patients in decision-making processes into context.

2.1 Concept of Public Participation

The concept of public participation is not a recent intervention. The debate about public participation as such and different levels of public participation goes back to the late 60s. Sherry R. Arnstein has published *"A Ladder of Citizen Participation"* in 1969 in the Journal of the American Institute of Planners. With this substantial contribution Arnstein set an import milestone in the delimitation of citizen participation. She developed an eight-rung ladder. Each rung stands for a different level of participation i.e. (1) manipulation, (2) therapy, (3) informing, (4) consultation, (5) placation, (6) partnership, (7) delegated power, and (8) citizen control**.** According to Arnstein only the highest rung is the real citizen participation. But what she has impressively highlighted in the following statement is that public participation should not be tokenistic:

> *„There is a critical difference between going through the empty ritual of participation and having the real power needed to affect the outcome of the process."* (Arnstein, 1969, p. 216)

She equates public participation with `*power*` and `*control*` that implies public participation can only be successful by the seizure of power without taking into account the usage of different methods and the intensity of public participation. Furthermore, the hierarchical structure of the ladder does not provide the flexibility needed to establish appropriate public participation programs (Tritter & McCallum, 2006).

Many years have passed since 1969, further concepts have been developed and evolved over time to adequately reflect the needs of our today´s understanding of public participation. Creighton (2005) defines public participation as follows:

> *"Public participation is the **process** by which the public concerns, needs, and values are **incorporated** into governmental and **corporate decision making**. It is a **two-way communication and interaction**, with the **overall goal** of **better decisions** that are supported by the public "*

According to the definition public participation is not a one-time event. It is more than simple completing of a voting paper. It is a dialogue. The author does not specify further which level of participation is required in order to meet the expectations on both sides. It is important to consider that the expectation on public participation among the stakeholder can be different (Arnstein, 1969; Creighton, 2005; IAP, 2018). The International Association for Public Participation (IAP) founded in 1990 established a two-dimensional *Public Participation Spectrum* presenting five level of public participation which has become an international standard (**Tab. 1**).

Table 1 IAP2's Public Participations Spectrum

	INFORM	**CONSULT**	**INVOLVE**	**COLLABORATE**	**EMPOWER**
PUBLIC PARTICIPATION GOAL	To provide the public with balanced and objective information to assist them in understanding the problem, alternatives, opportunities and/or solutions.	To obtain public feedback on analysis, alternatives and/or decisions.	To work directly with the public throughout the process to ensure that public concerns and aspirations are consistently understood and considered.	To partner with the public in each aspect of the decision including the development of alternatives and the identification of the preferred solution.	To place final decision making in the hands of the public.
PROMISE TO THE PUBLIC	We will keep you informed.	We will keep you informed, listen to and acknowledge concerns and aspirations, and provide feedback on how public input influenced the decision.	We will work with you to ensure that your concerns and aspirations are directly reflected in the alternatives developed and provide feedback on how public input influenced the decision.	We will look to you for advice and innovation in formulating solutions and incorporate your advice and recommendations into the decisions to the maximum extent possible.	We will implement what you decide.

Increasing Impact on the Decision

Source: Adapted with permission from IAP2 (2018)

With this tool, IAP is providing definitions about the role of the public in each level that helps the user to easily identify the appropriate level of public participation. The tool also indicates to which extent the public can potentially influence decision-making. It is important to understand that the different levels are no stages that requires the completion of the previous one before the next level can be started. All levels need to be read independently from each other. The only relation that could be derived from table 1 is: The higher the level of participation the higher the level of influence by the public on decision-making processes. According to Creighton (2005, p.11), the appropriate level of public participation is selected based on the context and the complexity of the decision. It might be of value to evaluate the appropriateness of the selected level during the course of the decision-making process and to adapted according to the objectives. Interestingly, different stakeholders may have different expectations towards public participation. The selection can be influenced by the different views and by the user assuming to know how the public may want to contribute. It does not necessarily mean that the selected level of public participation meets the expectation of the public or other way around.

There is a challenge to identify the appropriate public participation method. The *Public Participation Spectrum* does not provide any recommendations on public participation methods that can be used at each level. There might be methods that apply to all levels requesting feedback from the public i.e. *consult*, *involve*, *collaborate*, and *empower*. The selection of an appropriate public participation method is a multifactorial decision and requires different factors to be taken into account, e.g. the context, the definition of the public participation goal, the purpose of the public participation project, the expectations of the stakeholder (Rowe & Frewer, 2000, p. 24ff).

In the public domain there are a number of methods described that can be used to plan public participation programs. Rowe & Frewer (2000, p. 7ff) presented an overview on potential public participation methods (**Tab. 2**).

Table 2 Formalized Public Participation Methods

Participation Method	Nature of Participation	Time Scale/Duration	Characteristics/Mechanism
Referends	Potentially all members of national or local population; realistically, a significant proportion of these.	Vote cast at single point in time.	Vote is usually choice of one of two options. All participants have equal influence. Final outcome is binding.

Participation Method	Nature of Participation	Time Scale/Duration	Characteristics/Mechanism
Public hearing/inquires	Interested citizens, limited in number by size of venue. True participants are experts and politicians making presentations.	May last many weeks/ months, even years. Usually held during week- days/working hours.	Entails presentations by agencies regarding plans in open forum. Public may voice opinions but have no direct impact on recommendation.
Public opinion survey	Large sample (e.g., 100s or 1,000s), usually representative of the population segments of interest.	Single event, usually lasting no more than several minutes.	Often enacted through written questionnaire or telephone survey. May involve variety of questions. Used for information gathering.
Negotiated rule making	Small number of representatives of stakeholder groups (may include public representatives).	Uncertain: strict deadline usually set: days/weeks/ months.	Working committee of stakeholder representatives (and from sponsor). Consensus required on specific question (usually, a regulation).
Consensus conferences	Generally, ten to sixteen members of public (with no knowledge on topic) selected by steering committee as "representative" of the general public.	Preparatory demonstrations and lectures (etc.) to inform panelists about topic, then three-day conference.	Lay panel with independent facilitator questions expert witnesses chosen by stakeholder panel. Meetings open to wider public. Conclusions on key questions made via report or press conference.
Citizens´ jury/panel	Generally, twelve to twenty members of public selected by stakeholder panel to be roughly representative of the local population.	Not precise but generally involve meetings over a few days (e.g., four to ten).	Lay panel with independent facilitator questions expert witnesses chosen by stakeholder panel. Meetings not generally open. Conclusions on key questions made via report or press conference.
Citizen/public advisory committee	Small group selected by sponsor to represent views of various groups or communities (may not comprise members of true public).	Takes place over an extended period of time.	Group convened by sponsor to examine some significant issue. Interaction with industry representatives.
Focus groups	Small group of five to twelve selected to be representative of public; several groups may be used for one project (comprising members of subgroups).	Single meeting, usually up to two hours.	Free discussion on general topic with video/tape recording and little input/direction from facilitator. Used to assess opinions/attitudes.

Source: Adapted from Tab. 1 in Rowe & Frewer (2000, p 8ff)

The level of influence may vary among the different public participation methods. Rowe & Frewer (2000, p. 19ff) identified in their paper that the level of influence on decision-making are highest for negotiated rule-making processes and referenda, whereas for public hearing the level is rather moderate because the communication is more oriented in one direction. The public have the opportunity to give presentations about their concerns, but there are often no real dialogues. The influence of consensus conferences, of citizens' jury or panel, and of public advisory committees may vary and be impacted by different factors i.e. "[…] intentions and expectations of the institutions being advised" (Rowe & Frewer, 2000, p. 23).

The clarification of the theoretical framework is important to understand the complexity of *public participation* in decision-making processes and need to be considered in the development of public participation programs and initiatives. Public participation is negotiable. Seeking dialogue with all relevant stakeholder should be the preferred way of communication and can be beneficial in the selection of the appropriate level and method of public participation.

In the next subsection, patient participation in regulatory decision-making processes is discussed.

2.2 Patient Participation in Regulatory Decision-Making Processes

Involving patients in regulatory decision-making processes by the regulators has already been established for three decades at the EMA and FDA. Both agencies worked out areas where patients input is of value. As it has been outlined in the previous subsection, there are different level and methods of public participation. The aim of this subsection is to identify the level of patient involvement and the methods implemented by the EMA and FDA to allow patients to participate in regulatory decision-making processes. Detailed overviews on the initiatives and programs initiated by the agencies are presented in section 4 and section 5.

2.2.1 Level of Patient Participation at the European Medicines Agency

The EMA has developed a "*working methodology*" which resembles the IAP2 Spectrum of Participation developed by the International Association for Public Participation. The "*working methodology*" consists of four level of stakeholder involvement (**Tab. 3**) with the aim to provide a structured framework to ensure transparent and efficient communication and interaction with the various stakeholder

including *"patients and consumers"* (EMA, 2016). However, there are discrepancies in the details of both working methodologies. In comparison to the IAP2 Spectrum of participation, the EMA is covering 4 levels of the IAP2 spectrum. If "cooperate/participate" in the EMA´s "*working methodology*" is equal to "collaborate" in the IAP2 spectrum. This cannot be confirmed, as the EMA to not refer to the IAP2 spectrum. The level of involvement "*empower*" as outlined in the IAP2's Public Participations Spectrum, is entirely absent in the EMAs "*working methodology*".

Table 3 EMA´s Level of Stakeholder Involvement

Level of Involvement	Type of Involvement
Inform	E.g. announcement of review of policy or guidance; information days
Consult	Written – e.g. public consultation on policies or guidance, surveys
Consult and Involve	Direct interactions – e.g. stakeholder meetings, workshops, stakeholder conferences, public hearings
Cooperate/participate	Direct interactions - e.g. technical expert groups (Telematics, ENCePP, focus groups, technical expert groups, as appropriate

Source: Adapted and modified from EMA stakeholder relation management framework (EMA, 2016)

The EMA established a wide variety of methods to engage with patients in regulatory activities (EMA, 2016). The EMA have established a platform to continuously *inform* their stakeholder about their regulatory processes and about activities ahead requiring patient involvement. The decisions taken for a medicinal product will be made available to the public on the EMA homepage as European public assessment reports (EPAR).

The EMA *consults* with patients to review regulatory documents relevant for the public i.e. package leaflets and safety communication before being made public, but the EMA is also seeking for patients input in the review of guidance documents to ensure that patients' perspective is considered (EMA, 2016).

The Pharmacovigilance Risk Assessment Committee (PRAC) recently established public hearings to *consult and involve* the public including patients or patient organisations to obtain input for and experience with a particular medicinal product. The public is invited to support PRACs scientific safety review and decision-making process with their contribution (EMA, 2018) (EMA, 2018). Furthermore, patients can become formal members in scientific committees, working parties and the EMA Management Board. They can also be consulted as experts in scientific advisory group (SAGs) and ad-hoc expert group meetings (AHEG) to inform benefit-risk assessment

of new medicinal products. The EMA established in 2006 the Patients' and Consumers' Working Party (PCWP) representing the interest of patients and consumers at the EMA and in scientific committees (EMA, 2020). Over the time the EMA built a significant network of patient organisations and individual patients which can be consulted to obtain patient input for specific topics.

2.2.2 Level of Patient Participation at the U.S. Food and Drug Administration

At the FDA, no methodological framework about the level of patient participation exists. However, the FDA (2017) published an "*inventory of activity*" including the following five main activities: "*Host & attend meetings*", "*Respond to requests*", "*Outbound communications*", "*Solicit target input*", and "*Inform regulatory decisions*". The inventory provides an overview on the activities to engage with patients and outlines the responsibilities per relevant department i.e Office of Health and Constituent Affairs (OHCA), Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), or Center for Devices and Radiological Health (CDRH) (FDA, 2017). The FDA offers different initiatives as part of the activity "*Host & attend meetings".* The FDA consults with patient representatives in Advisory Committees on scientific product related or on strategy related topics. Expertise from patient representatives can be requested in more than 60 FDA Advisory committees and panels for medicinal products and medical devices (FDA, 2020).

Since 2012, the FDA is engaging with patients on topics related to different disease areas. The FDA conducted 26 FDA-led Patient-Focused Drug Development (PFDD) meetings to specifically obtain patients input on different aspects that i.e. arise by living with a particular disease with the aim to support regulatory decision-making (FDA, 2020). The FDA empowers patient organisations to organise externally led PFDD meetings following the concept of the FDA-led PFDD meetings. In addition to the formal PFDD meetings, the FDA is collaborating with the National Organization for Rare Disease (NORD) to conduct Patient Listening Sessions specifically on rare diseases which are not covered by the formal PFDD meeting program. The Patient Listening Sessions can be requested by the FDA or can be initiated by patients which are held in an informal manner without public involvement (FDA, 2020). Furthermore, the FDA involves patients in different types of public hearings i.e. to gain patients perspective on guidance documents or during the advisory committee meetings (FDA, 2013).

As part of the "*Outbound communication*", the FDA operates a large network of patient representatives who are registered via Patient Representative Program (PRP) (FDA, 2018). The OHCA is responsible for managing the PRP as one example for the "*Inform regulatory decisions*" activity.

The FDA also offers a portal to enable patients and other stakeholder, excluding industry, to ask questions to the FDA or to request a meeting like Patient Listening Sessions which are facilitated by the FDA Patient Affairs Staff (PAS) team (FDA, 2019).

2.2.3 Cross-Agency Program between European Medicines Agency and U.S Food and Drug Administration

In 2016, the FDA and EMA established a *Patient Engagement Cluster* as a platform for the exchange of experiences in the interactions with patients and methods that has been established by both agencies (EMA & FDA, 2016) (FDA, 2018). As one outcome of mutual learning, the FDA was inspired by EMA´s experience with its well-established PCWP. The FDA together with the public-private partnership Clinical Trials Transformation Initiative (CTTI) established a Patient Engagement Collaborative (PEC) following the concept of the EMA´s PCWP.

Regulators are engaging with patients in different ways. However, it is detrimental to identify potential challenges of patient participation in order to gain meaningful input from patients. These challenges are discussed in the following subsection.

2.3 Potential challenges of Patient Participation

Broadly spoken, when involving stakeholders in general, it is always necessary to pay particular attention to the potential challenges that can occur on the side of the regulators but also on the side of the patient representatives. Patient representatives report different challenges when involved in regulatory activities which need to be considered in order to develop measures to overcome them. Those challenges are not only organisational in nature but may be associated with managing limited resources and deficits related to specific content (EMA, 2019). This can be both related to the lack in regulatory background knowledge or scientific aspects (Kuehn, 2018).

The EMA and the FDA have implemented an assessment process to evaluate the aptitude of the patient organisations and the individual patients (EMA, 2018; FDA, 2018). Potential patient representatives need to fulfil a set of eligibility criteria and

receive a training before entering into operation with the agencies. In the US, FDA patient representatives serve as Special Government Employees at the FDA comparable to temporary workers (FDA, 2018).

Both agencies are providing comprehensive training and patient-facing materials on their websites to patients. The materials can be easily accessed like e.g. “EMA Basics” to make regulatory processes more transparent and understandable, or e.g. “FDA – When a patient speaks” videos to prepare the patients for the work in the FDA Advisory committees. At the EU level, there are a number of important initiatives to train patients. The European Patients’ Academy on Therapeutic Innovation (EUPATI) provides guidance to the regulators for the interaction with patients and also offers a 14-month patient expert training in medicines research and development including learning content on medicines regulation to the patients (EMA, 2020; EUPATI, 2020). In addition, patient organisations like the Rare Diseases Europe (EURORDIS) are also offering a very extensive modular training program including topics like the European regulatory framework, benefit-risk assessment and pharmacovigilance, regulatory processes at the EMA, and patient interactions with the EMA (EURORDIS, 2020).

Regulators need to deal with two essential challenges. One challenge is to decide at which timepoint patients needs to be involved and the second challenge is if the patient community is adequately represented to learn what matters most to the entire patient community in a specific disease area to inform regulatory decision-making (Mühlbacher, Juhnke, Beyer, & Garner, 2016; Postmus, et al., 2016; Kuehn, 2018) There is a common consensus that patient perspective is of utmost value in areas of unmet medical need (EMA, 2014; Biotechnology Innovation Organization & Parent Project Muscular Dystrophy, 2016; van Overbeeke, et al., 2019).

3 Regulatory Framework governing Patient Participation in Benefit-Risk-Assessment in the EU

In the EU, interaction with patients is legally embedded in European legislation (see section 3.1). Starting from there, the EMA is continuously working on establishing processes and initiatives to translate the legislation into practice and to enhance the interactions with patients (see section 3.2). Involving patients in the BRA process was successfully demonstrated in a pilot project conducted by the EMA in 2014. Patients were involved in oral explanation meetings for selected products to inform regulatory decision making (see section 3.3.). Patients can be consulted in BRA procedures if the agency deems this to be necessary. The CHMP and the PRAC are the two committees of the EMA that perform BRA of medicinal products. In section 3.4, an overview is provided to demonstrate how patients are involved in BRA today, what tools are used to document patient involvement, and by which method it is presented to the public.

3.1 Legal Framework

The legal foundation for patient representation at the EMA has been defined by the Article 78 of Regulation (EC) No. 726/2004 which regulates the involvement of patient representatives as advisor in EMA scientific committees and in the EMA Management board. The involvement of patient representatives in four of six scientific committees such as the Committee for Orphan Medicinal Products (COMP), the Paediatric Committee (PDCO), the Committee for Advanced Therapy (CAT) and Pharmacovigilance Risk Assessment Committee (PRAC) is regulated in the following provisions (chronological order):

Article 4 (3) of Regulation (EC) No 141/2000 on orphan medicinal products regulates the patient involvement in the COMP:

> *(3) The Committee shall consist of one member nominated by each Member State,* ***three members nominated by the Commission to represent patients' organisations*** *and three members nominated by the Commission on the basis of a recommendation from the Agency.*

Article 4 (1.d) of Regulation (EC) No 1901/2006 on medicinal products for paediatric use is the legal basis for patient involvement in the PDCO:

(d) ***three members and three alternates*** *appointed by the Commission, on the* ***basis of a public call for expressions of interest,*** *after consulting the European Parliament, in order to* ***represent patient associations.***

Article 21 (1.d) of Regulation (EC) No 1394/2007 on advanced therapy medicinal products provided legal framework for patient involvement in the CAT:

(*d)* ***two members and two alternates*** *appointed by the Commission, on the* ***basis of a public call for expressions of interest*** *and after consulting the European Parliament,* ***in order to represent patients' associations***

Articles 61a (d) of Regulation (EU) No 1235/2010 set the legal requirement in involve patients in the PRAC:

(*d)* ***one member and one alternate member*** *appointed by the Commission,* ***on the basis of a public call for expressions of interest****, after consulting the European Parliament, in order to represent patient organisations.*

The number of patient representatives varies across the different Committees. Compared to the CAT and the PRAC, the Regulation on orphan medicinal products does not foresee the nomination of an alternates. Referring to the previous mentioned legislations, committee members are nominated for a 3-year mandate with the option of renewal of three more years.

In addition to the patient representation in the PRAC as outlined above, the PRAC can call for public hearings during safety assessments, if it is deemed necessary. The Article 107j (2) of Directive 2001/83/EC provides the legal basis for this activity. Further patient input is requested per European legislation in case of safety aspects. The pharmacovigilance Regulation (EC) No 1235/2010 and Directive 2010/84/EU defines the legislative framework for the involvement of patients in the reporting of suspected adverse reactions.

The legal framework for involving patients in EMA's work is described in this chapter. In the next chapter, a historical outline and an overview summarizing EMA´s initiatives and programs further elaborating on the information discussed in subsection 2.2 are presented.

3.2 Overview of Initiatives and Programs at the EMA

The EMA has a long history of interacting with patients. Since its foundation, EMA is committed to partner with patients starting with the first patient dialogues in 1996 (**Fig. 1**) (EMA, 2014).As outlined in the previous section, the involvement of patient representatives as committee members was introduced for the first time in European legislation on orphan medicines in the year 2000.

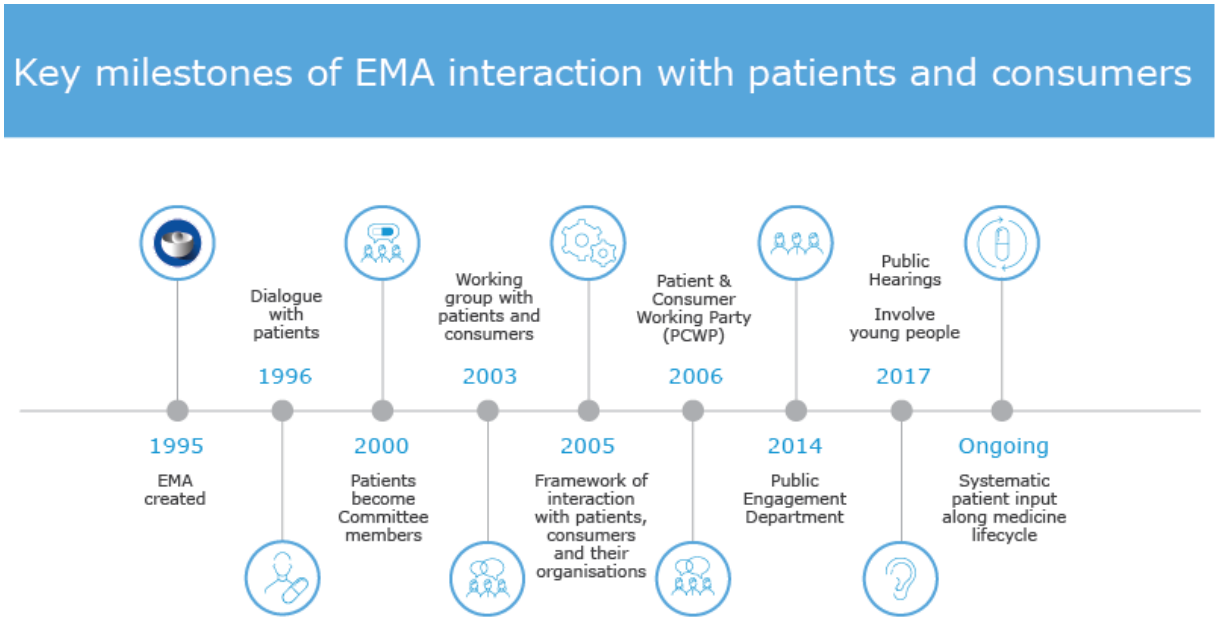

Figure 1 Key Milestones of EMA Interaction with Patients and Consumers
Source: Adapted from EMA Homepage - Patients and Consumer (EMA, 2020)

In 2003, a working group with patients and consumers was implemented for the first time at the EMA, which led to the emergence of the current Patients' and Consumers' Working Party (PCWP) in 2006 to comply with the obligation of the Article 78 (1) of Regulation (EC) No. 726/2004 to establish "[…] *contacts between the Agency and the representatives of […] consumers and patients* […]". The PCWP acts as an important connector between the authority and patients to represent the interests of the patient community in the authority, but also to provide advice in scientific committees and to contribute to the strategic objectives of the EMA. The working group brings together representatives of the Agency and patient organizations (EMA, 2019). The EMA translated the aforementioned legal provision into a strategic framework for the interaction with patients and consumers which was adopted for the first time in 2005 and is available in its amended form since 2014 (EMA, 2014). In this framework, the

EMA has defined the following objectives for the interaction with patients and consumers:

> *"1. Facilitate participation of patients and consumers in benefit/risk evaluation and related activities, to capture patients values and preferences and obtain information on the current use of medicines and their therapeutic environment, all along the lifecycle of the medicines, from early development throughout evaluation and post-marketing surveillance;*
> *2. Ensure that patients, consumers and their representative organisations are listened to and consulted and where appropriate involved in the development of EMA policies and plans;*
> *3. Enhance patients and consumers' organisations understanding of the mandate and role of the Agency and the EU Regulatory Network within the context of the development, evaluation monitoring and provision of information on medicines;*
> *4. Optimise communication tools (content and delivery) to facilitate and encourage the cascade of information to the constituencies of patients and consumers' organisations (i.e. to reach out to individual patients and consumers) with the aim of supporting their role in the safe and rational use of medicines;"*

Furthermore, the EMA has adopted a higher-level management framework in 2016 in which the EMA has defined overarching principles for the interaction with all key stakeholders to ensure a structured and transparent way of working and a trusting relationship with patients across the agency (EMA, 2016). In 2014, the EMA built-up a Public Engagement Department ensuring that these principles are followed.

As already mentioned in the previous chapter, the PRAC issues public hearings during a referral process with the aim to obtain feedback from a wider public on safety aspects concerning a particular medicinal product like the acceptability of risks and the measures proposed by the PRAC i.e. recommendation on additional risk minimisation measures. An example would be the implementation of educational material or incorporation of safety restrictions in the product information.
The following two meetings were held in the past (EMA, 2017) (EMA, 2018):

- 2017 - Valproate and related substances (28 out of 65 participants were patients/patient representatives)
- 2018 - Quinolone and fluoroquinolone antibiotics (40 out of 69 participants were patients/patient representatives)

After the first public hearing, the EMA performed an evaluation of the entire public hearing process based on feedback received via a survey which was provided to all participants. Interestingly, the public participants who responded to the survey judged the guidance document for public hearings covering the entire public hearing process very helpful. The majority of participants appreciated the information received before the public hearing and the introductory presentations given at the beginning of the hearing. The participants also felt that the PRAC was a good listener and engaged during the hearing. Not all participants confirmed that the meeting contributed to a better understanding of EMA's work. However, all meeting participants who responded to the survey found the event a positive experience (EMA, 2018).

Patients are involved in EMA activities based on the scope of representation (**Fig. 2**). There are patients representing the entire patient community in the EMA management board and in the scientific committees as standing members, whereas other patients are representing specific patient organizations. These are more likely involved in PCWP and more focused EMA consultations other than SAG/AHEG to present the view of the entire patient community. Individual patients are more involved in EMA activities that require advice on a specific topic on an ad-hoc basis i.e. SAG, AHEG or review of documents to bring in individual experiences by living with a particular disease (EMA, 2020).

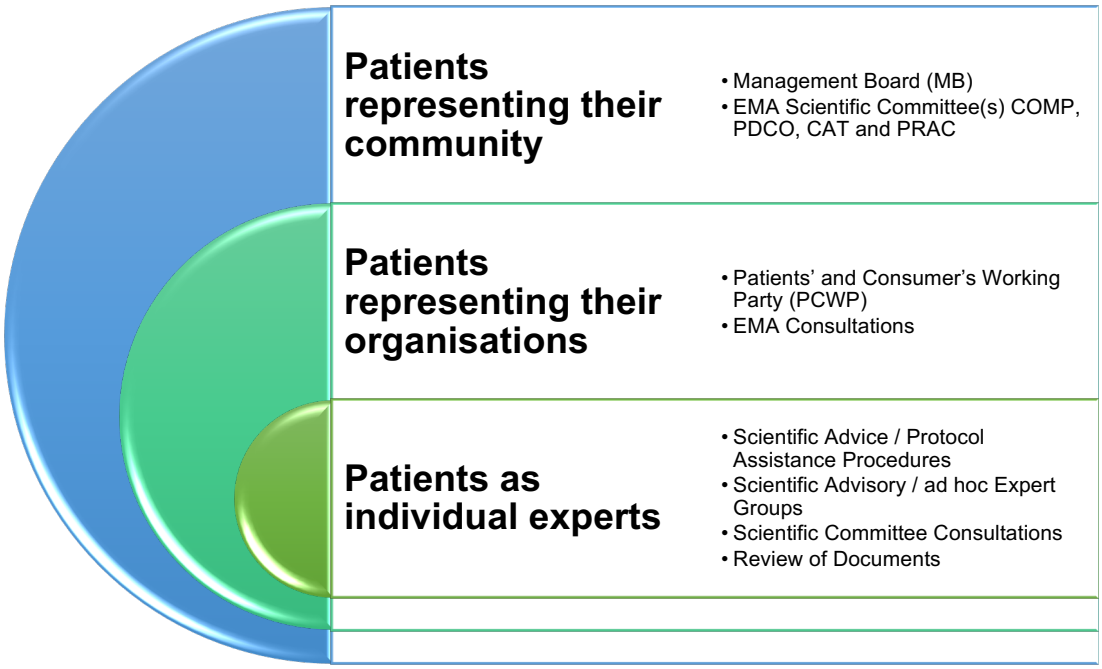

Figure 2 Overview of Patient Involvement in EMA Activities and Scope of Representation

Source: Adapted from EMA Homepage - Getting involved (EMA, 2020)

Patients are involved throughout the entire lifecycle of a medicinal product at the EMA. This can be either for aspects associated with orphan drug applications, pediatric investigational plan applications or scientific advices in the pre-submission phase or during the evaluation of an initial marketing authorization application. As PRAC and CHMP are also responsible for the evaluation of BRA during the post-authorisation phase, patients can also be consulted for any activities which requires patient input i.e. public hearings or variation applications (EMA, 2020).

Table 4 Patient Involvement in EMA Activities

Patient involvement in EMA activities (interactions)	2015	2016	2017	2018	2019
Scientific advice/protocol assistance	76	82	158	107	143
SAGs/ad-hoc expert meetings	23	28	46	37	46
Scientific committee/working party consultations	24	50	104	112	355
Workshops	115	141	138	N/A*	N/A*
Working groups and other ad-hoc activities	313	290	269	N/A*	N/A*
Patient membership in MB, committees, working parties	55	58	59	59	57
Document reviews conducted by patients and consumers	137	120	176	178	169
Total	**743**	**769**	**950**	**552**	**770**

* Following implementation of EMA's Business Continuity Planning in 2018, quantification of these activities has been discontinued.

Source: Adapted and modified from EMA Annual Report 2019 (2020, p. 77)

Over the last 5 years the patient involvement in EMA activities has overall increased (**Tab. 4**) (EMA, Annual Reports 2019, 2020). However, the EMA recorded a decline in the total number of patient interactions in 2018, whereas the patient involvement in Scientific committee/working party consultations increased strongly since 2015. The decline is attributable to the implementation of EMA´s Brexit Preparedness Business Continuity Plan in response the upcoming BREXIT and loss of employees associated with the move to Amsterdam. Some activities were temporarily suspended as a measure of maintaining business continuity of the EMA (EMA, 2017). The EMA conducts surveys on its communication activities every two years as a measure "*to monitor the interaction*" with its stakeholders as described in the *EMA stakeholder relations management framework.* The last survey was completed in 2017, the subsequent survey was postponed to 2020 which is correctly running. In the 2017 survey, 252 out of 615 responses were provided by EMA stakeholders. 16% of 252 respondents were members of patient and consumer organisations. About two-thirds of the stakeholders in the survey agree that the "*EMA engaged sufficiently with*

stakeholders" and the "*EMA was as good or better at engagement than other organisations"* (EMA, 2018). However, the data needs to be interpreted with caution as, it is reasonable to assume that only stakeholders who already interact with the Agency have primarily answered the survey (EMA, 2018).

In March 2020 the EMA adopted the "EMA Regulatory Science to 2025" for veterinary and human medicine. In this paper, the EMA describes the overall strategy for regulatory science for the next five years to prepare for the tasks in response to a rapidly changing and complex innovative pharmaceutical environment:

> *"The regulatory science strategy to 2025 aims to build a more adaptive regulatory system that will encourage innovation in human and veterinary medicine," said Guido Rasi, EMA's Executive Director.*

For the generation of this strategic document, the EMA actively involved from the beginning patient representative groups in the development process. Two stakeholder workshops were held in October 2018 and in November 2019 to gain input from various stakeholder including patient representations groups. The Regulatory Science was also subject of a consultation process to get input from the wider public. Five strategic goals were identified (**Fig. 3**). The objectives highlighted in green include potential areas where patient involvement is considered important. Furthermore, the EMA aims to enhance benefit-risk assessment and the communication to the public. Most important for the evaluation of this master thesis, the EMA committed to include patient preference to inform the benefit-risk assessment by developing guidance documents about patient preferences studies and internal procedures on how to manage patient preference data in the regulatory decision-making process.

The involvement of patients in benefit-risk assessment performed by the EMA is one essential component of this master thesis. In the following section, a selected example of patient involvement in the BRA process of the EMA is described in more detail.

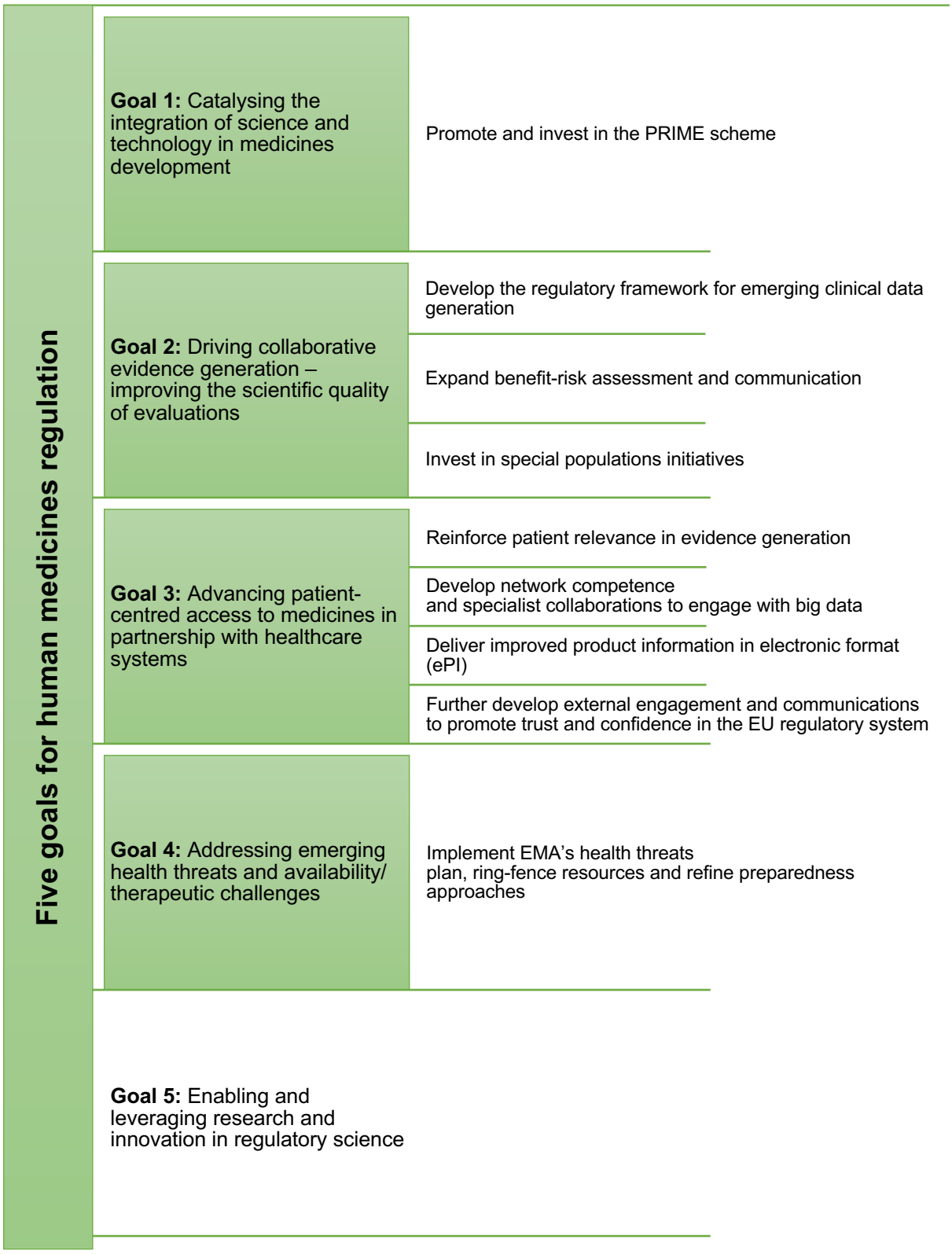

Figure 3 EMA Regulatory Science to 2025 - 5 Goals for Human medicines Regulation

Source: Own presentation based on EMA Regulatory Science to 2025 (EMA, 2020)

3.3 Pilot Project on the Involvement of Patients in Benefit-Risk Assessments

In 2014, the EMA initiated a pilot project to directly involve patients in the benefit-risk discussions at CHMP meetings. As outlined in section 3.4, patients are involved in the BRA process as experts as part of SAGs and AGEHs consulted on an ad-hoc basis (EMA, 2014). The scope of the pilot project was to expand the patient involvement to oral explanations as part of the BRA (EMA, 2014). The pilot project was conducted in the time period from 2014 - 2016 and comprised six oral explanation (OE) for five selected products (**Tab. 5**) (EMA, 2017). Oral explanations are verbal meetings which can be either requested by the EMA or by the Applicant. OEs are usually convened when there are still major concerns and outstanding issues brought up by the agency towards the end of the BRA process. The applicant is given the opportunity to comment on the major concerns in oral form (EMEA, 2008).

Table 5 Medicinal Products involved in the EMA Pilot to involve Patients in B/R Discussions

Invented name	Scenesse	Intuniv	Tecfidera	Kyndrisa	Translarna
Active Substance	Afamelanotide	Guanfacine	Dimethyl fumarate	Drisapersen	Ataluren
Proposed indication	Treatment of erythropoietic protoporphyria (EPP)	Treatment of ADHD in children & adolescents	Treatment of multiple sclerosis	Treatment of Duchenne muscular dystrophy	Treatment of Duchenne muscular dystrophy
Timing oral explanation	September 2014	June 2015	October 2015	May 2016	1. OE: June 2016 2. OE: November 2016
Underlying Procedure	Initial Marketing Authorisation	Initial Marketing Authorisation	Referral	Initial Marketing Authorisation	Initial Marketing Authorisation
Outcome	Approved 22/12/2014	Approved 17/09/2015	Approved 30/01/2014	Withdrawn by Applicant 31/05/2016	Approved 31/07/2014

Source: Own presentation based on EMA Outcome Report on Pilot to involve patients in benefit/risk discussions at CHMP meetings (EMA, 2017)

Abbreviation:

QE = Oral explanation

In total, 14 patients were involved in the pilot project. The products were considered eligible for the pilot project if the responsible rapporteur together with the EMA Product Lead decided that an oral explanation is required for the decision-making process. The patient representatives were supported before and during the oral explanation by EMA employees and members from PCWP. Patients were able to present their views and ask questions, however they were excluded from voting.

Interviewed after the meetings, all patients felt well prepared in terms of sufficient level of product-specific and role-specific aspects. The majority of patients confirmed that the patient perspective was specifically requested during the process, however not all patients were able to contribute to the oral explanation. Those who were able to ask questions or provide comment felt their contributions were considered for discussion during the oral explanation. Overall, the patients expressed that it was very positive experience for them. The feedback received from the CHMP members was largely positive. The vast majority had the impression that the patients were well informed about the topics and were able to provide useful contributions during the oral explanation. Overall, the 17 of 22 responders expressed that the involvement of patients in oral explanations was useful for the discussion. The EMA concludes that in the future patients will continue to be involved in oral explanations if required in that specific situation. However, the EMA also considers seeking patient input outside the formal framework of meetings from a wider audience (EMA, 2017).

In the next subsection it will be presented how patients are currently involved in the benefit-risk assessment process. It is briefly discussed which methods are used by the EMA to gain patients input as well as how the patient involvement and the input from the patient is documented in regulatory documents.

3.4 Patient Perspective in the Benefit-Risk Assessment by the EMA

The PRAC and the CMHP are those two committees performing benefit-risk assessments of medicinal products at the EMA. Patient representatives nominated as a member of the PRAC are directly involved in regulatory decision-making processes associated with the safety of a medicinal product. But patient representatives cannot be nominated as members of the Committee for Medicinal Products for Human Use (CHMP) responsible for regulatory procedures requiring a benefit-risk assessment i.e. initial marketing authorisations or any variations to the initial marketing authorisation (EMA, 2013). However, Article 56 (2) of Regulation (EC) No. 726/2004 provides the

legal foundation for the CHMP to consult with patient representatives via SAGs and AHEGs during the benefit-risk-assessment of a medicinal product and during the re-examination process, if required. In the context of a re-examination, the applicant has the opportunity to request a SAG consultation in accordance to Article 62(1) of Regulation (EC) No 726/2004.

For reasons of transparency, Article 61(8) of Regulation (EC) No 726/2004 requires the EMA to assure public availability of procedures involving working parties and SAGs publicly available. Following this request, the EMA published the following guidance documents associated with SAGs and AHEGs:

- Procedural Advice to CHMP Members (EMEA/361945/2007)
- Procedural Advice for CHMP on the need to convene a Scientific Advisory Group (SAG) or *Ad Hoc* Expert Meeting (EMA/CHMP/551508/2010)
- Mandate, objectives and rules of procedure for the scientific advisory groups (SAGs) and ad-hoc experts group (EMA/117014/2010)
- Incorporating patients' views during evaluation of benefit- risk by the EMA Scientific Committees EMA/413422/2013 – rev. 1)
- The role of members representing patients' and healthcare professionals' organisations on EMA Scientific Committees (EMA/351699/2018 revised).

In the context of the benefit-risk assessment, patient representatives are able to perform the following tasks (EMA, 2015):

- *Participation in scientific advisory / ad-hoc expert group meetings (SAGs) convened by CHMP or PRAC*
- *Respond to ad-hoc consultations on assessment of medicines from all Committees*
- *Review information on medicines: Package leaflets, European Public Assessment Report (EPAR) summaries, safety communications (Q&As)*

Patient representatives who are member of a SAG or AHEG are assigned as permanent experts to a particular SAG or AHEG. But the SAGs or AHEG will only be consulted on an ad-hoc basis by the requesting scientific committee in the following cases (EMA, 2010) (EMA, 2014):

- *When the CHMP is still undecided on a marketing authorisation application for a new medicinal product in an area where there remains an unmet medical need*

and would like to assess the impact of their recommendation on the relevant patient population;

- *When the PRAC and/or the CHMP would like to assess the impact of their recommendation, to maintain, suspend, revoke a marketing authorisation, or to restrict the indication of an authorised medicine, on the relevant patient population.*

The input of SAG or AHEG experts can be requested at different timepoints throughout the entire assessment process:

- Day 120, Day 180, prior to an oral explanation, during a re-examination procedure or during a post-authorisation procedure (EMEA, 2008).

The Rapporteur, Co-Rapporteur or any CHMP member can request a SAG or AHEG meeting, if it is deemed important to get additional input from experts in the field. The CHMP is responsible for the preparation of the list of questions for the SAG or AHEG meetings and confirms whether input from additional experts is required for the evaluation process. If no patient representative is member of a particular SAG or AHEG, suitable patient experts will be invited to cover this part. The SAGs or AHEGs the outcome will be presented to the CHMP by the SAG or AHEG chair (EMEA, 2008) (EMA, 2013). During the last five years, the number of SAG or AHEG consultation requests have increased. However, the number of consultations over the last three years has remained fairly constant (**Tab. 6**).

Table 6 Procedures with SAG or Ad-Hoc Expert Group Involvement

Procedures with SAG or ad-hoc expert group involvement (number of consultations)	**2015**	**2016**	**2017**	**2018**	**2019**
Marketing authorisation (new MAA, new MAA re-examination, art. 58)	7	8	14	19	15
Extension of indication (including line extensions)	2	6	3	10	3
Referral (including re-examination)	3	5	11	3	6
Guideline	1	0	1	0	1
Other topics (renewal, PSUR, signal, class review)	3	0	1	0	2
Total	**16**	**19**	**30**	**32**	**27**

Source: Adapted and modified from EMA Annual Report 2019 (2020, p. 76)

Table 7 EMA Overview on Assessment Reports

Day-80 Assessment Report Clinical Template with Guidance (Revision 02.20)[1]		
Section in the template	**Subsection**	**Guidance**
3. Clinical efficacy	N/A	The report should indicate whether additional expertise is needed e.g. a SAG meeting to address some unresolved clinical issues or the need for further assessment of pharmacovigilance issues.
Day-80 Assessment Report – Overview and D120 LOQ template with guidance (Revision 10.19)[2]		
Section in the template	**Subsection**	**Guidance**
1. <Co><Rapporteur><CHMP> Recommendations	Questions to be posed to additional experts	**Identify the need for additional expert involvement** (e.g. **SAG,** or pharmacovigilance expertise to for example review specific safety concerns or to assess the appropriateness and feasibility of draft protocols in the Pharmacovigilance) and the questions to be posed (e.g. need for pharmacovigilance plan?) Indicate if an Opinion is proposed to be requested from the PDCO related to aspects of the paediatric development. Special expertise in relation with novel emerging therapies (e.g. cellular, tissue products, gene therapy).
3.2.13. Discussion on clinical efficacy	N/A	Describe uncertainties by mentioning what is the source of the uncertainty (e.g., missing data), what is the item that you are uncertain about (e.g., efficacy in a subgroup) and what are the possible coping strategies if possible (e.g., submit further data to reduce uncertainty; acknowledge through labelling changes; **seek expert input**). Key uncertainties that cannot be resolved should be described also under the benefit-risk assessment
3.2.13. Discussion on clinical efficacy	Additional expert consultation	No guidance available
3.2.16. Discussion on clinical safety	Additional expert consultation	No guidance available
5.7.2. Balance of benefits and risks		This assessment will require subjective judgements, but expert (from literature or **expert meetings**) **and patient input** as well as previous decisions for other products in the field should be taken into account and explained, if available

[1] https://www.ema.europa.eu/documents/template-form/day-80-assessment-report-clinical-template-guidance-rev0220_en.docx
[2] https://www.ema.europa.eu/documents/template-form/day-80-assessment-report-overview-d120-loq-template-guidance-rev-1019_en.doc

Day 150 Joint Response Assessment Report – Overview and list of outstanding issues template (revision 07.18)[3] Day 120/180 Joint Response Assessment Report – Overview Template (Revision 07.18)[4]		
Section in the template	**Subsection**	**Guidance**
1. <Joint Co-Rapporteur><CHMP> Recommendation	Questions to be posed to additional experts	No guidance available
3.3.6. Discussion on clinical efficacy	Additional expert consultation	No guidance available
3.3.9. Discussion on clinical safety	Additional expert consultation	No guidance available
5.7. Benefit-risk assessment and discussion	5.7.1. Importance of favourable and unfavourable effects	This assessment will require subjective judgements; expert and patient input (e.g., from literature or expert meetings, Scientific Advisory Groups) as well as relevant previous decisions should be taken into account and explained, if available.
(Co) Rapporteur (Joint) Assessment Report of the Grounds for the Re-Examination Procedure (Revision 06.12)[5]		
Section in the template	**Subsection**	**Guidance**
8. Questions proposed to be addressed to the SAG <name>	N/A	The applicant has <not> requested a SAG. The Rapporteur has <not> recommended a SAG. The SAG should comment on the grounds for negative opinion in view of the grounds for re-examination submitted. In addition, the following questions are raised to the SAG in view of the grounds for re-examination:

Patient involvement is documented in regulatory documents used in the BRA process. **Table 7** provides an overview on all regulatory templates including sections, subsections and guidance provided in the template that address patient involvement which are publicly available on EMAs webpage.

No further instructions are given in the templates with regards to required information to be included in the section for additional expert consultation. These documents will

[3] https://www.ema.europa.eu/documents/template-form/day-150-joint-response-assessment-report-overview-list-outstanding-issues-template-rev-0718_en.doc
[4] https://www.ema.europa.eu/documents/template-form/day-180-joint-response-assessment-report-overview-template-rev-0718_en.doc
[5] https://www.ema.europa.eu/documents/template-form/co-rapporteur-joint-assessment-report-grounds-re-examination-procedure-rev-0617_en.doc

not be published for each centrally authorised product but serve as a basis for the public documentation.

According to Article 13 (3) of Regulation (EC) No 726/2004 the EMA is required to publish a public assessment report and public overview report for each centrally authorised medicinal product assessed by the CHMP in a clear and easy-to-understand format. The tool used for the publication is called European Public Assessment Report (EPAR) which includes the elements outlined in the following table (**Tab. 8**):

Table 8 Overview on the Content of the European Public Assessment Report

Section	Type of information
Overview	Public-friendly overview in question-and-answer format.
Authorisation details	Key details about the product and the marketing authorisation holder.
Product information	Package leaflet and summary of product characteristics; labelling; list of all authorised presentations; pharmacotherapeutic group; therapeutic indications.
Assessment history	Public assessment report for the initial authorisation; public assessment report(s) for any variation concerning major changes to the marketing authorisation; orphan maintenance assessment report or withdrawal assessment report (as of 17 January 2018); tabulated overview of procedural steps taken before and after authorisation.

Source: Adapted and modified from EMA Homepage - European public assessment reports: background and context

In the EPAR, information about patient involvement is reflected in the public assessment report attached to the EPAR. An example of the elements included in the public assessment using the example of Mavenclad is given below. Mavenclad is centrally authorised for the treatment of adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features. During the BRA of Mavenclad a SAG was consulted. The information about the consultations are addressed in the EPARs as follows (**Tab. 9**):

Table 9 Presentation of SAG Involvement in the EPAR - Public Assessment report

EPAR – Public Summary Report (Medicinal Product: Mavenclad)[6]		
Section in the document	**Subsection**	**Content**
1.2. Steps taken for the assessment of the product	N/A	Type of expert consultation
2.5.1. Discussion on clinical efficacy	Additional expert consultation	Reason for consultation, list of question including the answers provided by the experts
2.6.1. Discussion on clinical safety	Additional expert consultation	

[6] https://www.ema.europa.eu/en/medicines/human/EPAR/mavenclad

The EMA is continuously working to improve processes regarding the involvement of patients in benefit-risk assessment and to further optimize the documents relevant for the benefit-risk assessment of a medicinal product and for the public communication. In January 2020, the CHMP adopted a work plan for the year 2020 to define actions addressing these topics.

4 Regulatory Framework governing Patient Participation in Benefit-Risk-Assessment in the US

Patient participation plays an essential role in U.S. drug law. Interacting with patients has played an important role for the FDA ever since. However only since 2012, the request for the development of structured methodology to gain meaningful patient input in drug development and in the regulatory decision-making process of medicinal product is an integral part of FDA´s legislation (see section 4.1). Over time, the FDA implemented several initiatives to strengthen the collaboration with patients (see section 4.2). The FDA meets with patients to gather insights into daily life when living with specific disease to inform regulatory decision-making processes. Importantly, the FDA is continuously working on the development of documents to provide guidance to the external stakeholders for eliciting meaningful patient input during the drug development. This helps to translate the feedback from patients into meaningful endpoints to support patient-focus drug development (see section 4.3). Patients can express their view in oral explanation meetings during the decision-making process of a medical product (section 4.4). The consideration of the patient´s perspective is one import aspect in the FDA´s structured Benefit-Risk-Assessment Framework. The patient involvement is documented in regulatory documents concerning products approved by the FDA. In June 2017, the FDA included a brief statement regarding patient experience data into the medical or clinical review template. This master thesis is focussing on the aspect of incorporating the patient perspective in the BRA process of medicinal products, information relevant to medical devices are not further analysed.

4.1 Legal Framework

Engagement with patients is an essential aspect of the legislation for medicines and medical devices in the US. A significant milestone was achieved with the implementation of the Food and Drug Administration Safety and Innovation Act (FDASIA) in 2012, which amended the Federal Food, Drug, and Cosmetic Act (FD&C Act), and which includes reauthorisation of the Prescription Drug User Fee Act (PDUFA) for the fifth time.

The foundation for *patient participation in medical product discussions* was defined by the section 1137 of the FDASIA that requires the FDA to

- *"(a) develop and implement strategies to solicit the views of patients during the medical product development process and consider the perspectives of patients during regulatory discussions, including by—*
    - *(1) fostering participation of a patient representative who may serve as a special government employee in appropriate agency meetings with medical product sponsors and investigators; and ‘‘*
    - *(2) exploring means to provide for identification of patient representatives who do not have any, or have minimal, financial interests in the medical products industry."*

To meet the requirements, the FDA, together with various stakeholders, has developed performance goals and procedures for PDUFA V for the fiscal years (FY) 2013 - 2017. PDUFA was created by Congress in 1992 and authorizes the FDA to collect fees from pharmaceutical companies to ensure the funding of a 5-year-period and enable the FDA to allocate the necessary resources to enhance and accelerate approval processes. The PDUFA can be re-authorized every 5 years (FDA, 2020). As part of the re-authorisation process, the FDA is developing commitments which need to be agreed by the congress and become part of the respective amendment to the FD&C act. With PDUFA V, the FDA committed to enhance benefit-risk assessment in regulatory decision-making by develop a five-year plan to

> *"further develop and implement a structured benefit/risk assessment in the new drug approval process for the FY 2013 – 2017* and to *implement a more systematic and expansive approach to obtaining the patient perspective on disease severity or unmet medical need by hosting public meetings focussing on different diseases"* (FDA, 2013).

The FDA committed to conduct 20 Patient-Focused Drug Development (PFDD) meetings. In April 2013, the FDA announced in the Federal Register the assignment of the disease areas which are subject of the PFDD meetings. In the selection process of the disease areas the public was requested to provide input in a public meeting. In addition to PDUFA V commitments, the 21st Century Cures Act (21st CC Act) was signed by the U.S. President into law in December 2016. Further, the 21st CC Act, an amendment to the FD&C Act, *"[…] is designed to help accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently"* (FDA, 2020). This law built on already existing initiatives defined in PDUFA V. With this law, the FDA is committed to further strengthen activities

on developing processes to incorporate patient perspectives into regulatory decision-making.

It is described Section 3001/title III of the 21st CC Act is described that the FDA is obliged to include "[…] *a brief statement regarding the patient experience data and related information, if any, submitted and reviewed as part of such application patient experience data."*

Patient experience data (PED) are defined as follows in the 21st CC Act:

> *"(c) Patient experience data*
>
> *For purposes of this section, the term patient experience data includes data that—*
>
> > *(1) are collected by any persons (including patients, family members and caregivers of patients, patient advocacy organizations, disease research foundations, researchers, and drug manufacturers); and*
> >
> > *(2) are intended to provide information about patients' experiences with a disease or condition, including—*
> >
> > *(A) the impact of such disease or condition, or a related therapy, on patients' lives; and*
> >
> > *(B) patient preferences with respect to treatment of such disease or condition."*

The 21st CC Act requires the FDA to implement the patient experience statement for all New Drug Applications (NDA) according to section 505 (b) of the FD&C Act and for all Biologics License Applications (BLA) according to section 351(a) of the Public Health Service Act which have been submitted after 12 June 2017 - at least 180 days after the 21st CC Act came into force in December 2016. The publication of a brief statement concerning any patient experience data or related information that was part of the application is also requested in Section 2 of the Patient-Focused Impact Assessment Act, adopted in 2016. Furthermore, the FDA is required according to section 5 of the Patient-Focused Impact Assessment Act to include the involvement and evaluation of patient experience data in the assessment.

Section 3002/title III of the 21st CC Act requires the FDA to develop a plan for Patient-Focus Drug Development Guidance documents *"regarding the collection of patient experience data, and the use of such data and related information in drug development*." This section also describes specific requirements on content of the

guidance documents considering methodological aspect with regards to data collection, reporting, management and analysis of patient experience data. The guidance documents should address methods to collect patient experiences and preferences, methods to measure the impacts to patients and methods for clinical outcome assessments. The guidance documents should also include information about the content and format of a required submission for external stakeholder who wants to submit a draft guidance and on procedures for the management of such submissions. Finally, the law is requesting a concept on using patient experience data in the benefit-risk assessment.

Based on the experience gathered from the disease-specific PFDD meetings conducted under PDUFA V and the provisions outlined in the 21st CC Act, the FDA committed under PDUFA VI adopted in 2017 to sequentially develop four PFDD guidance documents during the fiscal years 2018 – 2022.

Building on the legal framework, the next chapter is providing an historical outline and overview on the initiative and programs associated with patient involvement at the FDA. As in the previous chapters, the following section will focus on initiatives and programs for patient involvement related to medicinal products.

4.2 Overview of Initiatives and Programs at the FDA

The FDA has a long track record of engaging with patients in the regulatory decision-making process. Starting in the late 1980ies, the FDA engaged with HIV/AIDS patients. This was triggered by the need to accelerate the development of anti-HIV treatments and the need of an expedited review process by the FDA to make adequate treatment to the HIV patients earlier than in the past (Levitan, Hauber, Damiano, Jaffe, & Christopher, 2017). The first patient representative became member of the FDA´s Advisory committee in 1993. However, it wasn't until three years later that patient representatives were eligible to vote. Over time, the role of a patient representative changed more into a consultative role (FDA, 2020).
As already outlined in the previous section, the FDA introduced in 2012 the Patient Focus Drug Development Initiative which is further described in the upcoming section.

In 2017, a new team was established within the FDA to ensure that patient engagement activities are well coordinated across the entire agency. The Patient Affairs Staff (PAS) team is not only responsible for collaborating with internal FDA departments on patient engagement activities but also for creating and maintaining relationships with the

pubic. The PAS team is coordinating the Patient Engagement Collaborative (PEC) which has been established by the FDA in collaboration with the CTTI (**Tab. 10**).

Table 10 Initiatives for Patients to Engage With FDA

	FDA-led Patient-Focused Drug Development (PFDD) Meetings	Externally led PFDD Meetings	NORD MOU Pilot Listening Sessions	Patient Engagement Collaborative (PEC)	Patient Representative Program (PRP)
Purpose	Public meetings that systematically obtain the patient perspective on specific diseases and their treatments	To allow patient organizations to identify and organize patient-focused collaborations to generate public input on other disease areas, using the process established through FDA-led PFDD meetings as a model	Pilot listening sessions in rare diseases to inform FDA staff of disease and treatment burden in rare diseases	A forum to discuss and share experiences on patient engagement in medical product development and regulatory discussions	FDA Patient Representative ℠ consultants provide direct input to inform the Agency's decision-making associated with medical products for drugs, biologics, and medical devices in a public advisory committee meeting or as part of agency-directed assignments
Medical Product Type Covered	Biologics, Drugs	Biologics, Drugs	Biologics, Devices, Drugs	Biologics, Devices, Drugs	Biologics, Devices, Drugs
Topics Covered	Symptoms and daily impacts that matter most to patients, patient perspectives on current treatment approaches, and topics such as clinical trial considerations and meaningful benefit may also be explored	FDA welcomes host organizations to have public meetings to discuss symptoms and daily impacts that matter most to patients, patient perspectives on current treatment approaches, and topics such as clinical trial considerations and meaningful benefit may also be explored.	Treatment, disease burden, quality of life, division-specific questions	Patient engagement operations	Regulatory medical product review

Source: Adapted and taken from Initiatives For Patients to Engage With FDA (FDA, 2019)

The PEC serves as a platform for individual patients and patient organisations to discuss with members from the FDA and CTTI on methods to enhance patient engagement in regulatory decision-making processes.
The PEC was explicitly requested by the public during the open review phase of the FDA activities proposed under FDASIA. As outlined in section 2.2, the PEC is based on EMA´s PCWP model. At present, 16 members were nominated after a public call published in the Federal register. Members are appointed for a period of 2 to 3 years. (FDA, 2018) Since the inaugural meeting held in August 2018, the PEC met four times discussing topics like i.e. the development of a How-To guide for patients, aspects associated with communication to the public, or discussions on a new program for FDA Community Ambassadors to enhance communication with the aim to reach the wider community (FDA and CTTI, 2019).

Table 10 gives a brief overview on all the patient engagement initiatives in the context of medicinal products which have been implemented so far by FDA. The NORD MOU Pilot Listening Sessions and the Patient Representative Program are briefly summarized in section 2.2.

In the next chapter, the underlying initiative for FDA-led PFDD meetings and externally led PFDD Meetings as outlined in table 10 is analysed in more detail. These measures provide the framework for integrating patient information into drug development and FDA´s decision-making processes.

4.3 Patient-Focused Drug Development Initiative

The Patient-Focus Drug Development initiative has been launched in 2012. FDASIA, passed in 2012, provided the foundation for this initiative. The Patient-Focus Drug Development Initiative connects different components triggered by FDA law with the aim to *ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation* (FDA, 2020).

Patient-Focused Drug Development Meetings

As already outlined in section 4.1 in this master thesis, the FDA was required to conduct 20 FDA-led Patient-Focused Drug Development meetings for specific diseases in order to obtain patients input on different aspects that arise by living with a particular disease to inform regulatory decision-making (FDA, 2020).

During the period 2013 – 2017, the FDA led 25 PFDD disease specific meeting which are documented in “The Voice of the Patient” reports (**Tab. 11**). All “The Voice of the Patients Reports” are publicly available. The first PFDD meeting was held in 2013 to obtain patient perspective living with the chronic fatigue syndrome and myalgic encephalomyelitis, the interviews were based on a pre-defined set of questions (FDA, 2013). The patients provided testimonials on specific disease symptoms as well as the impact on daily life and the patients shared their experiences concerning the available treatment options. The FDA-led meetings were considered meaningful with outcome that the meetings were to pursue outside the PDUFA V requirements. Since that time, the FDA conducted additional two meetings and there are plans to conduct another three meeting in 2020. Interestingly, the FDA is encouraging patient organisations to organise externally led PFDD meetings following the concept of the FDA-led PFDD meetings (FDA, 2019).

Table 11 FDA-led Patient-Focused Drug Development (PFDD) Meetings

Year	Disease
2013	• Chronic Fatigue Syndrome/Myalgic Encephalomyelitis • Human Immunodeficiency Virus (HIV) • Lung Cancer • Narcolepsy
2104	• Female Sexual Dysfunction • Fibromyalgia • Hemophilia A, B, and Other Heritable Bleeding Disorders • Idiopathic Pulmonary Fibrosis • Inborn Errors of Metabolism • Pulmonary Arterial Hypertension • Sickle Cell Disease
2015	• Alpha-1 Antitrypsin • Breast Cancer • Chagas Disease • Functional Gastrointestinal Disorders • Huntington’s disease • Non-tuberculous Mycobacterial Lung Infections • Parkinson’s Disease
2016	• Neuropathic Pain Associated with Peripheral Neuropathy • Patients Who Have Received an Organ Transplant • Psoriasis
2017	• Alopecia Areata • Autism • Hereditary Angioedema • Sarcopenia
2018	• Chronic Pain • Opioid Use Disorder

Source: Own presentation based on FDA PFDD Webpage (FDA, 2020)

To complement this effort, the FDA committed to develop a series of four PFDD guidance documents including methods to gather meaningful patient input during drug development of a medicinal products.

Patient-Focused Drug Development Guidance Series

Following section 3002 of the 21st CC Act, the FDA was requested to plan the development of PFDD guidance documents. The FDA published in 2017 a *Plan for the Issuance of Patient-Focused Drug Development Guidance* including a dedicated timetable. (FDA, 2017). Furthermore, the implementation of the plan and the development of the guidance documents is further specified in the PDUFA VI commitment letter agreed by the congress in 2017 (FDA, 2018). Based on requirements with regards to the content of each guidance as outlined in the 3002 (1) – (4) of the 21st CC Act, the FDA proposed the following four methodological guidance documents which will be developed sequentially until 2021 (FDA, 2018):

1. Patient-Focused Drug Development: Collecting Comprehensive and Representative Input. Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders
2. Patient-Focused Drug Development: Methods to Identify What Is Important to Patients - Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders
3. Patient-Focused Drug Development Guidance: Methods to Identify What is Important to Patients and Select, Develop or Modify Fit-for-Purpose Clinical Outcome Assessments
4. Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-Making

The first guidance describes points for consideration for the planning of collecting meaningful patient input (FDA, 2020). The draft guidance was published in June 2018. Building on the first guidance, the second guidance provides an overview on qualitative and quantitative methods for the elicitation of patient information. The draft guidelines have been published with a delay in October 2019 and the FDA scheduled the finalisation for beginning 2021 (FDA, 2017). The purpose of the third guidance document is to provide guidance for the identification and development of instruments to properly measure patient impacts. The fourth guidance is linked to the previous one and outlines the translation of Clinical Outcome Assessment into endpoint to inform regulatory decision-making. For the last two guidance documents, the FDA scheduled

the publication of the drafts in Q2 2020 (FDA, 2017). Until the issuance of this master thesis, the FDA had not yet published any drafts. Public consultation meetings for both guidance documents were hold in 2019 (FDA, 2020). With this set of guidance documents, the FDA is providing a solid basis to their stakeholder to collect meaningful patient input during drug development to inform regulatory decision-making.

In the next section, an outline is provided to describe the role which patients play in FDA advisory committee meetings. Furthermore, it is discussed how patient perspective is addressed in the FDA´s framework of structured benefit-assessment. The FDA make all review documents of approved medicinal products publicly available. Efforts have been made to investigate how patient perspective or patient involvement is documented in the FDA assessment documents.

4.4 Patient Perspective in the Benefit-Risk Assessment by the FDA

The FDA is engaging with patient at different levels to get their view on disease or product related aspects to inform regulatory decision-making. As outlined in the previous section the FDA listen to the patients on specific disease aspects either in FDA-led or in externally led PFDD meetings. The FDA leverages information from informal disease specific Patient Listening Session which are briefly mentioned in section 2.2 to gain patient input on diseases which are not covered by the PFDD initiative (FDA, 2020). The outcome of the disease specific PPFD meetings can be used by the medical reviewer to include the patient´s perspective in the regulatory decision-making process (FDA, 2018). In addition, patients are invited to contribute to the regulatory decision-making process of a particular medicinal product in advisory committee meetings.

Advisory Committee

The procedure for the conduct of FDA advisory committees it outlined in 21 CFR Part 14[7]. Advisory committee meetings will be scheduled on an ad-hoc basis during an ongoing evaluation of a medicinal product, if it is deemed to be necessary. As described in 21 CFR 14.25 (a), every advisory committee meeting includes an open public hearing (OPH) session. Patient who are interested to contribute on particular aspects discussed are invited to join those sessions for discussion. The public can provide input either in writing or via an oral presentation. Advisory meetings are

[7] 21 CFR Part 14 (https://www.ecfr.gov/cgi-bin/text-idx?SID=8ba66e254c1bc66ea11a1457159ea187&mc=true&node=pt21.1.14&rgn=div5#se21.1.14_125)

announced in the Federal Register. Patients can join individually or representing a patient organisation. Participants need to register for the participation. The contribution needs to be provided in writing as part of the registration upfront the meeting (FDA, 2013). Through the Patient Representative Program (PRP), the FDA has a pool of patient representatives being trained on regulatory aspects and the course of events in a scientific committee meetings (FDA, 2018). Patients who participate in this program are temporary employees of the FDA, so-called special government employees. The meeting minutes of each FDA advisory committees are published on the FDA´s Homepage. In the meeting minutes it is clearly highlighted if patient representatives participated in the FDA advisory committees. Furthermore, the outcome of the FDA advisory committee is also reflected in the medical review document section *9.3 Advisory Committee Meeting*[8]. If a meeting was conducted, the section summarises the questions and the documents provided to the advisory committee. The full results will be appended to the review document. The implications of the advisory committee input to the recommendations will also be discussed in section 9.3.

Framework of Structured Benefit-Risk Assessment at the FDA

Under PDUFA V, the FDA committed to enhance the benefit-risk assessment in the regulatory decision-making process by developing a structured framework which is the core of regulatory decisions concerning medicinal products (FDA, 2013).

Table 12 FDA Benefit-Risk Framework

Benefit-Risk Integrated Assessment		
Benefit-Risk Dimension		
Dimension	**Evidence and Uncertainties**	**Conclusion and Reason**
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk and Risk Management		

Source: Adapted and taken from Benefit-Risk Assessment in Drug Regulatory Decision-Making (FDA, 2018)

[8] FDA, Medical Review Template: https://www.fda.gov/media/72472/download

Table 12 presents the full concept in table format. The FDA Framework of the benefit-risk assessment consists of two components. The first component is the *Benefit-Risk Integrated Assessment* in the top part of the table. In *Benefit-Risk Integrated Assessment* section, all aspects identified in the second component of the framework, in the Benefit-Risk Dimension, are summarized and discussed. In the Dimension part, the *evidence and uncertainties* for the 4 dimensions *Analysis of Condition, Current Treatment Options, Benefit and Risk and Risk Management* are compiled and a conclusion is provided. These aspects in total serve as the basis for the regulatory decision (FDA, 2013) (FDA, 2018).

Table 13 Patient Perspective in the Framework of Benefit-Risk Assessment

Benefit-Risk Framework Section	Key Considerations	Common Sources of Uncertainty
Analysis of Condition	• Patient-focused disease burden	• Extent of patient input on disease burden
Current Treatment Options	• Burden of treatment (e.g., administration) • Aspects of disease burden not addressed by current therapies	• Extent of patient input on unmet needs
Benefit	• Clinical relevance of the study endpoints: ability to measure or predict clinical outcomes of importance to patients • Magnitude, duration of treatment effects o Nature of benefit (e.g., disease modifying, symptom reduction) o Ability for patient/provider to assess individual benefit o Patient perspectives on benefit	• Extent of patient input on the significance of expected benefits

Source: Adapted and taken from (Mullin, 2020)

The FDA has also considered the inclusion of the patient perspective in the development of the framework and identified areas where patient input is of importance for the benefit-risk assessment (FDA, 2013). The FDA concluded that patient perspective might be of relevance for the dimension *Analysis of Condition* and *Current Treatment Options* as highlighted in grey in **table 12**. Theresa M Mullin, PhD from FDA´s CDER, recently presented in the Drug Information Association (DIA) congress in June 2020 a more detailed overview on how patient input can contribute to the

overall benefit risk assessment (**Tab. 13**). The FDA updated the medical review template to incorporate the *Statement on Patient Experience Data and related Information* to comply with the provision under 3001 of the 21st CC Act. According to the 21st CC Act, the FDA is requested to publish the statement for all approved NDAs and BLAs submitted starting 180 days after enactment of the 21st CC Act, as from 12 June 2017. **Figure 4** presents the current structure of the documents.

1.4. **Patient Experience Data**

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.	

Figure 4 Statement on Patient Experience Data and Related Information
Source: Extract from medical review document for the medicinal product Revcovi[9]

The FDA is required to consider PED which are either part of the application or which are not part of the application but considered during the review. The first check box in column one of the statement covers patient experience data submitted by the Applicant. The second check box of the statement covers patient experience data gathered by the FDA. The third check box of the statement is to confirm that no patient experience data was submitted by the applicant.

[9] FDA, Medical Review Document for the medicinal product Revcovi: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761092Orig1s000MedR.pdf

5 Evaluation of Patient Perspective incorporated in the BRA of Medicinal Products

As presented in the previous section, the EMA and the FDA are engaging with patients in the benefit-risk assessment of medicinal products. Both Agencies implemented different methods to gain patient perspectives to inform regulatory decision-making. The following subsection will describe the objectives, methods, and results of the evaluation concerning structured incorporation of patient perspectives into benefit-risk assessments of medicinal products by the EMA and FDA.

5.1 Objective

The objectives of this evaluation are to (1) assess the type of methods which are used by both agencies to involve patients in benefit-risk assessment process. Furthermore, it will be investigated for (2) which type of medicinal products the EMA and FDA primarily consider the involvement of patients. The next step is to examine (3) how transparent patient involvement has been documented in regulatory assessment reports which are publicly available.

5.2 Method

The basis for this evaluation are the assessment reports for medicinal product approved by the FDA and EMA which are publicly available on their webpages. The following electronical sources were used for the identification of the relevant assessment reports:

- EMA Webpage - Download medicine data[10] - Excel File of all EPARs for human and veterinary medicines
- FDA Webpage - Drugs@FDA: FDA-Approved Drugs[11]

5.2.1 Selection Criteria

A search was conducted in the above-mentioned electronical sources. The search was limited to medicinal products which were approved in the time period from 01 January 2017 – 31 December 2019.

[10] EMA, Download medicine data: https://www.ema.europa.eu/en/medicines/download-medicine-data
[11] FDA, Drugs@FDA: FDA-Approved Drugs: https://www.accessdata.fda.gov/scripts/cder/daf/

For the FDA, monthly reports were exported from the Drugs@FDA webpage for the given time period. For the EMA, an excel file was downloaded including all the human and veterinary medicinal product data dating back to the year 1995.

For the U.S., only medicinal products which were submitted via a NDA with the submission classification code: *Type 1 - New Molecular Entity* and via BLA were considered in the evaluation (FDA, 2015)**.** For BLAs, no submission classification coding exists. For the EU, only medicinal products submitted in accordance to article 8 (3) of Directive 2001/83/EC representing a full and independent application were considered in the evaluation. By applying the above method, the focus was on new entity medicinal products. For both regions, Generics, Biosimilars, Vaccines, and Diagnostics were not specifically analysed.

Only approved medicinal products were included in the assessment. Furthermore, data of special regulatory pathway i.e. Orphan medicine, Priority Review, Breakthrough Therapy, Fast Track, Accelerated Assessment, Conditional Approval, or Exceptional Circumstances were collected for the assessment. The EMA provides that type information in the excel file of all EPARs for human and veterinary medicines. For the FDA, the reports listed in **table 14** were used the confirm the special regulatory grants. Information about priority review and orphan drug status is provided for each product on Drugs@FDA.

Table 14 Additional FDA Reports covering special regulatory Grants

Special Regulatory Grants	Report
Accelerated Approval	Cumulative report on CDER Drug and Biologic Accelerated Approvals Based on a Surrogate Endpoint[12]
Breakthrough Therapy	Cumulative report on CDER Breakthrough Therapy Designation Approvals[13]
Fast Track	2017 CDER Fast Track Calendar Year Approvals[14] 2018 CDER Fast Track Calendar Year Approvals[15] 2019 CDER Fast Track Calendar Year Approvals[16]

Source: Own presentation

[12] https://www.fda.gov/media/88907/download
[13] https://www.fda.gov/media/95302/download
[14] https://www.fda.gov/media/128780/download
[15] https://www.fda.gov/media/123571/download
[16] https://www.fda.gov/media/128976/download

5.2.2 Search method

In the first step, all relevant chapters of the included assessment reports regarding patient involvement were examined. The relevant chapters of the assessment reports are presented in **table 15**:

Table 15 Relevant Chapters in the Assessment Reports

Regulatory Body	FDA	EMA
Source	Medical or Clinical Review Document	European Public Assessment Reports and the attached Public Assessment Report
Relevant chapters	1.3 Benefit-Risk Assessment 1.4 Patient Experience Data 9.3 Advisory Committee Meeting	1.2. Steps taken for the assessment of the product 2.5.1. Discussion on clinical efficacy - Additional expert consultation 2.6.1. Discussion on clinical safety - Additional expert consultation

Source: Own presentation

In a second step, a manually search was conducted based on the keywords listed in **table 16**:

Table 16 Search Criteria for the Manual Research

Search Criteria for the Manual Research			
Represent*	Advisory	Perspective	Preference
Consumer	Committee	Input	Patient-focus*
Patient	Interviews	Involv*	Burden
Expert	Consult*	Experience	Disease

Source: Own presentation

5.2.3 Data analysis

Excel was used for the data analysis and the visualisation of the results. Two separate excel files were generated to cover the different aspects i.e. different types of application, special regulatory pathways and methods of patient involvement for both regions. The raw data for medicinal products approved by the EMA are attached as **Annex 1** to the thesis.

5.3 Results

The results of the evaluation of the assessment reports are presented separately per agency.

5.3.1 EMA - Presentation of Results

For the EMA, 118 out of 1170 medicinal products were included in the evaluation. Thousand-fifty-two medicinal products were excluded from the assessment based on the exclusion criteria listed in f**igure 5:**

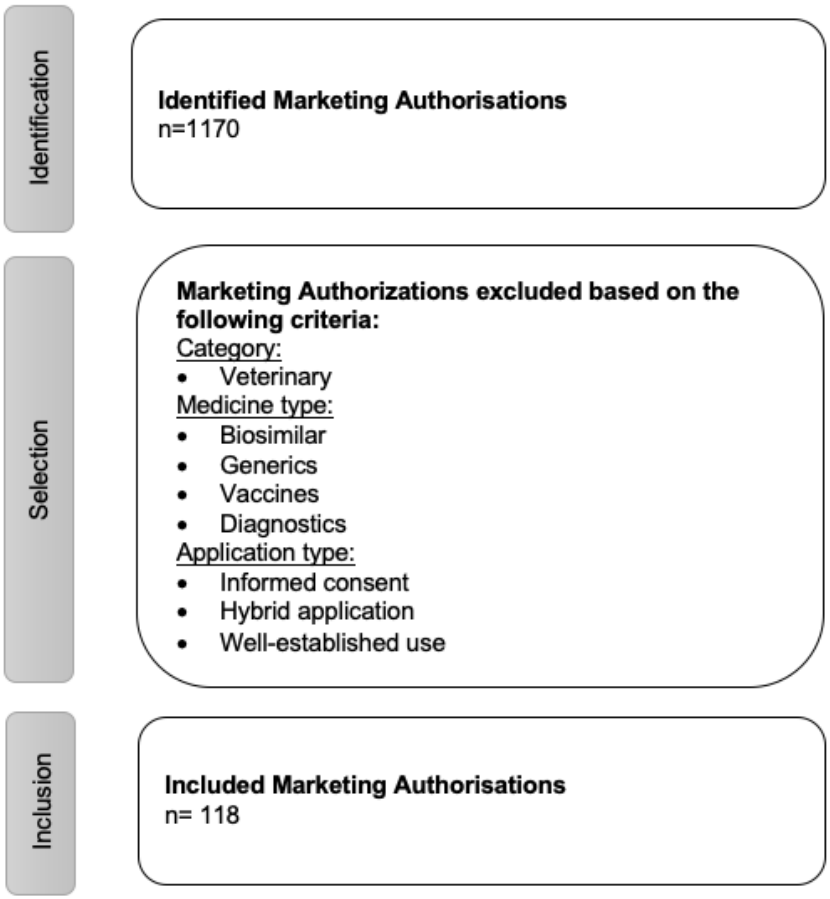

Figure 5 Selection Process for Medicinal Products approved by the EMA
Source: Own presentation

The majority (57%) of the medicinal products included in the evaluation are chemicals, while 37% of 118 were biologicals. Only three ATMPs and three Gene Therapies were included in the evaluation (**Fig. 6**).

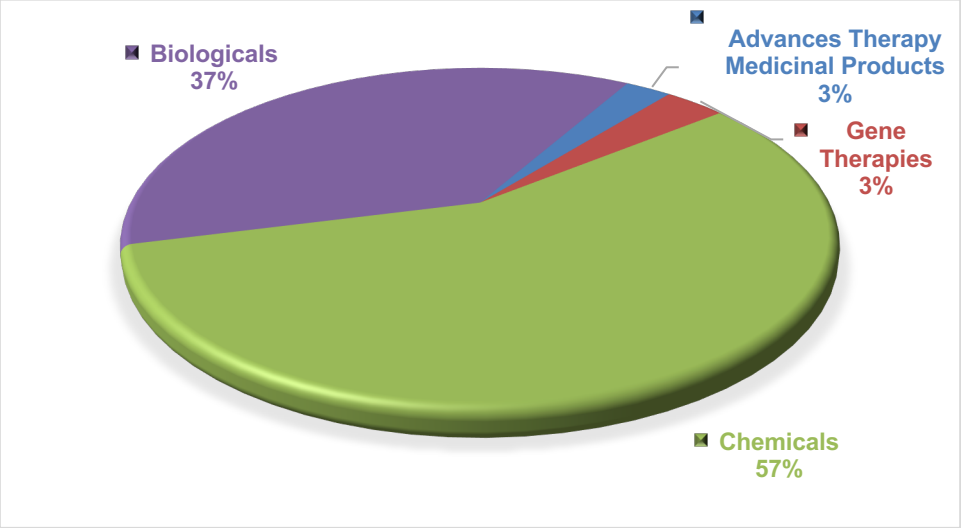

Figure 6 Characteristics: Type of Medicinal Products EMA (n=118)
Source: Own presentation

Thirty-seven out of 118 are orphan medicines. Only a few of the medicinal products were authorised via accelerated procedures (n=12), conditional approval procedure (n=10) or under exceptional circumstances (n=5) (**Fig. 7**).

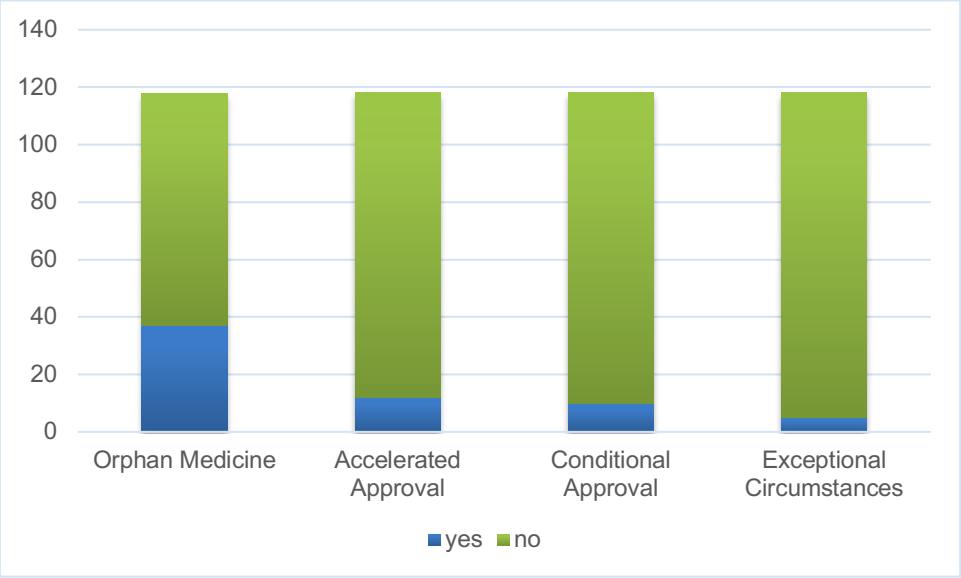

Figure 7 Characteristics: Special Regulatory Pathways EMA (n=118)
Source: Own presentation

Based on the included public assessment reports, the EMA consulted exclusively with patients via Scientific Advisory Groups and Ad-Hoc Expert Groups (**Fig. 8**).

Of 118 included medicinal products, SAGs or AHEGs were consulted for 22 medicinal products. Overall, 23 SAGs and AHEGs were requested by the EMA. For one medicinal product, the SAG was consulted two times. In only 9 out of 23 cases, the available documentation showed that patient representatives were consulted.

Three SAGs and AHEGs were consulted outside of the investigation time period. This is because the marketing authorisation date is used to limit the investigation period.

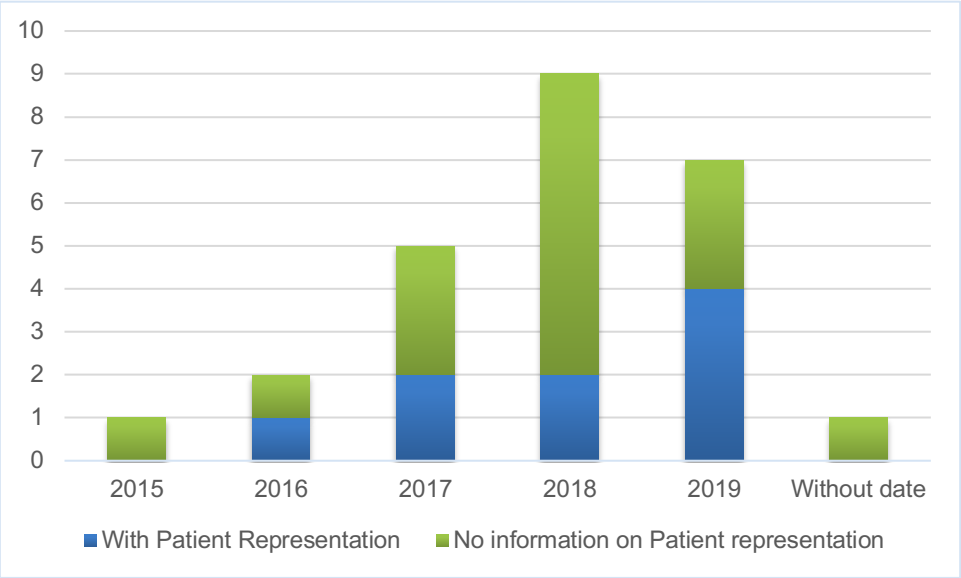

Figure 8 Number of SAGs and AHEGs per Year (n=23)

Source: Own presentation

Interestingly, for none of the included ATMPs SAG or AHEG were consulted. The majority (65%) of the SAGs or AHEGs were request for chemicals (**Fig. 9**).

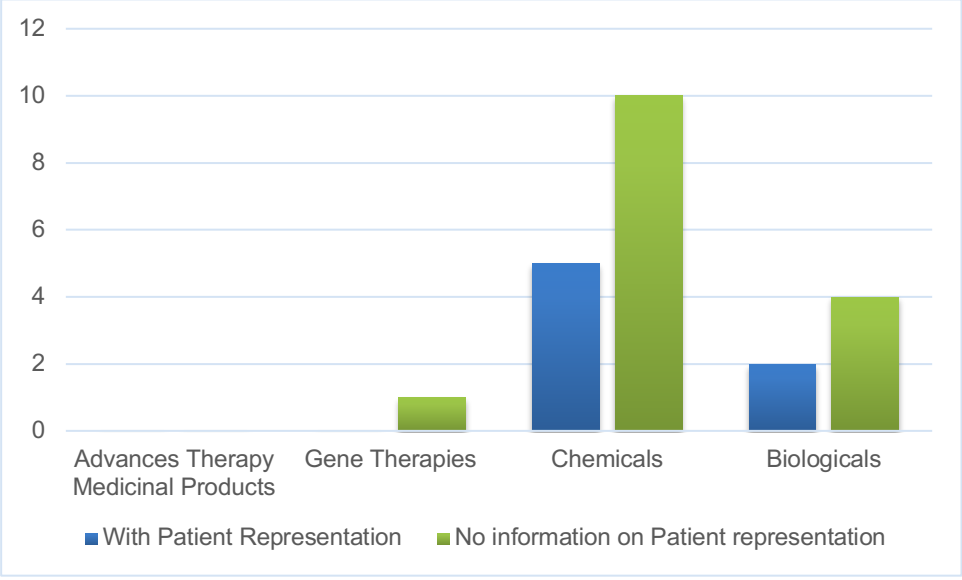

Figure 9 Number of SAGs and AHEGs per Type of Medicinal Product (n=23)

Source: Own presentation

The number of SAG or AHEG consultation (n=7) for the included medicinal products with special regulatory pathways i.e. Orphan Medicine or approval under exceptional circumstances are far behind the expected quantity. For medicinal products which received an accelerated approval (n=12) or conditional approval (N=10), the CHMP did not request advice from a SAG or AHEG (**Fig. 10**).

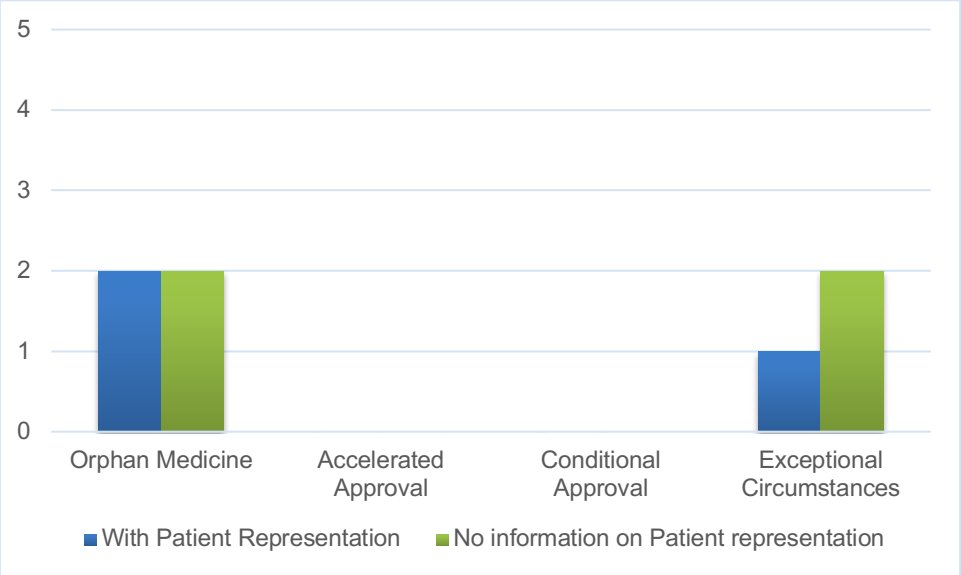

Figure 10 Number of SAGs and AHEGs per Special Regulatory Pathways (n=7)
Source: Own presentation

5.3.2 FDA - Presentation of Results

For the FDA, 137 of 460 identified medicinal products which were approved in the time period from 01 January 2017 – 31 December 2019 were eligible for the inclusion in the assessment. **Figure 11** presents the selection process of the identified medicinal products which submitted either via a NDA or BLA procedure. Three hundred-twenty-three medicinal products were excluded from the assessment based on the exclusion criteria listed in **figure 11**:

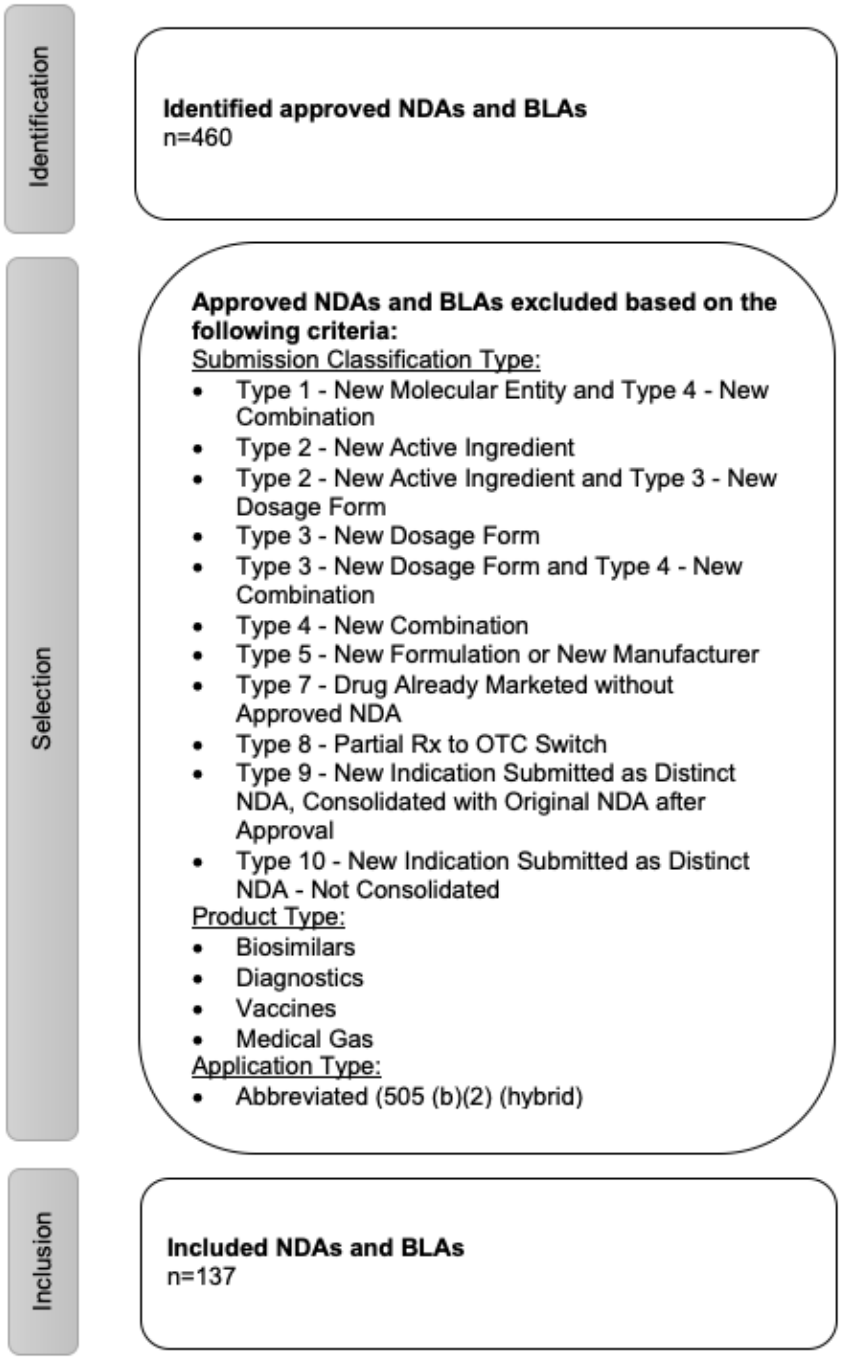

Figure 11 Selection Process for Medicinal Products approved by the FDA

Source: Own presentation

In 70% of the identified cases, die medicinal products were submitted and approved via a new drug application, whereas the remaining 30% of 137 cases were submitted via a biological license application (**Fig. 12**).

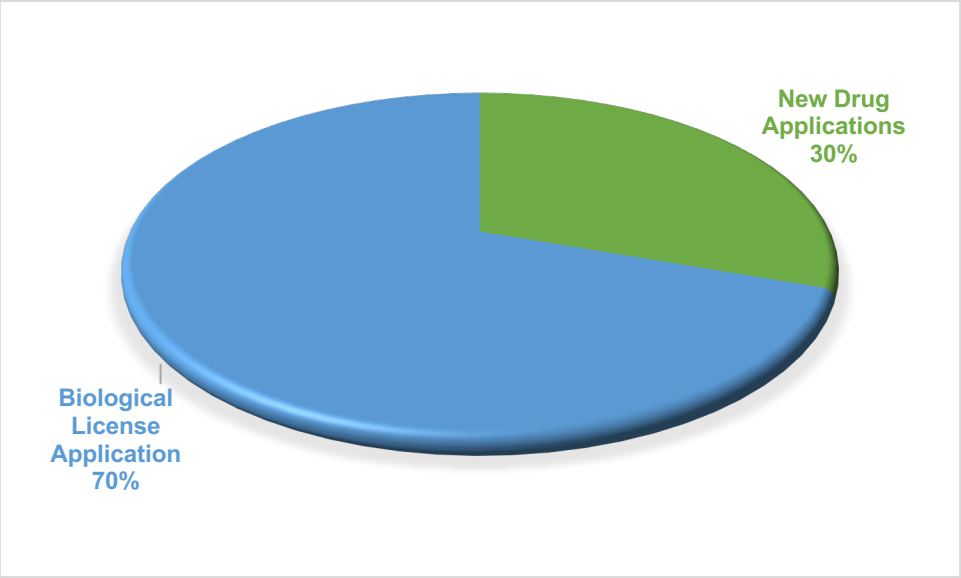

Figure 12 Characteristics: Type of Applications FDA (n=137
Source: Own presentation)

About half of the included medicinal products (n=66) were approved via Priority Review. Furthermore, 46% (n=64) of the medicinal products are orphan medicines. Only 14% of the approved medicinal products received accelerated approval as shown in **figure 13:**

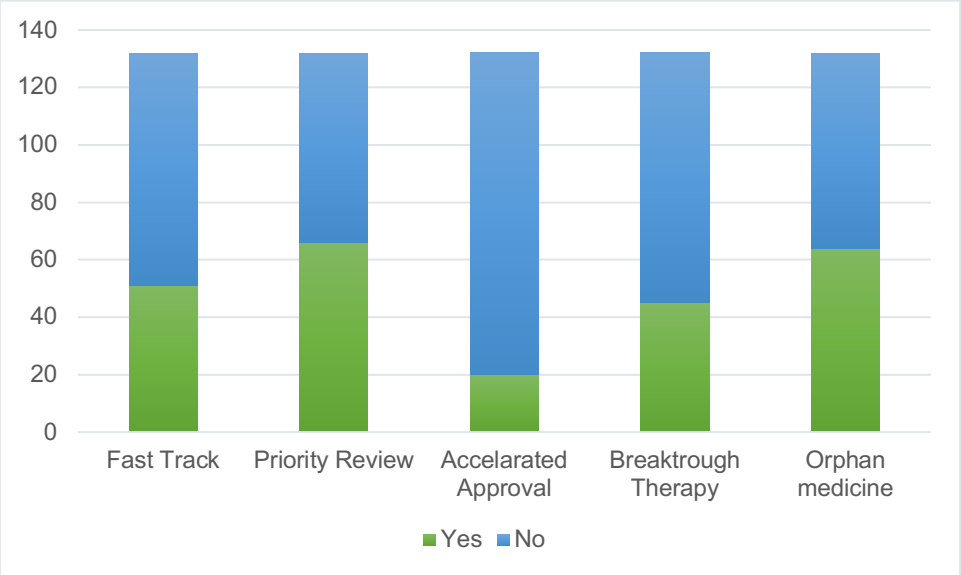

Figure 13 Characteristic: Special Regulatory Pathways FDA (n=137)
Source: Own presentation

For 17 out of 137 of the identified medicinal products, the FDA requested an advisory committee meeting or engaged with individual patient representatives.

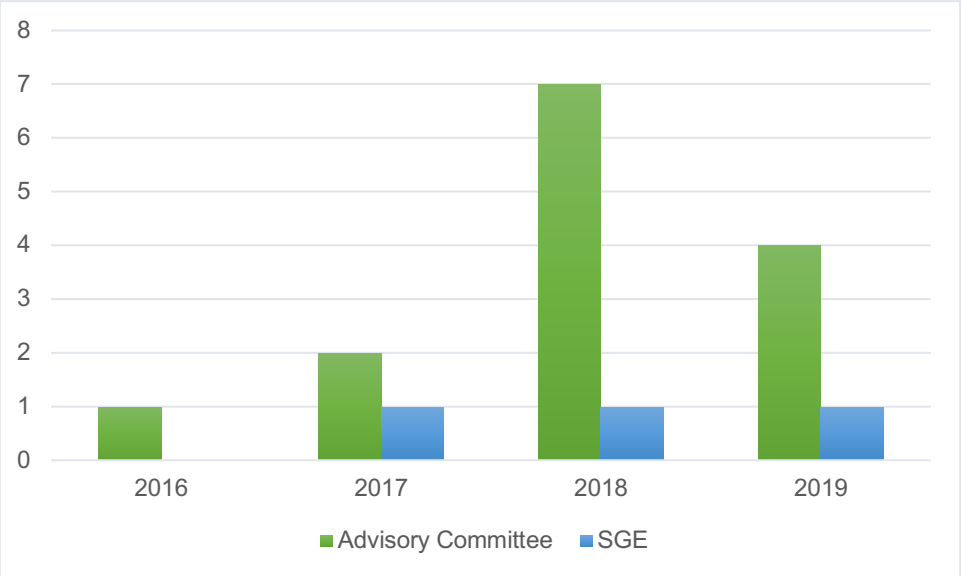

Figure 14 Number of FDA Advisory Committees and SGE Consultations per Year (n=17)
Source: Own presentation

Individual patient representatives were rarely consulted (n=3) (**Fig.14**). The method which was mainly used to collect patient perspectives was the consultation of patient in advisory committees. Overall, the number of advisory committees and individual patient representative contracted as special governmental employees (SGEs) is relatively small in relation to the total number of the included medicinal products.

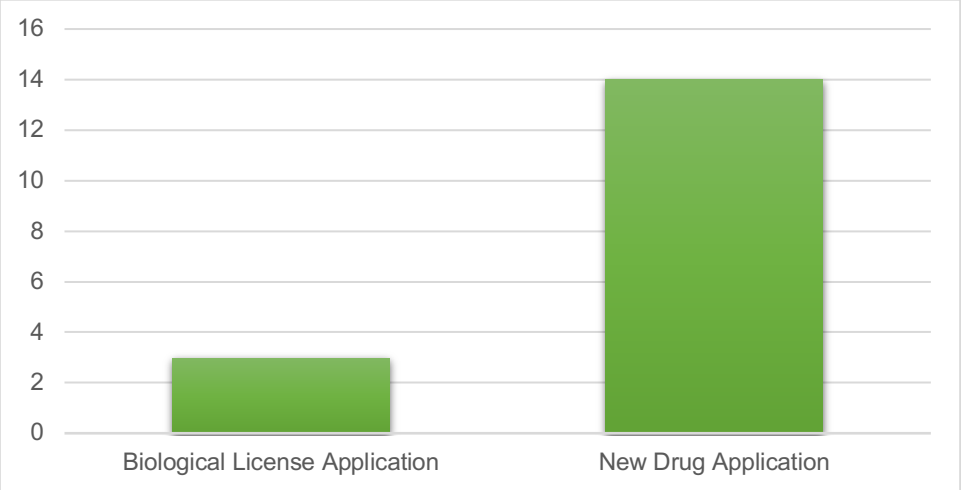

Figure 15 Number of Advisory Committee and SGE Consultations per Type of Application (n=17)
Source: Own presentation

One advisory meeting took place outside the investigation time period. This is because the approval date is used to limit the investigation period.

The majority (14 out of 17) of the advisory committees and SGE consultation were for medicinal products which were submitted as NDA, while three were submitted as BLA (**Fig. 15**).

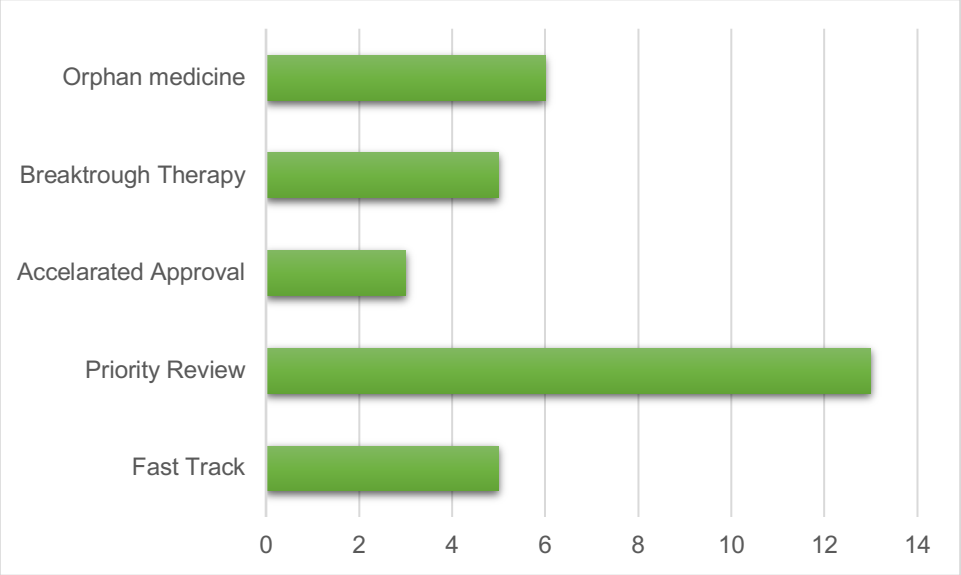

Figure 16 Number of Advisory Committees and SGE Consultation per Special Regulatory Authorisation (n=32)

Source: Own presentation

In 13 out of 17 advisory committees and SGE consultations, the medicinal products concerned had a Priority Review Designation.

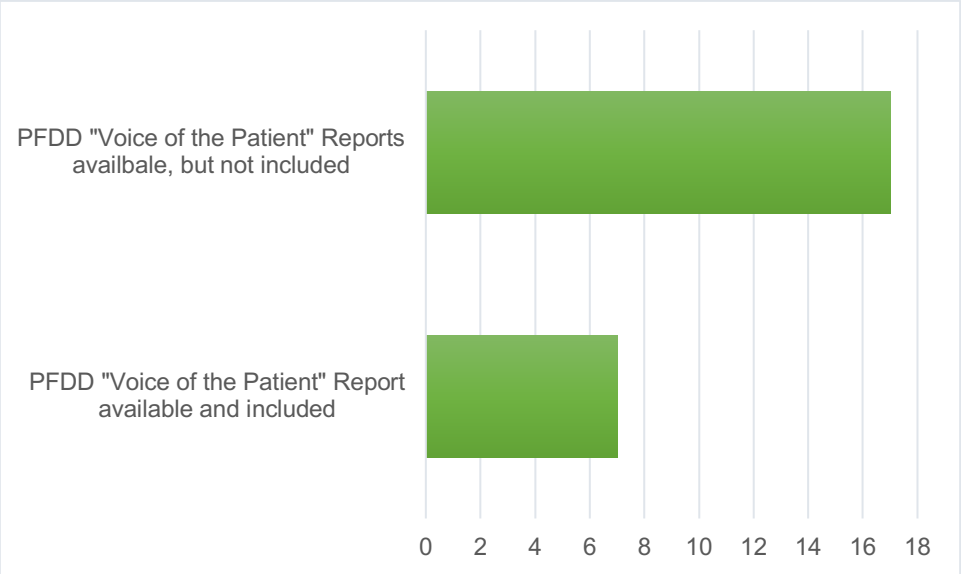

Figure 17 Inclusion of PFDD "Voice of the Patient" Reports (n=24)

Source: Own presentation

Only 3 advisory committees and SGE consultations were requested for medicinal products with an accelerated approval (**Fig. 16**).

For 7 of 137 identified medicinal products, the FDA considered PFDD “Voice of the Patients” reports in the assessment (**Fig. 17**). In 17 cases PFDD “Voice of the Patients” reports were available for the approved indications but were not mentioned in the assessment.

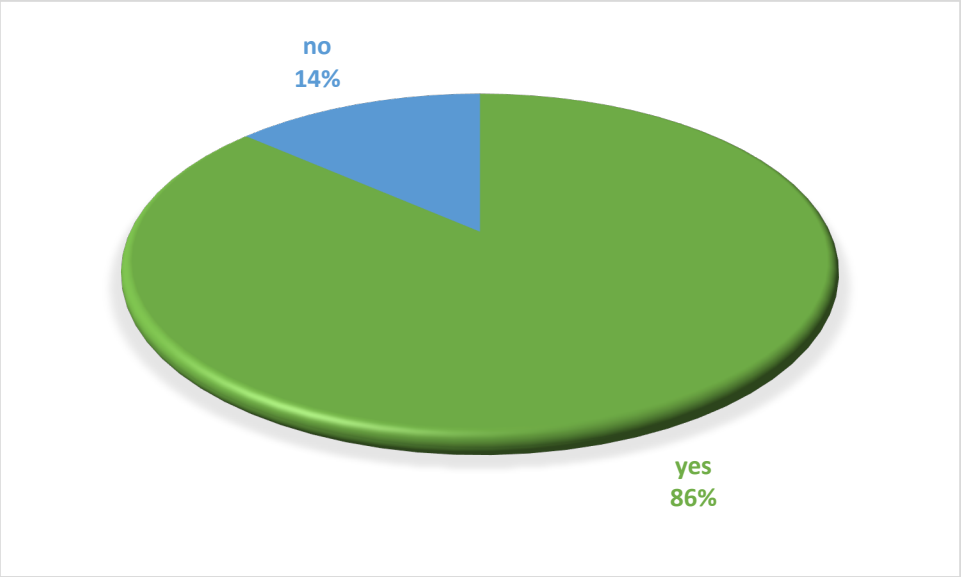

Figure 18 Patient Experience Date Statement (Application submitted after June 2017) (n=88)

Source: Own presentation

The FDA is requested by law to publish a PED statement for medicinal products which were submitted either as an NDA or BLA after 180 days after enactment of 21st CC Act in 13 December 2016. Since 12 June 2017, in 86% (n=76) of the identified medical review documents a statement is included (**Fig.18**).

6 Discussion

Based on the results presented, it can be confirmed that both agencies, EMA and FDA, engage with patients in the benefit-risk assessment process of medicinal products. There are differences in the management of the underlying processes, however it is important to note that assessors at both agencies request patient input when it is considered it to be important to inform regulatory decision-making. In the first part of this discussion the results derived from the EMA assessment reports are discussed. In the second part the outcomes of the evaluation of the medical review documents prepared by the FDA are put into perspective. In the final section, specific aspects concerning the EMA and FDA identified in the evaluation of this master thesis will be compared.

Discussion concerning EMA Results

The first objective: Assess the type of methods which are used by both agencies to involve patient in benefit-risk assessment process. The type of methods which are primarily used by the EMA to involve patients in benefit-risk assessment process are SAG or AHEGs. These platforms are commonly used to obtain expert public input. As outlined in **table 6**, the EMA recently presented in the Annual Report 2019 the total number of SAG and AHEG consultation covering the last 5 years. According to the annual report, the CHMP consulted 63 times with experts from SAGs and AHEGs in the context of new marketing authorisations, re-examinations, and article 58 procedures (EMA, 2020). However, this number cannot be confirmed by this assessment. In total, 23 SAG and AHEG meetings were identified based on the assessment report which were included in this evaluation. The exclusion of medicinal product like i.e. biosimilars, generics, diagnostics, vaccines and other specific types of application procedures i.e. well-established uses, informed consent and hybrid application might be reasons for this discrepancy. Furthermore, it cannot be confirmed if patients were involved in public hearings as part of the benefit-risk assessment process during the investigation period. No additional methods of patient involvement were identified in the assessment reports which were in scope of this analysis.

Furthermore, the second objective of this thesis was to analyse if the EMA requested more frequently a SAG or AHEG consultation for a specific type of medicinal product or for medicinal products registered under a specific regulatory pathway i.e. Orphan Medicine, Accelerated Approval, Authorisations under Exceptional Circumstances or

Conditional Approval. No SAG or AHEG were requested for medicinal products which were conditionally approved or approved via Accelerated Assessment. It might have been expected that for these type of products SAGs or AHEGs occur more frequently due to fact that there is a specifically high unmet medical need in the disease area or a major public health interest associated with the medicinal products (EMA, 2020). An explanation for this observation might be that there is already a close interaction during the drug development process of medicinal products eligible for an Accelerated Assessment or Conditional Approval procedure. As a consequence, no further expert consultation may be required during the benefit-risk assessment process. This can be supported by the finding that apparently patients are increasingly involved in Scientific Advices (**Tab. 4**) (EMA, 2013) (EMA, 2020). This information cannot be extracted from the public summary report. The vast majority of the medicinal products approved during the investigation time period for which SAG and AHEG consultation was requested do not have any special regulatory designation (Fig. 10).

As the third objective of this thesis it was assessed how transparent patient involvement has been documented in regulatory assessment reports which are publicly available. It is often not clear if patient representatives were involved in all the documented SAG and AHEG meetings. In almost 70% of the identified SAG and AHEG consultation it is not documented in the public assessment report if patient representatives were involved or not. As patient representatives are not involved in all SAGs at the EMA, it cannot be assumed that patients were involved in all the identified SAGs and AHEGs. Efforts were undertaken to confirm the involvement of patient participation in all identified SAG and AHEG consultations. However, no additional documentation is publicly available like i.e. SAG or AHEG meeting minutes to confirm the patient representation and to understand the full scope of patient contribution. If patient representatives were involved in SAGs and AHEGs, they provided feedback on symptoms under a specific treatment, treatment burdens, quality of life aspects as well as experience made with medicinal products used off-label and how products are used to achieve best possible benefit. They also contributed to potential warnings and labeling restrictions. As an outcome of this analysis, the author recommends for the sake of transparency to make patient involvement more visible in the EPAR, especially to facilitate access for patients who are interested to read this a kind of information. Further, it would be very insightful to highlight in the reports when no patient representative was consulted via SAGs or AHEGs. Based on the information extracted

from the assessment reports, only in 8 out of 118 medicinal products approved in 2017-2019 patient representatives were involved in the benefit-risk assessment.

Discussion concerning FDA Results

The first objective was to assess the type of methods which are used by the FDA to involve patients in benefit-risk assessment process. Concerning those medicinal products which were approved by the FDA in the investigation period for 14 out of 137 advisory committee meetings were held. The FDA is using PFDD "Voice of the Patients" reports as a specific source to incorporate patient perspective in the assessment. In 7 of 137 approved medicinal product reference is made to a PFDD "Voice of the Patients" reports. This number can be considered rather low; however, it can be justified on the basis that 25 disease-specific reports are available (**Tab. 17**). Interestingly, for 17 medicinal products approved for Psoriasis, Breast Cancer, Parkinson´s disease, Lung Cancer, Haemophilia A, Human Immunodeficiency Virus, and Narcolepsy available PFDD "Voice of the Patients" reports were not considered in the benefit-risk assessment of the affected medicinal products. Considering that the affected medicinal products were approved in the time period 2017 – 2019, it is questionable a proportion of these of reports could have contributed to the benefit-risk assessment since a number of reports go back to 2013 as for narcolepsy and lung cancer. Available treatment options and also knowledge about a specific disease usually change over time. However, the 17 out of 25 PFDD reports already provide a disease-specific framework of benefit-risk assessment which can serve as a basis for the reviewer to inform regulatory decision-making (FDA, 2018). In three cases FDA consulted individual patient representatives asking for advice.

Furthermore, the second objective of this thesis is to analyse if the FDA requested more frequently FDA advisory committees and SGE consultations for a specific type of medicinal product or for medicinal products registered under a specific regulatory pathway i.e. orphan medicine, accelerated approval, priority review, fast frack or breakthrough therapy designation. Advisory committees and SGE consultations were predominantly requested for medicinal products with a priority review designation, taking into consideration that the review timetables are shortened from 10 month to a 6-month review period (FDA, 2018). However, this information needs to be interpreted with caution because only for 13 of 66 medicinal product approved during the investigation period an advisory committee or SGE was consulted.

The third objective of this thesis is to assess how transparent patient involvement has been documented in regulatory assessment reports which are publicly available.

The evaluation of the review documents published on FDAs webpage covering the investigation period were based on two review strategies. The primary review strategy comprises the review of the Patient Experience Date Statement which has been incorporated into the medical review template in June 2017 and the secondary search review strategy was a manual search based on predefined keywords especially for those medicinal products which were approved before June 2017.

As already outlined in previous sections FDA is requested to publish "[…] a brief statement regarding the patient experience data and related information if any, submitted and reviewed as part of such application" to fulfil the commitment under the Sec. 3001 of the 21st CC Act. The statement is presented in tabular format and has been placed in the first chapter of the medical review document. In the PED statement only in 1 of 14 cases the FDA advisory committee was mentioned although patient perspective has been considered in the benefit-risk assessment. The conduct of advisory committees is documented in section 9.3 of the medical review document identified via the manual search. For none of the conducted advisory committee meetings patient participation were documented in the review document. However, the FDA is publishing the meeting minutes of all advisory committee meetings on the FDA webpage. For the medicinal products for which an advisory committee was convened, the publicly available documentation confirmed that in all 14 meetings one or two patient representatives participated in the meeting (FDA, 2020).

In 86% of 88 cases a PED statement is included in the medical review statement. However, it was noticed that the usage of the PED statement increased over time. In 2019 in only 4 of 43 cases the PED statement was missing. The PED statement was implemented the first time for the medicinal product Hemlibra (Emicizumab) indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors (FDA, 2017). The quality of completion of the statement differs across all the medicinal product concerned. In some cases, only the included PED types are selected in the PED statement which requires a full review of the clinical review document to identify the method being used. In some cases, the reviewer provides information on the method or instrument included in the application or the method considered in the review including the section where further information can be found.

Comparison of specific aspects EMA versus FDA

This analysis suggests that the EMA has consulted experts more often than the FDA for the medicinal products which were approved during the investigation period. This may be of specific interest considering the different organisational structures of both agencies. The EMA is a decentralised agency with approximately 900 permanent employees whereas more than 17,000 full-time employees are employed by the FDA (EMA, 2020) (FDA, 2020). The FDA, in addition, has mechanisms in place to ensure adequate resources and financial support to fulfil the commitments agreed in each PDUFA re-authorisation process.

The concept of being involved as a patient representative by the FDA and EMA is also slightly different. At the EMA, the Rapporteur or CHMP actively reaches out to the appointed SAGs or AHEGs asking for advice which will be finally presented by the chairs of each SAG or AHEG to the requesting scientific committee, whereas the FDA announces the planned advisory committees on their webpage. Patient representatives can apply for participation and can physically be present in these meetings to present their perspectives orally. Both approaches may have advantages based on the nature of questions but requiring different level of resources. It would be interesting to know which interaction patients prefer, if they feel more comfortable with expressing their views in smaller groups which will be brought back to the scientific committee via a designated person or if patients prefer to be in direct interaction with the broader committees. This cannot be answered with this evaluation. The EMA´s PRAC has implemented public hearings which also allows direct interactions with the scientific committee members.

Providing expert advice as a patient representative will not be remunerated, at the EMA and at the FDA. If the situation requires a personal presence in a meeting at the EMA, travel expenses are being paid when it is declared as such (EMA, 2016). However, patient representatives serving as a committee member at the FDA are contracted for around 6-month period as a Special Governmental Employee (FDA, 2020). A compensation is possible in exceptional cases.

Noteworthy, the FDA is more advanced in developing a regulatory framework to incorporate the patient perspective in BRA. One reason might be that patient participation is a key aspect in different U.S. pharmaceutical legislations that requires the FDA to keep track on the agreed deliverables. The FDA is providing regular

updates for each deliverable under the 21st CC Act, and PDUFA VI which are publicly available (FDA, 2020) (FDA, 2020).

Patients involvement is not only relevant at the timing of the benefit-risk assessment. Involvement of patient can be of benefit throughout the entire lifecycle of a medicinal product to various stakeholders including the industry and HTA bodies (Hoos, et al., 2015; du Plessis D, Morgan, Georgieva, & Bertelsen, 2017). So far, the necessary guidance documents are still lacking describing the appropriate methods to collect patient prefrence information during the drug development. In the U.S, the FDA committed to develop a series of guidance documents which are expected to be final beginning of 2022. At the EU level, the private-public partnership Innovative Medicines Initiative (IMI) initiated the project PREFER which stands for *Patient Preferences in benefit risk assessments during the drug life cycle* in order to develop methodologies and recommendations in collaboration with various stakeholder i.e. patient organizations, industry, and academics (Janssens, et al., 2019; Janssens, et al., 2019).

Although both authorities are currently progressing differently in the implementation of patient's perspective in BRA, and it seems to be still a significant effort to truly incorporate public input in regulatory decision making at EMA and FDA, it is nevertheless worth to acknowledge that both authorities are working on the implementation of their ambitious commitments to render BRA for medicinal products more relevant from patient perspective.

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Annex

Annex 1: List of Medicinal Products approved during the time period 01 January 2017 - 31 December 2019 by the EMA

Annex 2: List of Medicinal Products approved during the time period 01 January 2017 - 31 December 2019 by the EMA

Annex 1: List of Medicinal Products approved during the time period 01 January 2017 - 31 December 2019 by the EMA

Xeljanz	Ledaga	Alecensa	Olumiant	Cystadrops	Zinplava	Suliqua	Fiasp	Vemlidy	Afstyla	Medicine name
Tofacitinib citrate	Chlormethine	Alectinib hydrochloride	Baricitinib	Mercaptamine hydrochlorides	Bezlotoxumab	Insulin glargine, lixisenatide	Insulin aspart	Tenofovir alafenamide fumarate	Lonoctocog alfa	Active substance
Chemical	Chemical	Chemical	Chemical	Chemical	Biological	Biological	Biological	Chemical	Biological	Type of Medicinal Product
EMEA/H/C/004214	EMEA/H/C/002826	EMEA/H/C/004164	EMEA/H/C/004095	EMEA/H/C/003769	EMEA/H/C/004136	EMEA/H/C/004243	EMEA/H/C/004046	EMEA/H/C/004169	EMEA/H/C/004077	Product number
Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorisation status
no	no	no	no	no	no	no	no	no	no	Conditional approval
no	no	no	no	no	no	no	no	no	no	Exceptional circumstances
no	no	no	no	no	no	no	no	no	no	Accelerated assessment
no	yes	no	no	yes	no	no	no	no	no	Orphan medicine
21.03.2017	3.03.2017	16.02.2017	13.02.2017	18.01.2017	18.01.2017	11.01.2017	9.01.2017	9.01.2017	4.01.2017	Authorisation date
Pfizer Europe MA EEIG	Helsinn Birex Pharmaceuticals Ltd.	Roche Registration GmbH	Eli Lilly Nederland B.V.	Recordati Rare Diseases	Merck Sharp & Dohme B.V.	sanofi-aventis groupe	Novo Nordisk A/S	Gilead Sciences Ireland UC	CSL Behring GmbH	Marketing authorisation holder/company name
Xeljanz in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs. Xeljanz can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate (see sections 4.4 and 4.8).	Ledaga is indicated for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-type CTCL) in adult patients.	Alecensa as monotherapy is indicated for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). Alecensa as monotherapy is indicated for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib.	Olumiant is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying antirheumatic drugs. Olumiant may be used as monotherapy or in combination with methotrexate.	Cystadrops is indicated for the treatment of corneal cystine crystal deposits in adults and children from 2 years of age with cystinosis.	Zinplava is indicated for the prevention of recurrence of *Clostridium difficile* infection (CDI) in adults at high risk for recurrence of CDI.	Suliqua is indicated in combination with metformin for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control when this has not been provided by metformin alone or metformin combined with another oral glucose lowering medicinal product or with basal insulin.	Treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above.	Vemlidy is indicated for the treatment of chronic hepatitis B in adults and adolescents (aged 12 years and older with body weight at least 35 kg).	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Afstyla can be used for all age groups.	Approved Condition / Indication	
yes, SF-36 (S) Work Limitations Questionnaire (WLQ) (S) EQ-5D (S) Medical Outcomes Study Sleep scale (MOS sleep scale) (S) FACIT-fatigue scale (S)	no	yes, EORTC QLQ-C30 (S) EORTC QLQ- LC13 (S)	yes, ACR (P) Patient's assessment of pain (VAS) (P) Patient's Global Assessment of Disease Activity (VAS) (P) Patient's assessment of physical function as measured by the HAQ-DI (P) HAQ-DI (S) SDAI (S) DAS28-hs CRP and DAS28-ESR (S)	yes, Patient-reported diary-based AE	no	no	yes, SF-36 (vS) Treatment Related Impact Measure for Diabetes (TRIM-D) (vS)	no	no	PRO	
no	no	no	yes, ACR (P) Physician's Global Assessment of Disease Activity (VAS) (P) mTSS (S) DAS28-hs CRP and DAS28-ESR (S) CDAI (S)	no	no	no	no	no	no	CInRO	EMA
no	no	no	no	no	no	no	no	no	no	ObsRO	
no	no	no	no	no	no	no	no	no	no	PerfO	
no	no	no	no	no	no	no	no	no	no	Patient Preference Study	
no	no	no	no	no	no	no	no	no	no	Natural Disease History Study	
no	no	no	no	no	Patient's perspective the impact on the baseline episode i.e. clinical cure is considered as an important efficacy parameter. PBS	no	no	no	no	Others	
no	no	no	no	no	yes , SAG consulted on 3NOV2016 No information if patient representatives were involved	no	no	no	no	SAG	
no	no	no	no	no	no	no	no	no	no	AHEG	EMA
no	no	no	no	no	no	no	no	no	no	Other	

Reagila	Spherox	Ocverolo	Besponsa	Kevzara	Refixia	Spinraza	Strimvelis	Cerdelga (previously Dinutuximab beta EUSA and Dinutuximab beta Apeiron)	Natpar
Cariprazine hydrochloride	Spheroids of human autologous matrix-associated chondrocytes	Recombinant human Nerve Growth factor (rhNGF)	Inotuzumab Ozogamicin	Sarilumab	Nonacog beta pegol	Nusinersen sodium	Carliposase alfa	Dinutuximab beta	Parathyroid hormone
Chemical	ATMP	Biological	Biological	Biological	Biological	Gene Therapy	Biological	Biological	Biological
EMEA/H/C/002770	EMEA/H/C/002736	EMEA/H/C/004209	EMEA/H/C/004119	EMEA/H/C/004254	EMEA/H/C/004178	EMEA/H/C/004312	EMEA/H/C/004095	EMEA/H/C/003918	EMEA/H/C/003861
Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised
no	no	no	no	no	no	no	no	no	yes
no	no	no	no	no	no	no	yes	yes	no
no	no	yes	no	no	no	yes	yes	no	no
no	no	yes	yes	no	no	yes	yes	yes	yes
13.07.2017	10.07.2017	6.07.2017	28.06.2017	23.06.2017	2.06.2017	30.05.2017	30.05.2017	8.05.2017	24.04.2017
Gedeon Richter	CO.DON AG	Dompe farmaceutici s.p.a.	Pfizer Europe MA EEIG	Sanofi-Aventis groupe	Novo Nordisk A/S	Biogen Netherlands B.V.	BioMarin International Limited	EUSA Pharma (Netherlands) BV	Shire Pharmaceuticals Ireland Ltd
Reagila is indicated for the treatment of schizophrenia in adult patients.	Repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (International Cartilage Repair Society [ICRS] grade III or IV) with defect sizes up to 10 cm2 in adults.	Treatment of moderate (persistent epithelial defect) or severe (corneal ulcer) neurotrophic keratitis in adults.	Besponsa is indicated as monotherapy for the treatment of adults with relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (ALL). Adult patients with Philadelphia chromosome positive (Ph+) relapsed or refractory B cell precursor ALL should have failed treatment with at least 1 tyrosine kinase inhibitor (TKI).	Kevzara in combination with methotrexate (MTX) is indicated for the treatment, of moderately to severely active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti-rheumatic drugs (DMARDs). Kevzara can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate.	Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia B (congenital factor IX deficiency).	Spinraza is indicated for the treatment of 5q Spinal Muscular Atrophy.	Strimvelis is indicated for the treatment of neonatal cerebrotendinous cirrosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency	Cerdelga is indicated for the treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and stem cell trans plantation, as well as patients with history of relapsed or refractory neuroblastoma, with or without residual disease. Prior to the treatment of relapsed neuroblastoma, any actively progressing disease should be established by other suitable measures, in patients with a history of relapsed/refractory disease and in patients who have not achieved a complete response after first line therapy. Cerdelga should be combined with interleukin 2 (IL 2).	Natpar is indicated as adjunctive treatment of adult patients with chronic hypoparathyroidism who cannot be adequately controlled with standard therapy alone.
yes, PANSS-T (P) Schizophrenia Quality of Life Scale Revision 4 (SQLS-R4) (total Psychosocial vitality) (O) Calgary Depression Scale for Schizophrenia (CDSS) (O)	yes, Knee Injury and Osteoarthritis Outcome Score (KOOS) (P) International Knee Documentation Committee (IKDC) (S) Modified Lysholm Score (S) Absence from work (S)	no	yes, EORTC QLQ-C30 (S) EQ-5D (S) EQ-VAS (S)	yes, ACR (P) HAQ-DI (S) SF-36 (Physical/Mental) (S) FACIT-Fatigue (S) Morning Stiffness (S) Rheumatoid arthritis-specific Work Productivity Survey (WPS-RA) (S) Rheumatoid Arthritis Impact of Disease score (RAID) (S)	yes, HAEMO-QOL Hemophilia Patient Satisfaction Scale (HEMO-SAT) TNO-AZL preschool quality of life (TAPQOL)	yes, Hammersmith Functional Motor Scale Expanded (HFMSE)	no	no	yes, SF-36 (E)
yes, Personal and Social Performance Scale (PSP) (S) CGI-S (SIO) CGI-I (O) Negative Symptom Assessment (NSA-16) (O) Brief Psychiatric Rating Scale, (BPRS) (O) CDR attention battery and CTT scores (O) PANSS (O)	yes, Modified Lysholm Score (S)	no	no	yes, CDAI ACR (P)	yes, Haemostatic effect on 4-point scale (S)	yes, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)	no	no	no
no	no	no	no	no	yes, HAEMO-QOL TNO-AZL preschool quality of life (TAPQOL)	no	yes , PedsQL Parent Report for Toddlers (E) PedsQL Family Impact Module (E) CLN2 Disease-based QoL Instrument (E) No quality of life measurements of untreated patients exist in CLN2 disease	no	no
no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	yes , International SMA Consortium (ISMAC) natural history study	yes , Natural History Studies Study 199-901 1WQMC cohort Study 199-901 Supplement DEM-CHILD collaborative natural history database	no	no
no	no	no	no	no	no	TREAT-NMD Alliance registries	no	no	no
no	no	no	no	no	no	no	no	no	yes, SAG consulted on 16SEP2015 - **Patient representatives were involved** The patient representatives pointed out in particular the symptoms which can occur still under standard treatment, such as difficulties to control episodes of cramps, body stiffness with considerable impact on daily activities, or the feeling of "brain fog"; also they raised concerns about long-terms consequences from current standard of care. p50 The patient representatives pointed out that some patients, using the approved product in the US, or another PTH preparation off label in the EU, split the daily dose by using a syringe, because of the time-limited action of Natpar and symptom relief perceived. p51 e) Clinical improvement, Quality of life (QoL): The expert group found it disappointing that the applicant could not demonstrate any improvement of these parameters in their studies, as most expert group members felt this was the outcome in most need of improvement and could have been expected from such a hormone replacement treatment (see also section 5). However, it was acknowledged that instruments such as a general SF36 questionnaire might not be very sensitive and appropriate for hypoparathyroidism; further research in this field is encouraged. The patient representatives pointed out that there were many patients anecdotally reporting a significant improvement in quality of life, cognitive symptoms as well as cramps and tetanic equivalents, and that this was also very much their personal experience p52
no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no

Annex 1: List of Medicinal Products approved during the time period
01 January 2017 - 31 December 2019 by the EMA

Rydapt	Bavencio	Xermelo	Fotivda	Mavenclad	Kisqali	Vosevi	Maviret	Veltassa	Kyntheum	Trimbow
Midostaurin	Avelumab	Telotristat etiprate	Tivozanib	Cladribine	Ribociclib succinate	Sofosbuvir, Velpatasvir, Voxilaprevi	Glecaprevir / Pibrentasvir	Patiromer sorbitex calcium	Brodalumab	Beclometasone dipropionate, formoterol fumarate dihydrate, Glycopyrronium bromide
Chemical	Biological	Chemical	Chemical	Chemical	Chemical	Chemical	Chemical	Chemical	Biological	Chemical
MEA/H/C/004095	EMEA/H/C/004338	EMEA/H/C/003937	EMEA/H/C/004131	EMEA/H/C/004230	EMEA/H/C/004213	EMEA/H/C/004350	EMEA/H/C/004430	EMEA/H/C/004180	EMEA/H/C/003959	EMEA/H/C/004257
Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised
no	yes	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	yes	yes	no	no	no
yes	no	yes	no	no	no	no	no	no	no	no
19.09.2017	18.09.2017	17.09.2017	24.08.2017	22.08.2017	22.08.2017	26.07.2017	26.07.2017	19.07.2017	17.07.2017	17.07.2017
Novartis Europharm Ltd	Merck Europe B.V.	Ipsen Pharma	EUSA Pharma (Netherlands) BV	Merck Europe B.V.	Novartis Europharm Limited	Gilead Sciences Ireland UC	AbbVie Deutschland GmbH Co. KG	Vifor Fresenius Medical Care Renal Pharma France	LEO Pharma A/S	Chiesi Farmaceutici S.p.A.
Rydapt is indicated: • in combination with standard daunorubicin and cytarabine induction and high dose cytarabine consolidation chemotherapy, and for patients in complete response followed by Rydapt single agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation positive (see section 4.2); as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM AHN), or mast cell leukaemia (MCL).	Bavencio is indicated as monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC). Bavencio in combination with axitinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC)	Xermelo is indicated for the treatment of carcinoid syndrome diarrhoea in combination with somatostatin analogue (SSA) therapy in adults inadequately controlled by SSA therapy.	Fotivda is indicated for the first line treatment of adult patients with advanced renal cell carcinoma (RCC) and for adult patients who are VEGFR and mTOR pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for advanced RCC.Treatment of advanced renal cell carcinoma.	Treatment of adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features	Kisqali is indicated for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy. In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.	Vosevi is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults.,	Maviret is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults and in adolescents aged 12 to	Veltassa is indicated for the treatment of hyperkalaemia in adults	Kyntheum is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy.	Maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist or a combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist (for effects on symptoms control and prevention of exacerbations see section 5.1).
yes, Memorial Symptom Assessment Scale (MSAS) (E) SF-12 (E)	yes, EQ-5D (E) FACT-M (E)	yes, EORTC-QLQ-C30 (O) EORTC-QLQ-GINET21 (O) Subjective global assessment of symptoms associated with CS Need for rescue short-acting SSA therapy to treat bowel-related symptoms associated with CS Number of cutaneous flushing episodes, Stool consistency	yes, FACT-G (S) FKSI-DRS (S) EQ-5D (S)	no	yes, EORTC QLQ-C30 (S) EORTC QLQ-BR23 (S) EQ-5D-5L (S)	no	no	no	yes, DLQI (S) EQ-5D (S) SF-36 (S) PSI (S) Columbia-Suicide Severity Rating Scale (C-SSRS) PHQ-8 C-CASA	yes, St George's Respiratory Questionnaire (SGRQ) (S)
no	no	no	no	yes, Expanded Disability Status Score (EDSS)	no	no	no	no	yes, BSA (S) PASI (P/S) sPGA (P/S) NAPSI (S) SSA (S) PSSI (S) Columbia-Suicide Severity Rating Scale (C-SSRS) PHQ-8	no
no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	yes, SAG consulted on 8JUN2017 - **Patient representatives were involved** The oral route of administration and the need for very few treatment cycles only were considered a clear advantage for patients over most other available treatment options, many of which require frequent injections. This view was stressed by the patient representatives, who would welcome a therapeutic option with a low treatment burden.(p87)	no	no	no	no	no	no
no	no	no	no	no	no	yes, 2 AHEG meetings Additional expert group consulted on 07FEB2019 (p133) - **Patient representatives were involved** Additional expert group consulted on 3OCT2019 (p229) - **Patient representative were involved** The patient representatives (including a patient) participating in the meeting highly welcomed the possible future availability of such a treatment (p229). With regard to the clinical impact of fractures, the patient representatives participating in the meeting made a very strong case that even vertebral fractures can have a profound impact on pain- free living, mobility, independence, and life quality (p230).	no	no	no	no
no	no	no	no	no	no	no	no	no	no	Unrequested external feedback received - third parties - not specified

Prevymis	Ocrevus	Zejula	Vivia Seal	Tracleer	Tremfya	Dupixent	Lutathera	Symtuza	Tecentriq
Letermovir	Ocrelizumab	Niraparib dosylate monohydrate)	Human fibrinogen, human thrombin	Paediatric bosentan dispersible tablet	Guselkumab	Dupilumab	Lutetium (177Lu) oxodotreotide	Darunavir, Cobicistat, Emtricitabine, Tenofovir alafenamide	Atezolizumab
Chemical	Biological	Chemical	Biological	Chemical	Biological	Biological	Chemical	Chemical	Biological
EMEA/H/C/004036	EMEA/H/C/004043	EMEA/H/C/004249	EMEA/H/C/004446	EMEA/H/C/004182	EMEA/H/C/004271	EMEA/H/C/004390	EMEA/H/C/004123	EMEA/H/C/004391	EMEA/H/C/004143
Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised
no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no
yes	no	yes	no	no	no	no	yes	no	no
8.01.2018	8.01.2018	16.11.2017	1.01.2017	1.01.2017	1.01.2017	27.09.2017	26.09.2017	21.09.2017	20.09.2017
Merck Sharp & Dohme B.V.	Roche Registration GmbH	GlaxoSmithKline (Ireland) Limited	Instituto Grifols, S.A.	STEBA Biotech S.A	Janssen-Cilag International N.V.	Sanofi-Aventis groupe	Advanced Accelerator Applications	Janssen-Cilag International N.V.	Roche Registration GmbH
Prevymis is indicated for prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients (R+) of an allogeneic haematopoietic stem cell transplant (HSCT). Consideration should be given to official guidance on the appropriate use of antiviral agents.	Treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features. , Treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.,	Zejula is indicated as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum based chemotherapy.,	Supportive treatment in adults when standard surgical techniques are insufficient for improvement of haemostasis as suture support in vascular surgery	Tracleer is indicated as monotherapy for adult patients with previously untreated, unilateral, low risk, adenocarcinoma of the prostate with a life expectancy ≥ 10 years and Clinical stage T1c or T2a, Gleason Score ≤ 6, based on high-resolution biopsy strategies PSA ≤ 10 ng/mL 3 positive cancer cores with a maximum cancer core length of 5 mm in any one core or 1-2 positive cancer cores with ≥ 50 % cancer involvement in any one core or a PSA density ≥ 0.15 ng/mL/cm².	Tremfya is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy	Dupixent is indicated for the treatment of moderate-to-severe atopic dermatitis in adult patients who are candidates for systemic therapy.	Lutathera is indicated for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in adults.	Symtuza is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg). Genotypic testing should guide the use of Symtuza (see sections 4.2 and 5.1).	Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) after prior platinum containing chemotherapy, or who are ineligible for cisplatin, and whose tumours have a PD-L1 expression ≥ 5%. Tecentriq in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous non small cell lung cancer (NSCLC). In patients with EGFR mutant or ALK-positive NSCLC, Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies. Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK positive NSCLC should also have received targeted therapy before receiving Tecentriq.
no	yes, EDSS (P) SF-36 PCS (S)	yes, EQ-5D-5L (S) Neuropathy Questionnaire (S) Functional Assessment of Cancer Therapy - Ovarian Symptom Index (FOSI) (S)	no	yes, EQ-5D (S) International Prostate Symptom Score (IPSS) (S) International Index of Erectile Function (IIEF 15) (S)	yes, DLQI (S) HADS (S) (used in one CT only) Psoriasis Signs and Symptoms Diary (PSSD) (S) SF-36 (S) (used in one CT only) WLQ (S) (used in one CT only)	yes, DLQI (S) Pruritus NRS (S) POEM (S) GISS HADS Sino-Nasal Outcome Test (SNOT-22) EQ-5D-5L/VAS	yes, EORTC Quality of Life Questionnaire - Core Questionnaire (EORTC QLQ-C30) EORTC Quality of Life Questionnaire - Neuroendocrine Carcinoid Module (EORTC QLQ-GINET21)	no	yes, EORTC QLQ-LC13 (S)
no	no	no	no	no	yes, P-PGA IV-PGA NAPSI PGA PASI (PS) IGA (PS) ss-IGA (S)	yes, BASI (P) IGA (P) SCORAD (S) BSA	yes, Karnofsky Performance-Score	no	no
no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no
no	Reference to natural history studies - not further specified	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no
no	yes, SAG on 8JUN2017 - **Patient representatives were involved** The patient representatives supported the position that the effect size is small, but consistent as the results from most of the secondary endpoints point in the same direction and they represent the important aspects of everyday life for the PPMS patient. Additionally, they stressed the importance of the positive effects observed in the HRQoL (Health Related Quality of Life) scales, emphasising that after a certain level of progression (EDSS=7.0) the effects on non-motor aspects of disability (e.g., cognition) become even more important than EDSS progression. Regarding what may constitute a minimal clinically important difference (MCID), the SAG experts could not reach a consensus on a specific effect size in a relevant outcome measure that could be agreed as MCID throughout the spectrum of PPMS. The patient representatives supported the position that any effect in this population should be considered relevant and important. (p132) Other experts considered that the data from the RMS development programme for Ocrevus should be considered supportive as the different types of MS represent a disease continuum, rather than different diseases. This position was supported by the patient representatives. (p133)	no	no	yes, SAG consulted on 4APR2017 No information of patient representatives were involved	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no

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Lanzoprazole	Abilsia	Lutathera	Stagliptro	Hemlibra	Cyramza	Dovonex	Jorveza	Adynovi	Fasenra	Intrarosa
Valmanase a alfa	Darvadstrocel	Sodium zirconium cyclosilicate	Ertugliflozin l-pyroglutamic acid	Emicizumab	Sirukumab	Semaglutide	Budesonide	Rurioctocog alfa pegol	Benralizumab	Prasterone
Biological	ATMP	Chemical	Chemical	Biological	Biological	Chemical	Chemical	Biological	Biological	Chemical
EMEA/H/C/003922	EMEA/H/C/004258	EMEA/H/C/004329	EMEA/H/C/004315	EMEA/H/C/004406	EMEA/H/C/004275	EMEA/H/C/004174	EMEA/H/C/004655	EMEA/H/C/004195	EMEA/H/C/004433	EMEA/H/C/004138
Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised
no	no	no	no	no	yes	no	no	no	no	no
yes	no	no	no	no	no	no	no	no	no	no
no	no	no	no	yes	no	no	yes	no	no	no
yes	yes	no	no	no	yes	no	yes	no	no	no
23.03.2018	23.03.2018	22.03.2018	21.03.2018	23.02.2018	19.02.2018	8.02.2018	8.01.2018	8.01.2018	8.01.2018	8.01.2018
Chiesi Farmaceutici S.p.A.	Takeda Pharma A/S	AstraZeneca AB	Merck Sharp & Dohme B.V.	Roche Registration Limited	Kyowa Kirin Holdings B.V.	Novo Nordisk A/S	Dr. Falk Pharma GmbH	Baxalta Innovations GmbH	AstraZeneca AB	Endoceutics S.A.
Treatment of non-neurological manifestations in patients with mild to moderate alpha-mannosidosis. ,	Abilsia is indicated for the treatment of complex perianal fistulas in adult patients with non-active/mildly active luminal Crohn's disease, when fistulas have shown an inadequate response to at least one conventional or biologic therapy. Abilsia should be used after conditioning of fistula.	Lutathera is indicated for the treatment of hypercholesterolaemia in adult patients.	Stagliptro is indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control as monotherapy in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications, in addition to other medicinal products for the treatment of diabetes.	Hemlibra is indicated for routine prophylaxis of bleeding episodes in patients with haemophilia A with factor VIII inhibitors.	Treatment of X-linked hypophosphataemia with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons.	Treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise as monotherapy when metformin is considered inappropriate due to intolerance or contraindications, in addition to other medicinal products for the treatment of diabetes. For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.	Jorveza is indicated for the treatment of eosinophilic esophagitis (EoE) in adults (older than 18 years of age)	Adynovi is indicated as an add on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long acting β agonists.	Fasenra is indicated for the treatment of vulvar and vaginal atrophy in postmenopausal women having moderate to severe symptoms.	Intrarosa is indicated for the treatment of vulvar and vaginal atrophy in postmenopausal women having moderate to severe symptoms.
yes, EQ-5D (S)	yes, Inflammatory Bowel Disease Questionnaire (IBDQ) (S) Perianal Disease Activity Index (PDAI) (S) Clinical Disease Activity Index (CDAI) (S)	no	no	yes, Beliefs about Medicines Questionnaire (BMQ) Haemo-QoL (S)/Haemo-QoL-Short Form (S) EQ-5D-5L (S) Number of days away from schoolwork and differences in number of days in hospitalised (S)	yes, BPI/BPI-SF (S)	yes, DTSQ (S) SF-36 (S)	yes, Eosinophilic Oesophagitis Activity Index (EEsAI-PRO) (S) Visual Dysphagia Question (VDQ) score (S) Adult Eosinophilic Oesophagitis Quality of Life questionnaire (EoE-QoL-A) (eS) Modified Short Health Scale (mod SHS) (eS) Patients Global Assessment (PatGA) (eS)	yes, Treatment of bleeding events - subject's response to treatment was assessed using a 4-point efficacy rating scale (S)	yes, Asthma Quality of Life Questionnaire (AQLQ) (S) Tele-asthma symptom score (TASS) S) Asthma Control Questionnaire (ACQ-6) (S)	yes, Vaginal dryness severity score (P) Vulvar irritation/itching severity score (P) Menopause-specific Quality of Life Questionnaire (MENQOL) (S) Female Sexual Function Index (FSFI) (S) Unclear: ASF (S)
no	yes, Clinical Disease Activity Index (CDAI) (S) Van Assche Score (S)	no	no	no	yes, Rickets Severity Score (RSS) (S) Radiographic Global Impression of Change (RGI-C) (S)	no	no	yes, Efficacy in surgery - 4-point scale (S)	no	no
yes, Childhood Health Assessment Questionnaire (CHAQ) (S)	no	no	no	yes, Haemo-QoL (S)	yes, Pediatric Outcomes Data Collection Instrument (POSNA-PODCI) (S)	no	no	no	no	no
no	no	no	no	no	no	no	no	no	yes, Asthma Control Questionnaire (ACQ-6) (S)	no
no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	In study UX023-CL201, all included 62 subjects completed week 40. This supports a good tolerability of the drug as well as a patient/caregiver preference to the experimental therapy compared to the conventional therapy they had received before the study. (p119)	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	yes, AHEG consulted on 21 NOV 2018 - **Patient representatives were involved** The AHEG noted that results from 2 questionnaires (DTSQ and DDS2) did demonstrate patients' preference for this treatment option and therefore could be supportive of the benefit of reduced glucose variability seen in the study. The experts found it, however, difficult to judge the clinical relevance of such patient reported outcomes. A benefit, mentioned by the patients participating in the expert meeting, is that such an improvement helps to simplify insulin dose calculations (p105). The experts, including the 2 patients, raised some concerns that the proposed monitoring and precautionary advices may put quite a high burden on healthcare professionals and responsibility on patients (p106). From the patients' perspective the acceptance of another frequently to be self-measured laboratory parameter beyond glucose was questioned (p106).	no	no	no	yes, AHEG consulted on 19JUN2018 No information if patient representatives were involved
no	no	no	no	no	no	N/A	no	no	no	no

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Vyxeos liposomal (previously known as Vyxeos)	Kymriah	Myalepta	Rukobi	Aimovig	Verkazia	Tegsedi	Bildamy	Rubraca	Juluca	Mylotarg
Daunorubicin hydrochloride / cytarabine	Tisagenlecleucel	Metreleptin	Brexpiprazole	Erenumab	Cidofovir	Inotersen sodium	Bictegravir, Emtricitabine, Tenofovir alafenamide, fumarate	Rucaparib Camsylate	Dolutegravir sodium, Rilpivirine hydrochloride	Gemtuzumab ozogamicin
Chemical	Gene Therapy	Biological	Chemical	Biological	Chemical	Chemical	Chemical	Chemical	Chemical	Biological
EMEA/H/C/004282	EMEA/H/C/004093	EMEA/H/C/004218	EMEA/H/C/003841	EMEA/H/C/004447	EMEA/H/C/004411	EMEA/H/C/004782	EMEA/H/C/004449	EMEA/H/C/004272	EMEA/H/C/004427	EMEA/H/C/004204
Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised
no	no	no	no	no	no	no	no	yes	no	no
no	no	yes	no	no	no	no	no	no	no	no
no	no	no	no	no	yes	yes	no	no	no	no
yes	yes	yes	no	no	yes	yes	no	no	no	yes
23.08.2018	22.08.2018	09.07.2018	26.07.2018	26.07.2018	6.07.2018	5.07.2018	21.06.2018	23.05.2018	16.05.2018	19.04.2018
Jazz Pharmaceuticals Ireland Limited	Novartis Europharm Limited	Amryt Pharmaceuticals DAC	Otsuka Pharmaceutical Netherlands B.V.	Novartis Europharm Limited	Santen Oy	Akcea Therapeutics Ireland Limited	Gilead Sciences Ireland UC	Clovis Oncology UK Limited	ViiV Healthcare B.V.	Pfizer Europe MA EEIG
Vyxeos liposomal is indicated for the treatment of adults with newly diagnosed, therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).	Indicated for the treatment of Paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse. Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy.	Myalepta is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients with confirmed congenital generalised LD (Berardinelli-Seip syndrome) or acquired generalised LD (Lawrence syndrome) in adults and children 2 years of age and above with confirmed familial partial LD or acquired partial LD (Barraquer-Simons syndrome), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control.	Treatment of schizophrenia.	Aimovig is indicated for prophylaxis of migraine in adults who have at least 4 migraine days per month when initiating treatment with Aimovig.	Treatment of severe vernal keratoconjunctivitis (VKC) in children from 4 years of age and adolescents.	Treatment of stage 1 or Stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR).	Bildamy is indicated for the treatment of adults infected with human immunodeficiency virus 1 (HIV 1) without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir.	Rubraca is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. Rubraca is indicated as monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy.	Juluca is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who are virologically-suppressed (HIV-1 RNA	Mylotarg is indicated for combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of patients age 15 years and above with previously untreated, de novo CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia (APL).
no	yes, EQ-5D/VAS (S) FACT-Lym SF-36 Peds QL (S)	no	yes, CGH (P) CGI-S (S) PEC Score (S)	yes, Migraine Physical Function Impact Diary (MPFID) (S) MSQ (S) MIDAS (E) HIT-6 (E) Allodynia Symptom Checklist (ASC-12) (E) Patient-Reported Outcomes Measurement Information System (PROMIS) (E)	yes, QUICK questionnaire (O) Visual Analog Scale (S)	yes, Norfolk QoL-DN (PS) SF-36 (E)	no	no	yes, Willingness of switch (E) Change in adherence (E) SDMI (HIV Symptom Index (SDMI) (E) HIV Treatment Satisfaction Questionnaire - Status version (HIVTSQ) (E)	no
no	no	no	yes, Positive and Negative Syndrome Scale for schizophrenia (PANSS) (P) Personal and Social Performance scale (PSP) (S)	no	yes, Investigator Global Evaluation of Efficacy	yes, NIS (PS)	no	no	no	no
no	yes, Peds QL (S)	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	Approximately 200 subjects were planned for inclusion in the novel PRO substudy (p41)	no	no	no	no	no	no
no	yes, SAG consulted on 18JUN2018 No information if patient representatives were involved	no	no	no	no	no	no	yes, SAG-O consulted on 13FEB2019 No information if patient representatives were involved	no	no
no	no	no	no	yes, AHEG consulted on 5JUL2018 No information if patient representatives were involved	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no

Xerava	Slenyto	Mektovi	Braftovi	Ilumetri	Nerlynx	Mvaynd	Cablivi	Onpattro	Yescarta	Mepsevii
Eravacycline	Melatonin	Binimetinib	Encorafenib	Tildrakizumab	Neratinib	Vonicog alfa	Caplacizumab	Patisiran sodium	Axicabtagene ciloleucel	Vestronidase alfa
Chemical	Chemical	Chemical	Chemical	Biological	Chemical	Biological	Biological	Chemical	Gene Therapy	Biological
EMEA/H/C/004237	EMEA/H/C/004425	EMEA/H/C/004579	EMEA/H/C/004580	EMEA/H/C/004514	EMEA/H/C/004030	EMEA/H/C/004454	EMEA/H/C/004426	EMEA/H/C/004699	EMEA/H/C/004480	EMEA/H/C/004438
Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised
no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	yes
no	no	no	no	no	no	no	no	yes	no	no
no	no	no	no	no	no	no	yes	yes	yes	yes
20.09.2018	20.09.2018	03.09.2018	19.09.2018	17.09.2018	31.08.2018	31.08.2018	30.08.2018	27.08.2018	23.08.2018	23.08.2018
Tetraphase Pharmaceuticals Ireland Limited	RAD Neurim Pharmaceuticals EEC SARL	Pierre Fabre Médicament	Pierre Fabre Médicament	Amgen S.A	Pierre Fabre Médicament	Biogen Netherlands B.V.	Ablynx NV	Alnylam Netherlands B.V.	Kite Pharma EU B.V.	Ultragenyx Germany GmbH
Xerava is indicated for the treatment of complicated intra-abdominal infections (cIAI) in adults. Consideration should be given to official guidance on the appropriate use of antibacterial agents.	Slenyto is indicated for the treatment of insomnia in children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD) and / or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient.,	Stimetinib in combination with encorafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.	Encorafenib is indicated in combination with binimetinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy	Ilumetri is indicated for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy.	Nerlynx is indicated for the extended adjuvant treatment of adult patients with early-stage hormone receptor-positive HER2-overexpressed/amplified breast cancer and who are less than one year from the completion of prior adjuvant trastuzumab based therapy.	Myvynd is indicated in adults (age 18 and older) with von Willebrand Disease (VWD), when desmopressin (DDAVP) treatment alone is ineffective or not indicated for the Treatment of haemorrhage and surgical bleeding. Prevention of surgical bleeding. Myvynd should not be used in the treatment of Haemophilia A.	Cablivi is indicated for the treatment of adults experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression.	Onpattro is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy.,	Yescarta is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.	Mepsevii is indicated for the treatment of non-neurological manifestations of Mucopolysaccharidosis VII (MPS VII; Sly syndrome).
no	yes, Composite Sleep Disturbance Index (CSDI Score) (S) Strength and Difficulties Questionnaire (SDQ) (S) Caregiver - Epworth Sleepiness Scale (ESS) (S) Caregiver - Well-being Index (WHO-5) (S) Caregiver - Pittsburgh Sleep Quality Index (PSQI) (S)	no	yes, Functional Assessment of Cancer Therapy - Melanoma (FACT-M) (oS) EORTC QLQ-C30 (oS) EQ-5D-5L (oS)	yes, DLQI (S)	yes, FACT-B (E) EQ-5D (E)	yes, SF-36 (E) VWD Impact Questionnaire (E)	no	yes, Norfolk Quality of Life Questionnaire - Diabetic Neuropathy (Norfolk QoL- DN) (S) Rasch-built Overall Disability Scale (R-ODS) (S) Composite Autonomic Symptom Score 31 (COMPASS 31) (S) EQ-5D/VAS (E)	yes, EQ-5D (S)	yes, MPS Health Assessment Questionnaire (HAQ) PedsQL (S)
no	yes, Children's Global Assessment Scale (CGAS) (S)	no	no	no	no	no	no	yes, Neuropathy Impairment Score (NIS) (PE)) PND-Score FAP Stage	no	yes, PGI-C
no	yes, Caregiver - Pittsburgh Sleep Quality Index (PSQI) (S)	no	no	no	no	no	no	no	no	yes, PedsQL (S) MPS HAQ
no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	yes, SAG consulted on 11 JAN 2018 - **Patient representative(s) were involved** From a patient and clinical perspective, as long as benefits, risks, and uncertainties were clearly understood by patients and clinicians, it was considered that meaningful treatment decisions could be made and that treatment with neratinib could be a good option for some patients (e.g., based on risk factors such as patients with many involved lymph nodes). p11 7	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no

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Pifeltro	Luxturna	Jivi	Takhzyro	Potelligeo	Darzalex	Vabomere	Engerix	Symkevi	Verzenios	Imfinzi
Doravirine	Voretigene neparvovec	Damoctocog alfa pegol	Lanadelumab	Mogamulizumab	Daratumumab, Hyaluronidase (human recombinant)	Meropenem trihydrate, Vaborbactam	Gadoxetic acid	Tezacaftor, Ivacaftor	Abemaciclib	Durvalumab
Chemical	Gene Therapy	Biological	Biological	Biological	Chemical	Chemical	Biological	Chemical	Chemical	Biological
EMEA/H/C/004747	EMEA/H/C/004451	EMEA/H/C/004054	EMEA/H/C/004806	EMEA/H/C/004232	EMEA/H/C/004796	EMEA/H/C/004669	EMEA/H/C/004648	EMEA/H/C/004692	EMEA/H/C/004302	EMEA/H/C/004771
Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised
no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no
no	no	yes	yes	no	no	no	no	no	no	no
no	yes	no	yes	yes	no	no	no	yes	no	no
22.11.2018	22.11.2018	22.11.2018	22.11.2018	22.11.2018	22.11.2018	20.11.2018	14.11.2018	31.10.2018	26.09.2018	21.09.2018
Merck Sharp & Dohme B.V.	Novartis Europharm Limited	Bayer AG	Shire Pharmaceuticals Ireland Ltd	Kyowa Kirin Holdings B.V.	Merck Sharp & Dohme B.V.	Menarini International Operations Luxembourg S.A.	Eli Lilly Nederland B.V.	Vertex Pharmaceuticals (Ireland) Limited	Eli Lilly Nederland B.V.	AstraZeneca AB
Pifeltro is indicated, in combination with other antiretroviral medicinal products, for the treatment of adults infected with HIV 1 without past or present evidence of resistance to the NNRTI class	Luxturna is indicated for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells.	Treatment and prophylaxis of bleeding in previously treated patients ≥ 12 years of age with haemophilia A (congenital factor VIII deficiency).	Takhzyro is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older.	Potelligeo is indicated for the treatment of adult patients with mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy	Darzalex is indicated for the treatment of adults infected with HIV 1 without past or present evidence of resistance to the NNRTI class, lamivudine, or tenofovir.	Vabomere is indicated for the treatment of the following infections in adults: Complicated urinary tract infection (cUTI), including pyelonephritis Complicated intra-abdominal infection (cIAI) Hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP) Treatment of patients with bacteraemia that occur in association with, or is suspected to be associated with, any of the infections listed above Vabomere is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options. Consideration should be given to official guidance on the appropriate use of antibacterial agents.	Engerix is indicated for the prophylaxis of migraine in adults who have at least 4 migraine days per month.	Symkevi is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who are heterozygous for the F508del mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T.	Verzenios is indicated for the treatment of women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy. In pre or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.	Imfinzi as monotherapy is indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.
no	no	yes, Haemophilia Quality of Life Questionnaire for Children (Haemo-QoL) (S) Haemophilia-specific Quality of Life Questionnaire for Adults (Haemo-QoL-A) (S)	yes, AE-QoL (T)	yes, Skindex-29 (S) FACT-G (S) EQ-5D-3L (S) Pruritus Evaluation (Likert scale & Itch-Qo L) (S)	no	no	yes, PGI-I (S) PGI-S (S) Migraine Specific Quality of Life Questionnaire (MSQ) (S) MIDAS (S) Healthcare resource utilization (HCRU) Employment Status	yes, Cystic Fibrosis Questionnaire-Revised (CFQ-R) (Child/Parent) (S) SF-12 (no further information available)	yes, EORTC QLQ-C30 (S) QLQ-BR23 (S) EQ-5D-5L (S) mMPI-sf (S)	yes, EORTC QLQ-C30 (S) EORTC QLQ-LC 13 (S)
no	no	no	no	no	no	no	no	no	no	no
no	no	yes, Haemophilia Quality of Life Questionnaire for Children (Haemo-QoL) (S)	no	no	no	no	no	yes, CFQ-R (Child/Parent) (S)	no	no
no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no
no	yes, Natural History of Individuals with Retinal Degeneration Due to Autosomal Recessive Mutations in the RPE65 Gene	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	Reference to Global Burden of Disease study (p7)	no	no	no
no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	yes, AHEG consulted on 19JUN 2018 No information if patient representatives were involved	no	no
no	no	no	no	no	no	no	no	no	no	no

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Zynquista	Skyrizi	Cresemba	Vizimpro	Aiovy	Rizmoic	Mulpleo (previously Lusutrombopag Shionogi)	Besremi	Erleada	Nerlynda	Alunbrig
Sotagliflozin	Risankizumab	Anidulafungin	Dacomitinib monohydrate	Fremanezumab	Naldemedine tosilate	Lusutrombopag	Ropeginterferon alfa-2b	Apalutamide	Mavacitinib	Brigatinib
Chemical	Biological	Biological	Chemical	Biological	Chemical	Chemical	Biological	Chemical	Chemical	Chemical
EMEA/H/C/004889	EMEA/H/C/004759	EMEA/H/C/004108	EMEA/H/C/004779	EMEA/H/C/004833	EMEA/H/C/004256	EMEA/H/C/004720	EMEA/H/C/004128	EMEA/H/C/004452	EMEA/H/C/004594	EMEA/H/C/004248
Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised
no	no	yes	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	yes	no
26.04.2019	26.04.2019	06.04.2019	04.04.2019	26.03.2019	18.02.2019	18.02.2019	15.02.2019	14.01.2019	18.12.2018	22.11.2018
Navigant Germany GmbH	AbbVie Deutschland GmbH & Co. KG	Pertola Netherlands B.V.	Pfizer Europe MA EEIG	Teva GmbH	Shionogi B.V.	Shionogi B.V.	AOP Orphan Pharmaceuticals AG	Janssen-Cilag International N.V.	Lupin Europe GmbH	Takeda Pharma A/S
Zynquista is indicated as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus with a Body Mass Index (BMI) ≥ 27 kg/m2, who have failed to achieve adequate glycaemic control despite optimal insulin therapy.	Skyrizi is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.	For adult patients treated with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when rev ersal of anticoagulation is needed due to life-threatening or uncontrolled bleeding..	Vizimpro, as monotherapy, is indicated for the first-line treatment of adult patients with locally advanced or metastatic non small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) activating mutations..	Aiovy is indicated for prophylaxis of migraine in adults who have at least 4 migraine days per month.	Rizmoic is indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have previously been treated with a laxative.	Mulpleo is indicated for the treatment of severe thrombocytopenia in adult patients with chronic liver disease undergoing invasive procedures	Besremi is indicated as monotherapy in adults for the treatment of polycythaemia vera without symptomatic splenomegaly.	Erleada is indicated in adult men for the treatment of non metastatic castration resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease.in adult men for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT).	Nerlynda is indicated for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders.	Alunbrig is indicated as monotherapy for the treatment of adult patients with anaplastic lymphomak inase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor. Alunbrig is indicated as monotherapy for the treatment of adult patients with anaplastic lymphomak inase ALK)positive advanced NSCLC previously treated with crizotinib
yes, Diabetes Treatment Satisfaction Questionnaire, status and change versions (DTSQ) (S) Brief Diabetes Distress Screening Instrument (DDS2) (S) Patient Safety Daily Diary-Numeric Rating Scale (PSDD-NRS) (Diary)	yes, DLQI Hospital Anxiety and Depression Scale (HADS) HAQ-DI Psoriasis Symptom Scale (PSS) DAS sPGA	n/a	yes, EQ-5D QLQ-C30 QLQ-LC13	yes, Migraine Disability Assessment (MIDAS) (S) Headache Impact Test (HIT-6) (S) Migraine Specific Quality of Life Questionnaire Migraine Specific Quality of Life Questionnaire (MSQoL) (E) PGIC (E) EQ-5D-5L (E) PHQ-2-9 (E) Work Productivity and Activity Impairment Questionnaire	yes, Patient Assessment of Constipation Quality of Life questionnaire (PAC-QOL) (S) Patient Assessment of Constipation Symptoms (PAC-SYM) (S) Subject Global Satisfaction (E) SF-36 (E) BMOA eDiary BSS e-Diary	no	yes, EQ-5D (oS) Change of JAK-2 allelic burden (oS)	yes, FACT-P (E) EQ-5D (E)	yes, Score of stiffness severity VAS (P) Individualized Neuromuscular Quality of Life Questionnaire (INQoL) (S)	yes, EORTC-QLQ-C30 (S)
no	yes, Nail Psoriasis Severity Index (NAPSI) Psoriasis Area and Severity Index (PASI) Psoriasis Scalp Severity Index (PSSI)	n/a	n/a	no	no	no	no	no	yes, CGI Efficacy index (Arzt/Patient) (P) Score of CMS (SE)	no
no	no	n/a	n/a	no	no	no	no	no	no	no
no	no	n/a	n/a	no	no	no	no	no	no	no
no	no	n/a	n/a	no	no	no	no	no	no	no
no	no	n/a	n/a	no	no	no	no	no	no	no
no	no	n/a	n/a	no	no	no	no	no	Assess the reliability and v alidity of a new clinical myotonia rating scale (CMS) to ev aluate myotonia sev erity (S) Patient's preference and willingness to continue treatment (p82/74) Preference between the 2 treatment periods	no
no	no	n/a	n/a	no	no	no	yes, SAG On cology consulted on 07/NOV/2018 Indication restriction No information if patient represenatives were involved	no	yes, SAG consulted on 6 JUL 2018 No information if patient represenatives were involved	no
no	no	n/a	n/a	no	no	yes, AHEG consulted on 4 DEC 2017 No information if patient represenatives were involved The Expert Advisory Group which was consulted for this application (see below, Additional expert consultation) also considered that trials of longer duration than the time frame of the placebo-controlled study would be required to establish the true magnitude of effect of velmanase alfa, especially in adult patients. However, the CHMP acknowledged that such trials could not realistically be expected in this very rare condition (p79.)	no	no	no	no
no	no	n/a	n/a	no	no	no	no	no	no	no

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Dectova	Zanamivir	Chemical	EMEA/H/C/004102	Authorised	no	no	no	no	26.04.2019	GlaxoSmithKline Trading Services Limited	Dectova is indicated for the treatment of complicated and potentially life-threatening influenza A or B virus infection in adult and paediatric patients (aged ≥6 months) when:The patient's influenza virus is known or suspected to be resistant to anti-influenza medicinal products other than zanamivir, and/orOther anti-viral medicinal products for treatment of influenza, including inhaled zanamivir, are not suitable for the individual patient.Dectova should be used in accordance with official guidance.	no	no	yes, Katz activities of daily Living Score (S)	no	no	no	no	yes, SAG consulted on 21JAN2019 No information if patient represenatives were involved	no	no
Waylivra	Volanesorsen sodium	Chemical	EMEA/H/C/004538	Authorised	yes	no	no	yes	3.05.2019	Akcea Therapeutics Ireland Limited	Waylivra is indicated as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate.	yes, Patient reported abdominal pain (Severity/Frequency) (S)	no	no	no	no	no	no	no	no	no
Palynziq	Pegvaliase	Chemical	EMEA/H/C/004744	Authorised	no	no	no	yes	3.05.2019	BioMarin International Limited	Palynziq is indicated for the treatment of patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood phenylalanine control (blood phenylalanine levels greater than 600 micromol/l) despite prior management with available treatment options.	yes, Profile of Mood States - Phenylketonuria (PKU-POMS) Self-Reported Total Mood Disturbance Score (S/T) Profile of Mood States - Phenylketonuria (PKU-POMS) Self-Reported Confusion Score (S/T)	yes, Total Score and Hyperactivity/Impulsivity Subscale Score (ADHD-RS HI) (S/T) ADHD-RS Inattention score - investigator-rated inattention score (S/T)	no	no	no	no	no	no	no	no
Lorviqua	Lorlatinib	Chemical	EMEA/H/C/004646	Authorised	yes	no	no	no	6.05.2019	Pfizer Europe MA EEIG	Lorviqua as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive advanced non small cell lung cancer (NSCLC) whose disease has progressed after: alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy; or, crizotinib and at least one other ALK TKI.,	yes, EORTC QLQ-C30 (S) EORTC Quality of Life Questionnaire - Lung Cancer Module (EORTC QLQ-LC13) (S)	no	no	no	no	no	no	no	yes, AHEG consulted on 28NOV2016 No information if patient represenatives were involved	no
Zynteglo	Autologous CD34+ cell enriched population that contains hematopoietic stem cells transduced with lentiglobin BB305	ATMP	EMEA/H/C/003691	Authorised	yes	no	yes	yes	29.05.2019	bluebird bio (Netherlands) B.V.	Zynteglo is indicated for the treatment of patients 12 years and older with transfusion-dependent β thalassaemia (TDT) who do not have a β0/β0 genotype, for whom haematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available.	yes, EuroQol-5D (E) EQ-5D-Y (E) Functional Assessment of Cancer Therapy - Bone Marrow Transplantation (FACT-BMT) (E) SF-36 (E) PedsQL €	no	yes, PedsQL (E)	no	no	no	no	no	no	no
Trecondi	Treosulfan	Chemical	EMEA/H/C/004751	Authorised	no	no	no	no	20.06.2019	medac Gesellschaft für klinische Spezialpräparate mbH	Treosulfan in combination with fludarabine is indicated as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in adult patients with malignant and non malignant diseases, and in paediatric patients older than one month with malignant diseases.	no	yes, Karnofsky Performance-Score	no	no	no	no	no	no	no	no
Esperoct	Turoctocog alfa pegol	Biological	EMEA/H/C/004883	Authorised	no	no	no	no	20.06.2019	Novo Nordisk A/S	Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency).	yes, PROs (not specified) (S) Bleed related health economic resource use and patient/caregiver burden (S)	no	no	no	no	no	no	no	no	no
Doptelet	Avatrombopag	Chemical	EMEA/H/C/004722	Authorised	no	no	no	no	20.06.2019	Dova Pharmaceuticals Ireland Limited	Doptelet is indicated for the treatment of severe thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo an invasive procedure.	no	no	no	no	no	no	no	no	no	no
Talzenna	Talazoparib	Chemical	EMEA/H/C/004674	Authorised	no	no	no	no	20.06.2019	Pfizer Europe MA EEIG	Talzenna is indicated as monotherapy for the treatment of adult patients with germline BRCA1/2 mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments (see section 5.1). Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine-based therapy, or be considered unsuitable for endocrine-based therapy.	yes, EORTC Quality of Life Questionnaire - Breast Cancer Module (EORTC QLQ-BR23) (E) QLQ-C30 (E) HRQoL - Data are not considered interpretable due to open study design	no	no	no	no	no	no	yes, SAG-Oncology (Date not provided) No information if patient represenatives were involved	no	no
Libtayo	Cemiplimab	Biological	EMEA/H/C/004844	Authorised	yes	no	no	no	28.06.2019	Regeneron Ireland U.C.	Libtayo as monotherapy is indicated for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation.	yes, EORTC QLQ-C30	no	no	no	no	no	no	no	no	no
Ultomiris	Ravulizumab	Biological	EMEA/H/C/004954	Authorised	no	no	no	no	2.07.2019	Alexion Europe SAS	Ultomiris is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH):, , in patients with haemolysis with clinical symptom(s) indicative of high disease activity, in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months.,	yes, FACIT-Fatique Scale (S) EORTC QLQ-C30 (oS)	no	no	no	no	no	no	no	no	no

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Giapreza	Angiotensin II acetate	Chemical	EMEA/H/C/004930	Authorised	no	no	no	no	23.08.2019	La Jolla Pharmaceutical II B.V.	Giapreza is indicated for the treatment of refractory hypotension in adults with septic or other distributive shock who remain hypotensive despite adequate volume restitution and application of catecholamines and other available vasopressor therapies.,	no	no	no	no	no	no	no	no	no	no
Epidyolex	Cannabidiol	Chemical	EMEA/H/C/004675	Authorised	no	no	no	yes	19.09.2019	GW Pharma (International) B.V.	Epidyolex is indicated for use as adjunctive therapy of seizures associated with Lennox Gastaut syndrome (LGS) or Dravet syndrome (DS), in conjunction with clobazam, for patients 2 years of age and older.	yes, ePRO - recording of Seizures Global Impression of Change in Seizure Duration (GICSD) (S) Quality of Life in Epilepsy Inventory-31 (QOLIE-31) (S) Cognitive Assessment Battery score (S) Sleep Disruption 0–10 Numerical Rating Scale (0–10 NRS) score (S) Epworth Sleepiness Scale (ESS) score (S)	no	yes, Quality of Life in Childhood Epilepsy Questionnaire (QOLCE) (S) Vineland-II Score (S)	no	no	no	no	yes, SAG consulted on 13JUN2019 - **Patient representatives were involved** the patient representatives supported adding a clear warning about the potential worsening while on treatment with the product, since there is the perception in the patient community that this is a "natural" product and hence should not be expected to have any negative effects. This perception will potentially affect the reports of worsening that may come from the parents and caregivers (p152). Other experts, including the patient representatives, were against a restriction, stating the following reasons (p153) • Such an indication will require the use of clobazam in order to prescribe CBD, thus patients who cannot tolerate clobazam (often observed in children) will not be given the option to use CBD for treatment. This situation was highlighted by the patient representatives as undesirable. • It is likely that a restricted indication may not be followed in practice – it will potentiate off- label use • Individual patients may still exist that will show clinically relevant benefit and having an additional effective treatment option is appreciated. A Scientific Advisory Group (SAG) convened to discuss the issue of the clinical relevance of effect of CBD-OS in patients not receiving clobazam "were not fully convinced that they (the efficacy data) are reliably demonstrating an effect in patients OFF –clobazam treatment, mainly, from a statistical point of view." (p188)	no	no
Vitrakvi	Larotrectinib sulfate	Chemical	EMEA/H/C/004919	Authorised	yes	no	no	no	19.09.2019	Bayer AG	Vitrakvi as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion,who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, andwho have no satisfactory treatment options.	no	no	no	no	no	no	no	yes, SAG consulted on 27FEB2019 No information if patient represenatives were involved Based on the results of Phase I clinical trials in a specific, yet limited patient population, minimal development work was done with respect to the capsule finished product. While simple blends were considered as a formulation approach, given the clinical response, and in order to expedite drug to patients, active substance in a capsule was chosen as the preferred finished product (p22).	no	no
Inbrija	Levodopa	Chemical	EMEA/H/C/004786	Authorised	no	no	no	no	19.09.2019	Acorda Therapeutics Ireland Limited	Inbrija is indicated for the intermittent treatment of episodic motor fluctuations (OFF episodes) in adult patients with Parkinson's disease (PD) treated with a levodopa/dopa-decarboxylase inhibitor.	yes, PGI-C MDS-UPDRS	yes, MDS-UPDRS	no	no	no	no	no	no	no	no
Trogarzo	Ibalizumab	Biological	EMEA/H/C/004961	Authorised	no	no	no	no	26.09.2019	Theratechnologies Europe Limited	Trogarzo, in combination with other antiretroviral(s), is indicated for the treatment of adults infected with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen.	yes, QoL (S) not further specified	no	no	no	no	no	no	yes, SAG consulted on 11APR2019 No information if patient represenatives were involved	no	no
Xospata	Gilteritinib fumarate	Chemical	EMEA/H/C/004752	Authorised	no	no	no	yes	24.10.2019	Astellas Pharma Europe B.V.	Xospata is indicated as monotherapy for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation.	yes, Functional Assessment of Chronic Illness Therapy - Dyspnea (FACIT-Dyspnea) (E) Functional Assessment of Cancer Therapy - Leukemia (FACT-Leu) (E) EQ-5D-5L (E)	no	no	no	no	no	no	no	no	no
Rhokiinsa	Netarsudil	Chemical	EMEA/H/C/004583	Authorised	no	no	no	no	19.11.2019	Aerie Pharmaceuticals Ireland Ltd	Reduction of elevated intraocular pressure (IOP) in adult patients with primary open-angle glaucoma or ocular hypertension.	no	no	no	no	no	no	no	no	no	no
Rinvoq	Upadacitinib	Chemical	EMEA/H/C/004860	Authorised	no	no	no	no	16.12.2019	AbbVie Deutschland GmbH & Co. KG	Rinvoq is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). Rinvoq may be used as monotherapy or in combination with methotrexate.	yes, Health Assessment Questionnaire (HAQ-DI) (S) FACIT-F (S) SF-36 (S) EuroQoL-5D-5L Rheumatoid Arthritis Work Instability Scale (RA-WIS) (S) Patient Global Assessment of Disease Activity Severity and duration of morning stiffness (S)	yes, Physician Global Assessment of Disease Activity VAS	no	no	no	no	no	no	no	no
Quofenix	Delafloxacin meglumine	Chemical	EMEA/H/C/004860	Authorised	no	no	no	no	16.12.2019	A. Menarini Industrie Farmaceutiche Riunite s.r.l.	Quofenix is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections (see sections 4.4 and 5.1).Consideration should be given to official guidance on the appropriate use of antibacterial agents.	yes, ePRO - pain reduction	no	no	no	no	no	no	no	no	no
Baqsimi	Glucagon	Biological	EMEA/H/C/003848	Authorised	no	no	no	no	16.12.2019	Eli Lilly Nederland B.V.	Baqsimi is indicated for the treatment of severe hypoglycaemia in adults, adolescents, and children aged 4 years and over with diabetes mellitus.	no	no	no	no	no	no	no	no	no	no
Spravato	Esketamine hydrochloride	Chemical	EMEA/H/C/004535	Authorised	no	no	no	no	18.12.2019	Janssen-Cilag International N.V.	Spravato, in combination with a SSRI or SNRI, is indicated for adults with treatment-resistant Major Depressive Disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode.	yes, Patient Health Questionnaire (PHQ-9 Depression) (S) Sheehan Disability Scale (SDS) (S) Generalized Anxiety Disorder - 7 (GAD-7) (S) EQ-5D-5L (S)	yes, Sheehan-Clinical Global Improvement Scale (S-CGI)	no	no	no	no	no	no	no	no

Annex 2: List of Medicinal Products approved during the time period 01 January 2017 - 31 December 2019 by the FDA

DUPIXENT	OCREVUS	ZEJULA	AMVENDO	SYMPROIC	ADAGO	KISQALI	XERMELO	SILIQ	EMFLAZA	PARSABIV	TRULANCE	**Medicines name**
DUPILUMAB	OCRELIZUMAB	NIRAPARIB TOSYLATE	AVELUMAB	NALDEMEDINE TOSYLATE	SAFINAMIDE MESYLATE	RIBOCICLIB SUCCINATE	TELOTRISTAT ETIPRATE	BRODALUMAB	DEFLAZACORT	ETELCALCETIDE	PLECANATIDE	**Active substance**
BLA #761055	BLA #761053	NDA #208447	BLA #761049	NDA #208894	NDA #207145	NDA #209092	NDA #208794	BLA #761032	NDA #209894	NDA #208325	NDA #208745	**Number**
Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	**Authorisation status**
no	yes	yes	yes	no	no	no	yes	no	yes	no	no	**Fast Track**
no	no	yes	no	no	no	yes	yes	no	yes	no	no	**Priority Review**
no	no	no	yes	no	no	no	no	no	no	no	no	**Accelerated Approval**
yes	yes	yes	yes	no	no	yes	yes	no	no	no	no	**Breakthrough Therapy**
no	no	yes	yes	no	no	no	yes	no	yes	no	no	**Orphan medicine**
28.03.17	28.03.17	27.03.17	23.03.17	23.03.17	21.03.17	13.03.17	28.02.17	15.02.17	09.02.17	07.02.17	09.01.17	**Authorisation date**
29.07.16	28.04.16	31.10.17	23.09.16	23.03.16	29.12.15	29.09.16	30.03.16	18.11.15	09.06.16	24.08.15	29.01.16	**Submission date**
REGENERON PHARMACEUTICALS	GENENTECH INC	GLAXOSMITHKLINE	EMD SERONO INC	BDSI	MODUS	NOVARTIS	LEXICON PHARMS INC	VALEANT LUXEMBOURG	PTC THERAP	KAI PHARMS INC	SALIX	**Marketing authorisation holder / company name**
DUPIXENT is an interleukin-4 receptor alpha antagonist indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids	OCREVUS is a CD20-directed cytolytic antibody indicated for the treatment of patients with relapsing or primary progressive forms of multiple sclerosis	ZEJULA is a poly(ADP-ribose) polymerase (PARP) inhibitor indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy	AMVENDO is a programmed death ligand-1 (PD-L1) blocking antibody indicated for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC). (1)	SYMPROIC is an opioid antagonist indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain	ADAGO is a monoamine oxidase type B (MAO-B) inhibitor indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes	KISQALI is a kinase inhibitor indicated in combination with an aromatase inhibitor as initial endocrin-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer	Xermelo is a tryptophan hydroxylase inhibitor indicated for the treatment of carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy.	SILIQ is a human interleukin-17 receptor A (IL-17RA) antagonist indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies	EMFLAZA is a corticosteroid indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients 5 years of age and older (1).	Secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis	TRULANCE is a guanylate cyclase-C agonist indicated in adults for treatment of chronic idiopathic constipation (CIC).	**Approved condition / indication**
BLA	BLA	Type 1 - New Molecular Entity	BLA	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	BLA	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	**Submission Classification**
yes, Pruritus Numeric Rating Scale (S) Pruritus Categorical Scale Patient-Oriented Eczema Measure (POEM) (S) Dermatology Life Quality Index (DLQI) (S) EQ-5D Hospital Anxiety and Depression Scale (HADS) (S) Patient Global Assessment of Disease e Patient Global Assess ment of Treatment Sino-Nasal Outcome Test (SNOT) Asthma Control Questionnaire (ACQ-6)	yes, Columbia-Suicide Severity Rating Scale (C-SSRS) (S) SF-36 (S)	yes, Functional Assessment of Cancer Therapy - Ovarian Symptom Index (FACT-FOSI) (S) EQ-5D-5L (S) Neuropathy questionnaire (S) Reviewer Comments: The composite FOSI score is problematic from a regulatory perspective because it combines assessments of disease symptoms and treatment side effects, with more global impacts, such as quality of life and worry about prognosis. Elements more distal to disease and treatment related symptoms, such as worry and global quality of life, are influenced by multiple non-drug factors. Including these global elements in the overall score may decrease responsiveness to the effect of a drug, making the composite FOSI results difficult to interpret. (pt 1-94) Reviewer Comments: The neuropathy questions have not been developed among patients with chemotherapy induced peripheral neuropathy.	yes, EuroQol EQ-5D - not further described Functional Assessment of Cancer Therapy – Melanoma questionnaires - not further described Added optional patient interviews to the health-related quality of life assessments and a new exploratory endpoint regarding the subjects experience with their disease and treatment - not further described	yes, Subject eDiary (PS) - Bowel Movement and Constipation Assessment (BMCA), laxative and opioid medication use Patient Assessment of Constipation Symptoms (PAC-SYM) S/E) Patient Assessment of Constipation Quality of Life question naire (PAC-QOL) (S/E) SF-36 Health Survey (SF-36® / SF-36v2®) (E) Subject Global Satisfaction (SG S) (S/E) Subjective Opiate Withdrawal Scale (SOWS) 11-item questionnaire (Severity of pain)	yes, EuroQol EQ-5D - not further described Functional Assessment of Cancer Therapy – Melanoma questionnaires - not further described Added optional patient interviews to the health-related quality of life assessments and a new exploratory endpoint regarding the subjects experience with their disease and treatment - not further described	yes, Unified Parkinson's Disease Rating Scale (UPDRS) (I & II & III & IV) Part II - self-evaluation (S) Parkinson's Disease Questionnaire (PDQ-39) (S) Cognitive PD Battery test (S)	yes, EORTC Quality of Life Questionnaire - Core Questionnaire (EORTC QLQ-C30) (S) EORTC Quality of Life Questionnaire - Breast Cancer Module (EORTC QLQ-BR23) (S) EuroQoL 5-Dimension 5-Level (EQ-5D-5L) (S)	yes, EORTC QLQ-C30 (Supp) EORTC Quality of Life Questionnaire - Neuroendocrine Carcinoid Module (EORTC QLQ-GINET21) (Supp) Adequate relief of CS symptoms associate with GI symptoms (Supp) Part of a sub-study: Patient perception of Change in BMs Patient Satisfaction with Study medication	yes, Psoriasis Symptom Inventory (PSI) (S) Columbia-Suicide Severity Rating Scale (C-SSRS) (S) Patient Health Questionnaire (PHQ) (PHQ-8) (S)	no	yes, Naus ea Vomiting System Assessment (NVSA)	yes, Complete spontaneous bowel movement (CSBM) stool frequency (PS) Spontaneous bowel movement (SBM) stool frequency (S) stool consistency (S) straining (S) Patient Global Assessment (PGA) severity and change anchor scales (A) Patient Assessment of Constipation Symptoms (PAC-SYM) (A) Patient Assessment of Constipation Quality of Life questionnaire (PAC-QOL) (A) Daily Bowel movement (BM) and Symptoms Diary (PS) Applicant did not submit a full Patient reported outcome (PRO) evidence dossier (pt0	**PRO**
yes, Investigator's Global Assessment Scale (IGA Scale) (P) Eczema Area and Severity Index (EASI) (S) Global Individual Signs Score (GISS) (S) Scoring in Atopic Dermatitis (SCORAD) (S) Body Surface Area (BSA) (S)	yes, Columbia-Suicide Severity Rating Scale (C-SSRS) (S) No Evidence of Disease Activity (NEDA) (S) Expanded Disability Status Scale (EDSS) Functional Systems Score (FSS) Ambulation Score	no	no	yes, Clinical Opiate Withdrawal Scale (COWS)	yes, Unified Parkinson's Disease Rating Scale (UPDRS) (I & II & III & IV)	no	yes, Clinician rated patient reported meaningful change in BMs. In a semi-structured interview patients were asked about symptom changes, including their perception of the clinical relevance of a reduction in BM frequency	yes, Physician Global Assessment (+PGA) (P) Psoriasis Area and Severity Index (PASI) (P) Body surface area (BSA) (S) Psoriasis Scalp Severity Index (PSSI) (S) SSA (S) Nail Psoriasis Severity Index (NAPSI) (S) PHQ-8 (S) Columbia-Suicide Severity Rating Scale (C-SSRS) (S)	yes, Physician global assessment	no	no	**ClinRO**
no	no	no	no	no	no	no	no	no	no	no	no	**ClinRO**
yes, Asthma Control Questionnaire (ACQ-5)	yes, Multiple Sclerosis Functional Composite Score (MSFCS Score) (S)	no	no	no	no	no	no	no	no	no	no	**PerfO**
no	no	no	yes, Natural disease history study of metastatic Merkel cell carcinoma Study 100070-Obs001 (KnowMerkel Health record database)	no	no	no	no	no	no	no	no	**Natural Disease History Study**
no	no	no	no	no	no	no	no	no	no	no	no	**Patient Preference Study**
yes, Human factor's validation study (Consumer study reviews) https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761055Orig1s000TherR.pdf	no	no	no	no	no	no	no	no	no	no	no	**Other**
no	no	no	no	no	no	no	no	yes, Dermatologic and Ophthalmic Drug Advisory Committee of the FDA on 19JUL2016 (Safety specs--> Suicide **One patient representatives** involved in the meeting confirmed by final meeting roster	no	no	no	**Advisory Committee**
no	no	no	no	no	no reference made to existing Voice to Patient for Parkinson's disease date Sep 2015	no	no	no reference made to existing Voice to the Patient Reports for Psoriasis March 2016	no	no	no	**Voice of the Patient report (PFOD Meeting)**
no	no	no	no	no	no	no	no	No	no	no	no	**Patient Experience Data Statement**
no	no	no	no	no	no	no	no	no	no	no	no	**Patient Consultation (SGE)**
no	no	no	no	no	no	no	no	Yes, Reference to a survey in 2014 conducted by National Psoriasis Foundation (NPF) about impact on Quality of Life	no	no	no	**Other**

EMA

FDA

BESPONSA	IDHIFA	NERLYNX	TREMFYA	BIDV XXIA	BAVDELA	REVZARA	RADICAVA	IMFINZI	ALUNBRIG	RYDAPT	BRINEURA	INGREZZA
INOTUZUMAB OZOGAMICIN	ENASIDENIB MESYLATE	NERATINIB MALEATE	GUSELKUMAB	BEFRIXABAN	DELAFLOXACIN MEGLUMINE	SARILUMAB	EDARAVONE	DURVALUMAB	BRIGATINIB	MIDOSTAURIN	CERLIPONASE ALFA	VALBENAZINE TOSYLATE
BLA #761040	NDA #209606	NDA #208051	BLA #761061	NDA #208383	NDA #208810	BLA #761037	NDA #209176	BLA #761069	NDA #208772	NDA #207997	BLA #761052	NDA #209241
Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised
no	yes	no	no	yes	yes	no	no	no	no	yes	no	yes
no	yes	no	no	yes	yes	no	no	yes	yes	yes	no	yes
no	no	no	no	no	no	no	no	yes	yes	no	no	no
yes	no	no	no	no	no	no	no	yes	yes	yes	yes	yes
yes	yes	no	no	no	no	yes	no	yes	yes	yes	yes	no
17.08.17	01.08.17	17.07.17	13.07.17	23.06.17	19.06.17	22.05.17	05.05.17	01.05.17	28.04.17	28.04.17	27.04.17	11.04.17
20.12.16	30.12.16	19.07.16	16.11.16	23.10.16	18.10.16	30.10.15	16.06.16	13.10.16	28.08.16	29.08.16	27.05.16	11.08.16
WYETH PHARMS INC	CELGENE CORP	PUMA BIOTECH	JANSSEN BIOTECH	PORTOLA PHARMS INC	MELINTA	SANOFI SYNTHELABO	MITSUBISHI TANABE	ASTRAZENECA UK LTD	ARIAD	NOVARTIS	BIOMARIN PHARM	NEUROCRINE
BESPONSA is a CD22-directed antibody-drug conjugate (ADC) indicated for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).	IDHIFA is an isocitrate dehydrogenase-2 inhibitor indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA- approved test	NERLYNX is a kinase inhibitor indicated for the extended adjuvant treatment of adult patients with early stage HER2-overexpres sed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy.	TREMFYA is an interleukin -23 blocker indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are c andidates for systemic therapy or phototherapy.	BIDV XXIA is a factor Xa (FXa) inhibitor indicated for the prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illn ess who are at risk for thromboembo lic complications due to moderate or severe restricte d mobility and other risk factors for VTE.	BAVDELA is a fluoroquinolone antibacterial ind icated in adults for the t reatment of acute bacterial skin and skin structure infections (ABSSSI) caused by desi gnated susceptible bacteria. (1.1) To reduce the d evelopment of drug-resistant b acteria and maintain th e effectiveness of BAVDELA and other antibacterial dru gs, BAVDELA should be used only to treat infections that are prove n or strongly suspected to be caused by b acteria.	REVZARA® is an interleukin-6 (IL-6) receptor antagonist indicated for treatment of adult patients with moderately to severely activ e rheumatoid arthritis who hav e had an inadequate resp onse or intoler ance to one or more disease-modifyin g antirheumatic drugs (DMARDs).	RADICAVA is indicated for the treatment of amyotrophic lateral sclerosis (ALS)	IMFINZI is a programmed death-ligan nd 1 (PD-L1) blocking antibody indicated for the treatment of patients with: . Loc ally advanced or metastatic uro thelial carcinoma who: . hav e disease progression during o r following platinu m-containing c hemotherapy. (1) . hav e disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-conta ining chemothe rapy.	ALUNBRIG is a kinase inhibitor indicated for the treatment of patients with anaplastic ly mphoma kinase (ALK)-p ositive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.	RYDAPT is a kinase inhibitor indicated for the treatment of adult patients with: • Newly diagnosed acute myeloid leuke mia (AML) that is FLT3 mutation- positive as detected by an FDA-approved test , in combination with standard cytarabine and dauno rubicin induction and cytarabine consolidation (1.1) Limitations of Use: RYDAPT is not indicated as a s single-agent induction therapy for the treatment of patients with AML. • Aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm	Brineurais a hydrolytic lysosomal N-terminal tripeptidyl-peptidase in dicated to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinos is type 2 (CLN2), als o known as tripeptidyl peptidase 1 (TPP1) deficiency.	INGREZZA is a vesicular monoamine transporter 2 (VMAT 2) inhibitor indicated for the treatment of adults with tardive dyskinesia.
BLA	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	BLA	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	BLA	Type 1 - New Molecular Entity	BLA	Type 1 - New Molecular Entity	Type 1- New Molecular Entity	BLA	Type 1- New Molecular Entity
yes, EORTC Quality of Life Questionnaire - Core Questionnaire (EORTC QLQ -C30)	no	yes, Functional Assessment of Cancer Therapy - Breast Cancer (FACT-B) (E) EuroqolEQ-5D (EQ-5D) (E)	yes, DLQI (S but FDA proposed to use as explo ratory; not included in the review) Psoriasis Signs and Symptoms Diary (PSSD) (S)	yes, Economic and Quality of Life (EQ OL)	no	yes, Health Assessm t Questionnaire (HAQ-DI) (P) Pa ient's assessment of pain (P) Pa ient's global assessment of disease activity (P) SF -36 Health Sur vey (SF-36® / SF-36v2®) Eu roQol, 5-Dime nsion 3-Level (EQ-5D-3L) FACIT Fatigue Scale Morning stiffness Visual Analog Scale Rheumatoid Arthritis Work Productivity Survey Rheumatoid Arthritis Impact of Dis ease Clinical Disease Activity Index (CDAI) Disease Activity Score 28 (DAS-28) (P) Simple Disease Activity Index (SDAI)	yes, Amy otrophic Lateral Sclerosis Assessment Scales (ALSAS) (P)	no	yes, EORT C Quality of Life Questionnaire - Core Questio nnaire (EORT C QLQ -C30) (S)	yes, Memorial Symptom Assessment Scale (MSAS scale) (E) SF -12 Heal th Survey (SF -12® / SF -12v2®) (E)	yes, CLN2 spec Quality of Life questionnaire (O) Pediatric Quality of Life Inv entory™ (PedsQL™) Parent Family Impact Module (O) EuroQol, 5-Dimension 5-Level (EQ-5D-5L) (O)	yes, Patient Global Impression of Change (PGIC) (S) Tardive Dyskinesia Impact Sc ale (TDIS) (Eff) Assessment of Most Bothersome Movement in Tardive Dyskinesia (AMBMTD) (Eff) Calgary Depression Scale for Schizophrenia (CDSS) (Saf) Montgomery-Asberg Depression Rating Scale (MADRS)
no	no	no	yes, IGA (PS) PASI (S)	no	no	yes, American College of Rheumatology 2050/70 criteria (ACR2050/70) (PS) Ph ysician's global assessment of disease activity Helpe modified Total Sharp Score (mTSS) (P) Clinical Disease Activity Index (CDAI) Disease Activity Score 28 (DAS-28) (P) Simple Disease Activity Index (SDAI)	yes, Amy otrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) (S) Limb modified Norr is scale	no	no	no	yes, CLN2 (Hamburg) rating scale (P) Denver II De velopment Scale (O)	yes, Abnormal Involuntary Movement Scale (AIMS) (P) Clinical Global Impression of Change-Tardive Dyskinesi (CGI-TD) (S) Columbia-Suicide Severity Rating Scale (C-SSRS) (Saf) Brief Psychiatric Rating Scale (BPRS) (Saf) Simpson-Angus Scale (SAS) (Saf) Positive and Negative Syndrome Scale (PANSS) (Saf) Young-Mania Rating Scale (YMRS) (Saf)
no	no	no	no	no	no	no	no	no	no	no	yes, Pediatric Quality of Life Inv entory™ (PedsQL™) Parent Family Impact Module (O)	no
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	yes, Given the uncertainty sur rounding the be nefit-risk profile of neratinib in the extended adjuvant setting, the multiple amendments which led to uncertainty in the magnitude of treatment effect, and the totality of neratinib's efficacy data in the context of other approvals in the adjuvant setting, a n Oncology Drug Advisory Co mmittee was convene d on May 24, 2017 to discuss and provide advice on this NDA. (p13 4) - Comittee voted in favor **Two patient representatives** involved in the meeting confirme d by final meeting roster	no	no	no	no	no	no	no	no The Div ision did not obtain the advice of the Oncologic Drug Ad visory Committee (ODAC) for this NDA. The Division obtained the ad vice of a practic ing oncologist with exp ertise in lung cancer and a patie nt (physician) with a history of lung cancer. Both Spec ial Government Employe es provided agreement in rega rds to the favorable risk-benefit a ssessment in the indicated patient population with u nmet need.	no	no	no, On January 4, 2017, the review division determined that this NDA did n ot require a public discussion, so the application was not taken to an Advisory Committee. The rationale for this decision was that while valbenazine is a new molecular entity, it has a similar mechanism to the previously-approved VMAT2 inhibitor tetrabenazine. Furthermore, while there are no currently-approved treatments for TD, the primary eff cacy endpoint (Abnormal Involuntary Movement Scale) is a widely-used c linical and research measure for assessing tardive dyskinesia. Finally, the application review did not identify any major safety issues that
no	no	no reference no made to ex isting 'Voice to Patient for breast cancer' dated Apr 2015	no reference made to existing 'Voice to Patient for psoriasis date March 2016	no	no	no	no	no	no reference made to e xisting 'Voice to Patient' for lung cancer dated June 2013	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no

Annex 2: List of Medicinal Products approved during the time period 01 January 2017 - 31 December 2019 by the FDA

RHOPRESSA	XIIPI	OZENPIC	HEMLIBRA (First product with 1.4 PED section)	MEPSEVII	FASENRA	RYDYMIS	VYZULTA	QALQUENCE	VIRZENIO	SOLOSEC	ALIQOPA	BENZNIDAZOLE
NETARSUDIL DIMESYLATE	OZENOXACIN	SEMAGLUTIDE	EMICIZUMAB	VESTRONIDASE ALFA-VJBK	BENRALIZUMAB	UBLITUXIMAB	LATANOPROSTENE BUNOD	ACALABRUTINIB	ABEMACICLIB	SECNIDAZOLE	COPANLISIB DIHYDROCHLORIDE	BENZNIDAZOLE
NDA #209254	NDA #209845	NDA #209637	BLA #761083	BLA #761047	BLA #761070	NDA #209939	NDA #210259	NDA #212115	NDA #212116	NDA #209363	NDA #209839	NDA #209570
Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised
no	no	no	no	no	no	yes	no	no	yes	yes	yes	no
no	no	no	no	no	no	yes	no	yes	yes	yes	yes	yes
no	no	no	no	no	no	no	no	yes	no	no	yes	yes
no	no	no	yes	no	no	yes	no	yes	yes	no	no	no
no	no	no	yes	yes	no	yes	no	yes	no	no	yes	yes
18.12.17	11.12.17	05.12.17	16.11.17	15.11.17	14.11.17	09.11.17	02.11.17	31.10.17	28.09.17	15.09.17	14.09.17	29.08.17
28.02.17	23.06.16	06.12.16	23.07.17	16.03.17	16.11.16	09.03.17	21.07.15	13.06.17	05.05.17	17.01.17	16.03.17	29.12.16
AERIE PHARMS INC	FERRER INTERNACIONAL	NOVO	GENENTECH INC	ULTRAGENYX PHARM INC	ASTRAZENECA AB	MERCK SHARP DOHME	BAUSCH AND LOMB	ASTRAZENECA	ELI LILLY AND CO	LURIN	BAYER HEALTHCARE	CHEMO RESEARCH SL
RHOPRESSA® (netarsudil ophthalmic solution) 0.02% is a Rho kinase inhibitor indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.	XIIPI is a quinolone antimicrobial indicated for the topical treatment of impetigo due to Staphylococcus aureus or Streptococcus pyogenes in adult and pediatric patients 2 months of age and older	OZEMPIC is a glucagon-like peptide 1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	HEMLIBRA is a bispecific factor IXa- and factor X-directed antibody indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors	MEPSEVII is a recombinant human lysosomal beta glucuronidase indicated in pediatric and adult patients for the treatment of Mucopolysaccharidosis VII (MPS VII, Sly syndrome)	FASENRA is an interleukin-5 receptor alpha-directed cytolytic monoclonal antibody (IgG1, kappa) indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.	RYDYMIS is a CMV DNA terminase complex inhibitor indicated for pro phylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients (R+) of an allogeneic hematopoietic stem cell transplant (HSCT).	VYZULTA is a prostaglandin analog indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.	CALQUENCE is a kinase inhibitor indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.	VIRZENIO TM is a kinase inhibitor indicated: • in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2-(HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy. (1) • as monotherapy for the treatment of adult patients with HR- positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.	SOLOSEC is a nitroimidazole antimicrobial indicated for the treatment of bacterial vaginosis in a dult women.	ALIQOPA is a kinase inhibitor indicated for the treatment of adult patients with relapsed follicular lymphoma (FL) who have re ceived at least two prior systemic therapie	Benznidazole Tablets, a nitroimidazole antimicrobial, is indicated in pediatric patients 2 to 12 years of age for the treatment of Chagas disease (American trypanosomiasis), caused by Trypanosoma cruzi
Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	BLA	BLA	BLA	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity
yes, Visual Function Index (VF-14) questionnaire	yes, Skin Infection Rating Scale (P)	yes, PRO (not further specified) (S)	yes, Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) (S) EQ-5D-5L (S) Haemo-QoL-Short Form Inhibitor-Specific Quality of Life with Aspects of Caregiver Burden (Adapted INHIB-QoL)	yes, MPS Health Assessment Questionnaire (MPS HAQ) (O) PROMIS Health Assessment Questionnaire (PROMIS HAQ) (O) Physician and Subject/Parent/Caregiver Clinical Global Impression (CGI) scales (O)	yes, Asthma Control Questionnaire (ACQ6) (S) Asthma Quality of Life Questionnaire (AQLQ) (S) EQ-5D-5L (S)	no	no	yes, EORTC QLQ-C30 (S)	yes, EORTC QLQ -C30 (S) PROMIS Fatigue SF 7a (S) Modified Brief Pain Inventory-Short Form (mBPI-sf) (S) EQ-5D -5L (FACIT -D, Bowel habits , Stool assessment tool)	yes, Telephone diary questions	yes, Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym) (S)	no
no	no	no	no	yes, Physician and Subject/Parent/Caregiver Clinical Global Impression (CGI) scales (O)	no	no	no	no	no	yes, Nugent Score (S) Investigator's Clinical Assessment (E)	no	no
no	no	no	no	yes, PedsQL (S) Childhood Health Assessment Questionnaire (CHAQ)	no	no	no	no	no	no	no	no
no	no	no	no	yes, Bruininks-Oseretsky Test of Motor Proficiency Second Edition (BOT-2) (S)	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	yes, Observational survey studies designed to captur e patient experience data	no	no	no	no	no	no	no	no	no
no	no	yes, on October 18, 2017, the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) convened to discuss the overall findings in EMPA-REG (outcome study), and to s pecifically address the questions --> voted in favor (Medical review p6/8) **One patient re presentatives** was involved in that meeting confirmed in the final meeting roster	no	no	no	no	no	no	no	no	no	no	no
no	no	no	n o reference made to existing 'Voice to Patient' for hsamophili a dated Oct 2014	no	no	no	no	no	no relerence made to a existing 'Voice to Patient' for bre ast Cancer dated Apr 2015	no	no	yes, Also available is the Voice of the Patient report (Chagas Disease), prepared to fulfill the objective of the Patient-Focused Drug Development. This is a commitment under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) that aims to more systematically gather patients' perspectives on their condition and available therapies to treat their condition. For the 'Voice of the Patient re port on Chagas disease please go to: https://www.fd a.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm606042.htm (pd7/48 in me dical review) Direct link to re port
no	no	no	First Product with a new section in the medical assessment section: 1.4. Patient Experience Data. Check list: Patient Experience Data Relevant to this Application (check all that apply) (PROs, ObsRO, Observational study) ObsRO - Cannot be confirmed	no	no	no	no	no	no	no	no	no
no	no	no	yes, Patient consultation 31OCT 2017. This Application was not presented to the Oncologic Drug Advisory Committee. The Application was discussed with a special government employee (SGE), Christopher Templin. He is a patient representative with experience with hemophilia B with a prior FIX inhibitor and exten sive involvement in advocacy for hemophilia. Mr. Templin was provided with a briefing document discussing the relevant efficacy and safety information related to the emicizumab development program. Specifically, Mr. Templin was asked to evaluate the benefit risk profile for emicizumab in light of the u nexpected TMA/TE safety signal. The Division held a teleconferenc e with Mr. Templin on October 31, 2017. He	no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	FDA includes information about external natural disease history studies (O) due to lack of natural history data provided by Applicant	no	no	no	no	no	no	no	no

Annex 2: List of Medicinal Products approved during the time period 01 January 2017 - 31 December 2019 by the FDA

AIMOVIG	LUCEMYRA	AKYNZEO	CRYSVITA	TAVALISSE	ILUMYA	TROGARZO	ERLEADA	BYMZIBO (COPACKAGED)	LUTATHERA	GIAPREZA	MACRILEN	SITAGLATIN
ERENUMAB-AOOE	LOFEXIDINE HYDROCHLORIDE	FOSNETUPITANT CHLORIDE HYDROCHLORIDE; PALONOSETRON HYDROCHLORIDE	BUROSUMAB-TWZA	FOSTAMATINIB	TILDRAKIZUMAB-ASMN	BALOZUMAB-UYK	APALUTAMIDE	IVACAFTOR; IVACAFTOR, TEZACAFTOR	LUTETIUM DOTATATE LU-177	ANGIOTENSIN II	MACIMORELIN ACETATE	SITAGLIPTIN
BLA #761077	NDA #209229	NDA #211493	BLA #761068	NDA #209291	BLA #761067	BLA #761069	NDA #210951	NDA #211601	NDA #208700	NDA 208360	NDA 209318	NDA #209803
Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised
no	yes	no	yes	no	no	yes	yes	yes	yes	no	no	no
no	yes	no	no	no	no	no	yes	yes	yes	yes	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	yes	no	no	yes	no	yes	no	no	no	no
no	no	no	yes	yes	no	yes	no	yes	yes	no	yes	no
17.05.18	16.05.18	19.04.18	17.04.18	17.04.17	20.03.18	06.03.18	14.02.18	12.02.18	26.01.18	21.12.17	20.12.17	19.12.17
17.07.17	26.07.17	20.04.17	17.09.17	15.04.17	23.03.17	03.05.17	09.10.17	28.06.17	18.04.18	29.06.17	04.11.13	19.12.16
AMGEN INC	US WORLDMEDS LLC	HELSINN HLTHCARE	ULTRAGENYX PHARM INC	RIGEL PHARMACEUTICALS INC	SUN PHARMA GLOBAL	TAIMED BIOLOGICS USA	JANSSEN BIOTECH	VERTEX PHARMS INC	AAA USA INC	LA JOLLA PHARMACEUTICAL CO	AETERNA ZENTARIS GMBH	MERCK SHARP DOHME
AIMOVIG is a calcitonin gene-related peptide receptor antagonist indicated for the preventive treatment of migraine in adults	LUCEMYRA is a central alpha-2 adrenergic agonist indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults.	AKYNZEO capsules is in dicated in combination with dexamethasone in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. AKYNZEO for injection is indicated in combination with dexamethasone in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.	CRYSVITA is a fibroblast growth factor 23 (FGF23) blocking antibody indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older.	TAVALISSE is a kinase inhibitor indicated for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.	ILUMYA is an interleukin-23 antagonist indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy	TROGARZO, a CD4-directed post-attachment HIV-1 inhibitor, in combination with other antiretroviral(s), is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing th eir current antiretroviral regimen.	ERLEADA is an an drogen receptor inhibitor indicated for the treatment of patients with non -metastatic cas tration-resistant prostate cancer	BYMZIBO is a combination of tezac aftor and ivacaftor, indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have a t least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezac aftor/ivacaftor based on in vitr o data and/or c linical evidence. (12.1, 14) If the patient's genotype is unknown, an FDA-clea red CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencin g when recommended by the	LUTATHERA is a radiolabeled somatostatin analog indicated for the treatment of somatostatin receptor - positive gastroenteropancreatic neuro-endocrine tumo rs (GEP-NETs), including foregut, midgut, and hindgut neuroen docrine tumors in adults.	GIAPREZA is a vasoconstrictor to increa se blood pressure in adults with se ptic or other dis tributive shock.	MACRILEN is a growth hor mone (GH) secretagogue receptor ag onist indicated for the diagnos is of adult growth hormone deficiency. (1).	SITAGLATIN is a sodium glucose co-transporter 2 (SGLT2) inhibitor indicated a s an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus
BLA	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	BLA	Type 1 - New Molecular Entity	BLA	BLA	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity
yes, C-SSRS Migraine Physical Function Impact Diary (MPFID) (S)	yes, Short Opiate Withdrawal Scale (SOWS) (P/S) Visual Analog Scale for Efficacy (VAS-E) (S)	yes, VAS (Diary) (S)	yes, Western Ontario and McMaster Universities Arthritis Index (WOMAC) (P) Brief Pain Inventory (BPI Q.3) (P)	no	yes, DLQI (O-E) IIF-36 (O-E) EQ-5D (O-E)	yes, QoL (not further specified) (S)	yes , FACT-P EQ-5D-3L	yes, Cystic Fibrosis Questionnaire-Revised (CFQ-R) (S)	yes, EOT C QLQ-30 (S/E) EORT C Quality of Life Questionnaire - Neuroendocrine Carcinoid Module (EORT C QLQ-GINET21) (S/E)	no	no	no
yes, C-SSRS	yes, Objective Opiate Withdrawal Scale-Handelsman (OOWS) (S) Clinical Opiate Withdrawal Scale Modified Clinical Global Impression Scale (MCGI) Subjec t Rater (S)	no	yes, Rickets Se verity Score (RSS) (P) RGI -Score (S)	yes, WHO bleeding scale (S) ITP Bleeding Scale (S)	yes, PGA (Co-PI S) PASI (Co-PI S)	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	yes, CPQ-R (S) (For age 8 -12)	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	yes, Natural History study - retro spective natura l history study was conducted in ch ildren age 5 – 14 years (CL002)	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	yes, Observ ational Study (CL001)	no	no	no	no	no	no	no	no	no
no	yes, a meeting of the Psychopharmacologic Drugs Advisory Committee was held on March 27, 2018 to discuss this application - voted in favor The committee members concluded that there is no signific ant improvement in efficacy from 2.4 mg/da 3.2 mg dose, but the incid ence of side effects such as bradycardia and hypotension is higher for the 3.2 mg/day dose. It was agreed that 2.4 mg/day should be approved, and some members recommended 3.2 mg/day dose if the 2.4 mg/day dose is not working. (p103, summary review)	no	no	no	no	no	no	no	no	no	no	no
no	no	no	yes, PFDD or other stakeholder meeting summary report: meeting with patients and the X-linked hypophosphatemia (XLH) network was held 04 DEC 2017 (No access to documentation)	no	yes, the impact of p soriasis on the daily lives of patients was among the topi cs discussed at a PatientFocused Drug Development Meeting for psoria sis held by the Agency on March 17, 2016.	no reference mad e to existing Voice to Patient for HIV dated Jun 2014	no	no	no	no	no	no
no, applic ation submitted after transition phase	yes, PRO and observ ational study Observ ation study cannot be confirmed, but ClinRO identified in this asses sment	no	yes, PRO, ClinRO, Obser vation study, natural history study Considered by FDA PFDD or other stakeh older meeting summary report	no	no	no	yes , PROs	no, but application submitted after transition phase	yes, PROs	no, application submitted after transition phase	no	yes, but no patient experience data were submitte d for this application
no	no	no	no	no	no	no	no	no	no, the Divi sion attempted to solicit the ad vice of three Special Government Employees (SGEs) who have expertise in the treatment of patients with GEP-NETs and one patient advocate. Because of clearance issu es for all SGEs identified and contacted, as well as time limitations precluding the completion of applications for waivers , no external con sultations were conducted.	no	no	no
no	n	no	no	no	no	no	no	no	no	no	n	no

Annex 2: List of Medicinal Products approved during the time period 01 January 2017 - 31 December 2019 by the FDA

GALAFOLD	POTELIGEO	MULPLETA	ORILISSA	TIBSOVO	VRKNTAFEL	TPOXX	ZEMDRI	MOXIDECTIN	OLUMIANT	PALYNZIQ	DOPTELET	LOKELMA
MIGALASTAT HYDROCHLORIDE	MOGAMULIZUMAB-KPKC	LUSUTROMBOPAG	ELAGOLIX SODIUM	IVOSIDENIB	TAFENOQUINE SUCCINATE	TECOVIRIMAT	PLAZOMICIN SULFATE	MOXIDECTIN	BARICITINIB	PEGVALIASE-PQPZ	AVATROMBOPAG MALEATE	SODIUM ZIRCONIUM CYCLOSILICATE
NDA #208623	BLA #761051	NDA #210923	NDA #210450	NDA #211192	NDA #210705	NDA #208627	NDA #210303	NDA #210357	NDA #207924	BLA #761079	NDA #210239	NDA #207078
Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised
yes	no	yes	no	yes	no	yes	no	no	no	yes	no	no
yes	no	yes	yes	yes	yes	yes	yes	yes	no	no	yes	no
yes	no	no	no	no	no	no	no	no	no	no	no	no
no	yes	no	no	no	yes	no	no	no	no	no	no	no
yes	yes	no	no	yes	yes	no	no	yes	no	yes	yes	no
10.06.18	09.08.18	31.07.18	23.07.18	20.07.18	20.07.18	13.07.18	25.06.18	13.06.18	31.05.18	24.05.18	21.05.18	18.05.18
13.12.17	04.10.17	26.12.17	23.08.17	21.12.17	27.11.17	08.12.17	25.10.17	13.10.17	15.01.16	30.06.17	21.09.17	26.05.15
AMICUS THERAPEUTICS	RYOVA KIRIN	SHIONOGI INC	ABBVIE INC	AGIOS PHARMACEUTICALS INC	GLAXOSMITHKLINE	SIGA TECHNOLOGIES	CIPLA USA	MOGH	ELI LILLY AND CO	BIOMARIN PHARM	AMARX INC	ASTRAZENECA PHARMS
GALAFOLD TM is an alpha-galactosidase A (alpha-Gal A) pharmacological chaperone indicated for the treatment of adults with a confirmed diagnosis of Fabry disease and an amenable galactosidase alpha gene (GLA) variant based on in vitro assay data.	POTELIGEO is a CC chemokine receptor type 4 (CCR4)- directed monoclonal antibody indicated for the treatment of adult patients with mycosis fungoides or Sézary syndrome after at least one prior systemic therapy	MULPLETA is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure.	ORILISSA is a gonadotropin-releasing hormone (GnRH) receptor antagonist indicated for the management of moderate to severe pain associated with endometriosis.	TIBSOVO is an isocitrate dehydrogenase-1 (IDH1) inhibitor indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test (1.1)	ARKNTAFEL is an antimalarial indicated for the radical cure (prevention of relapse) of Plasmodium vivax malaria in patients aged 16 years and older who are receiving appropriate antimalarial therapy for acute P. vivax infection	TPOXX is an inhibitor of the orthopoxvirus VP37 envelope wrapping protein and is indicated for the treatment of human smallpox disease in adults and pediatric patients weighing at least 13 kg.	ZEMDRI is an aminoglycoside antibacterial indicated for the treatment of patients 18 years of age or older with Complicated Urinary Tract Infections (cUTI) including Pyelonephritis. (1.1) As only limited clinical safety and efficacy data are available, reserve ZEMDRI for use in patients who have limited or no alternative treatment options. (1.1) To reduce the development of drug-resistant bacteria and maintain effectiveness of ZEMDRI and other antibacterial drugs, ZEMDRI should be used only to treat infections that are proven or strongly suspected to be caused by susceptible microorganisms.	Moxidectin is an anthelmintic indicated for the treatment of onchocer ciasis due to Onchocerca volvulus in patients aged 12 years and older.	Olumiant® (baricitinib) is indicated for the treatment of adult patients with moderately to se verely active rh eumatoid arthritis who have had an inadequate r esponse to one or more tumor necrosis factor (TNF) antago nist therapies.	Palyn ziq is a phenylalanine-metabolizing enzyme indicated to reduce blo od phenylalani ne concentrations in adult patients with phenylketon uria who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management	DOPTELET (avatrombopag) is a thrombopoietin receptor ag onist indicated for the treatment of thrombocytopenia in adult patients with ch ronic liver disease who are scheduled to undergo a p rocedure.	LOKELMA is a potassium binder indicated fo r the treatment of h yperkalemia in adults.
Type 1 - New Molecular Entity	BLA	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	BLA	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity
no	yes, Skindex-29 sc ore (S) FACT-G total score (S) EQ-5D-3L index score (S) Pruritus Evaluation (Likert Sc ale, Itchy QoL) (oS)	no	yes, Patient Global Impression of Change (PGIC)	no	no	no	yes, but not described	no	yes, Severity of Worst Tinnitu s ea NRS Patient's Assessm ent of Pain (VAS) (P) Patient's Global Assessment of Disease Activ ity (VAS) (P)Health Assessment Ques tionnaire-Disab ility Index (HAQ-DI) (P) American Colle ge of Rheumatology 20/50/70 criteria (ACR20/50/70) (P) Disease Activity Score (DAS)-28 Simple Disea se Activity Index (SDAI)	no	no	no
no	no	no	no	no	no	no	no	no	yes, Physician 's Global Assessment of Disease Activity (VAS) (P) American Colle ge of Rheumatology 20/50/70 criteria (ACR20/50/70) (P) Disease Activity Score (DAS)-28 Simple Disea se Activity Index (SDAI)	no	yes, Child-T urcotte-Pugh Score Model for End Stage Liver Disease Scale (MELD) World Health Organization (WHO) Bleeding Score Bleeding Academic Resear ch Consortium (BARC) score	no
no	no	no	no	no	no	no	yes, Acute Physiology And Chronic Health Evaluation (APACHE II)	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	fio	no	no	no	no	fio
no, the application for Galafold was not refer red to an FDA advisory co mmittee beca use outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.	no, Mogamulizumab was not pre sented to the Oncologic Drug Advisory Committee or other external consultants because the application did not raise significant efficacy or safety issues for the propo sed indication.	no	no, the Division deter mined that the NDA did not ra ise issues requiring external expert advice. Therefore, an advisory committee meeting was not convened to discuss the application.	no	yes Antimicrobial Drugs Ad visory Committee (AMDAC) held on 12.07.2018 **On e patient represen tatives** was involved in that meeting confirmed in the final meeting roster	yes, Antimicrobial Drugs Advisory Committee (AMDAC) on 01.052018 (Medical rev iew: p86-89) **On e patient represen tatives** was in volved in that meeting confirmed inthe final meeting roster	yes, Antimicrobial Drugs Advisory Committee (AMDAC) held on 2MAY2018 incl patient representatives (Medical review: p128) https://www.fda.gov/media/113161/download **On e patient represen tatives** was involved in that meeting confirmed in the final meeting roster	no not referred to an FDA advisory committee because there were no issues that would benefit from an advisory committee discussion	no An Advisory Committee meeting was not held to discuss this application because the safety and efficacy of DMARDs for RA are well understood. Another JAK inhibitor tofacitinib for RA was previously disc ussed at an AC meeting. There were no unique findings in the baricitinib program that would warrant a discussion at an Advisory Co mmittee meeting.	no	no not referred to an FDA advisory committee because the drug is not the first in its class and the app lication did not raise significant safety or efficacy issues that were unexpected for a drug of this class	no as noted in the CDT L review, the NDA was not presented to the FDA Cardiovascular and Renal Drugs Advisory Committee. Although the drug is a new molecular entity with a novel structure, we thought that the efficacy and safety were well characterized, straightforwar d, and in no way controversial. The clinical trials were co nventional in bo th their designs and their t endpoints. We did not anticipate novel efficac y or safety issues that would warrant discussion.
no	no	no	no	no	no	no	no	no	no	yes, FDA public meeting on Patient on RFDD for Neurological Manifestations of inborn err ors of metabolism. Jun 10, 2016 https://www.fda.gov/downloads/DrugsNewsEventsUCM536456.pdf	no	no
yes, see "FDA, Other"	yes, PROs	yes, but no patient experience data were submitted in the application	yes, PROs and qualitative study Qualitative study c annot be confirmed	yes, but no patient experience data were submitted in the application	no, but application submitted after transition phase	yes, but no patient experience data were su bmitted in the application	yes; PRO s Sit Clear RO identified in this assessment	yes, but no patient experience data were s ubmitted for this application	no Application before 21st CC ins ciment	yes Submission after transit on phase	yes, but not completed	no
no	no	no	no	no	no	no	no	no	no	no	no	no
yes, Patient experience data that was not submitted in the application, but was considered in this review: literature review on available therapies and unmet needs in the treatment of Fabry disease	no	no	no	no	no	no	no	no	no	Patient experience data that was not su bmitted in the application, but were co nsidered in the Review: 1) Meeting between FDA and treated patients in pegvaliase trials, with the National PKU Alliance, on October 31, 2017.	no	no

MAZYRA	SEYSARA	UBTAYO	EMGALITY	COPIKTRA	AJOVY	LUMOXITI	RYBELTRO	XERAVA	TAHNZYRO	QUERPAITE	QUACOMIT	ONPATTRO
OMADACYCLINE TOSYLATE	SARECYCLINE HYDROCHLORIDE	DSMPLIMAB-RWLC	GALCANEZUMAB-GNLM	DUVELISIB	FREMANEZUMAB-VFRM	MOXETUMOMAB PASUDOTOX-TDFK	DORAVIRINE	ERAVACYCLINE DIHYDROCHLORIDE	LANADELUMAB (SHPR-KD)	CENEGERMIN-BKBJ	ETRIPRENTOL	PATISIRAN SODIUM
NDA #209816	NDA # 209521	BLA #761097	BLA #761063	NDA #211155	BLA #761069	BLA #761104	NDA #210806	NDA #211109	BLA #761090	BLA #761094	NDA #209709	NDA #210922
Authorised	Autho rised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised
yes	no	no	yes	yes	no	yes	no	yes	yes	yes	no	yes
yes	no	no	no	yes	yes	no	no	yes	no	no	yes	yes
no	no	no	no	yes	no	no	no	no	no	no	no	no
no	no	yes	yes	no	no	no	no	no	yes	yes	no	yes
no	no	no	no	yes	no	yes	no	no	yes	yes	yes	yes
02.1.0.18	01.10.18	28.09.18	27.09.18	24.09.18	14.09.18	13.09.18	30.08.18	27.08.18	23.08.18	22.08.18	20.08.18	10.08.18
28.0.2.18	20.10.17	28.02.18	27.09.17	05.02.18	16.10.17	29.01.18	23.10.17	28.12.17	26.12.17	22.12.17	20.12.17	11.12.17
PARATEK PHARMS INC	ALMIRALL	RESVERATROL PHARMACEUTICALS	ELI LILLY AND CO	VERASTEM INC	TEVA BRANDED PHARMACEUTICAL PRODU	ASTRAZENECA AB	MSD MERCK CO	TETRAPHASE PHARMS	OYAX CORP	DOMPE FARMACEUTICI	BIOCODEX SA	ALNYLAM PHARMS INC
MAZYRA is a tetracycline class antibacterial indicated for the treatment of adult patients with the following infections caused by susceptible microorganisms: (1) Community-acquiredbacterialpneumonia(CABP)(1.1) Acutebacterialskinandskinstructure infections(ABSSSI)(1.2) To reduce the development of drug-resistant bacteria and maintain the effectiveness of MAZYRA and other antibacterial drugs, MAZYRA (6.4) should be used only to treat or prevent infections that are proven or strongly suspected to be caused by	SEYSARATM is a tetracycline-class drug indicated for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 year s of age and older.	UBTAYO is a programmed death receptor-1 (PD-1) blocking antibody indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation	EMGALITYTM is a calcitonin gene-related peptide antagonist indicated for the preventive treatment of migraine in adults.	COPIKTRA is a kinase inhibitor indicated for the treatment of adult patients with: • Relapsed or refractory chronic lymphocytic leukemia (CLL), or small lymphocytic lymphoma (SLL) after at least two prior therapies. (1.1) • Relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies. (1.2). This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and	AJOVY is a calcitonin gene-related peptide antagonist indicated for the preventive treatment of migraine in adults.	LUMOXITI is a CD22-directed cytotoxin indicated for the treatment of adult patients with relapsed or refractory hairy cell leukemia (HCL) who received at least two prior systemic therapies, including treatment with a purine nucleoside analog (PNA).	RYBELTRO is a non-nucleoside reverse transcriptase inhibitor (NNRTI), is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients with no prior antiretroviral treatment history.	XERAVA is a tetracycline class antibacterial indicated for the treatment of complicated intra-abdominal infections in patients 18 years of age and older.	TAHNZYRO is a plasma kallikrein inhibitor (monoclonal antibody) indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older.	QUERPAITE is a recombinant human nerve growth factor indicated for the treatment of neurotrophic keratitis	DIACOMIT is indicated for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam. There are no clinical data to support the use of DIACOMIT as monotherapy in Dravet syndrome.	ONPATTRO contains a transthyretin-directed small interfering RNA and is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.
Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	BLA	BLA	Type 1 - New Molecular Entity	BLA	BLA	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	BLA	BLA	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity
no	no, PRO mentioned in 1.4 cannot be confirmed	yes, EORTC QLQ-C30	yes, Migrain-Specific Quality of Life Questionnaire (MSQ) Patient Global Impression of Severity (PGI-S) Patient Global Impression of Improvement (PGI-I) Daily Headache Diary Migraine Disability Assessment test (MIDAS) Self-harm supplement form (SHSF) Self-harm follow-up form (SHFU) Non-migraine chronic pain assessment Employee status Columbia-Suicide Severity Rating Scale (C -SSRS)	yes, EuroQoL-5D FACT-F	yes, Daily Headache Diary MIDAS questionnaire (Migraine Disability Assessment) Headache Impact Test (HIT-6) eC-SSRS Headache Diaries PHQ-2/9 MSQ QL EQ-5D-5L PGIC WPA	no	yes, Work Productivity and Activity Impairment Questionnaire (WPAI)	no	yes, Angioedema quality of life (AE-QoL) EQ-5D-5L	no	no	yes, Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) questionnaire (3) Rasch-built Overall Disability Scale (R-ODS) s core (3) Autonomic symptoms questionnaire (Composite Autonomic Symptom Score (COMPASS 31) (3) EuroQOL (EQ-5D) questionnaire (E)
yes, Early clinical response (ECR) (not clear if the reviewer refers to that as outline in 1.4)	yes, Investigator Global Assessment of Inflammatory Acne	no	yes, Columbia-Suicide Severity Rating Scale (C -SSRS)	no	yes, eC-SSRS	no	no	yes, APACHE II Score	no	no	no	yes, Neurological impairment score (NIS)-weakness (NIS-W) score (S) Neuropathy Impairment Score (NIS) (E) Grip strength (E) FAP stage (E) Polyneuropathy Disability (PND) score (E)
no	no	no	no	no	no	no	no	no	no	no	no	no, ObsRO not identified as outlined in 1.4 PED
no	no	no	no	no	no	no	no	no	no	no	no	yes, Timed 10-meter walk test (10-MWT, gait speed (S)
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	yes, Patient and provider preference survey Teva provided supportive information from survey summaries in section 5 of the ISE from indep endently conducted physicians and patient surveys querying the general anti-CGRP class of products under review for migraine prophylaxis marketing approval, in order to understand perceptions and preferences for monthly versus quarterly dosing, preferences for various	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
yes, Antimicrobial Drugs Advisory Committee (AMDAC) met on August 8, 2018 (p222/223) **One patient representative** was involved in that meeting confirmed in the final meeting roster	no	no	no	no	no	no	no	no	no, a pulmonary allergy drug advisory committee (PADAC) meeting was considered for this application. However, given the results of the studies submitted, the Division decided that the evidence supporting approval for the indicated population was sufficiently robust that discussion at an AC was not necessary.	no	no, this application was not presented at an Advisory Committee Meeting.	no, this application was not referred for review to an advisory committee because the safety profile of patisiran is acceptable for the intended population, the clinical trial designis acceptable, and the efficacy findings were clear.
no	no	no	no	no	no	no	no	no	yes, HAE PFDD workshop, 'Voice of the Patient report (Discussed on page 19)	no	no	no
yes, ClinRO	yes, PRO and ClinROs	yes, PRO	yes, PRO But one ClinRO identified in this assessment - Safety measure	yes, PRO	yes, PRO and Other (Patient and Provider Pref Survey) But one ClinRO identified in this assessment - Safety measure	yes, but no patient experience data were submitted in the application	yes,PRO	yes, PRO (not specified). One ClinRO identified in this assessment.	yes, PRO	no, application submitted after transition phase	no, application submitted after transition phase	yes, PROs, ObsRO, ClinRO, and PerfO
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no

Annex 2: List of Medicinal Products approved during the time period 01 January 2017 - 31 December 2019 by the FDA

MOTEGRITY	XOSPATA	TRYDMYSE	VITRAKVI	DAURISMO	GAMIFANT	AEMCOLO	YUPELRI	LORBRENA	XOFLUZA	TALZENNA	REVCOVI	TEGSEDI
PRUCALOPRIDE SUCCINATE	GILTERITINIB FUMARATE	AMIFAMPRIDINE PHOSPHATE	LAROTRECTINIB SULFATE	GLASDEGIB MALEATE	EMAPALUMAB-LZSG	RIFAMYCIN SODIUM	REVEFENACIN	LORLATINIB	BALOXAVIR MARBOXIL	TALAZOPARIB TOSYLATE	ELAPEGADEMASE-LVLR	INOTERSEN SODIUM
NDA #210166	NDA #211349	NDA #209279	NDA #210861	NDA #210854	BLA #761107	NDA #210810	NDA #210698	NDA #210868	NDA #2 10854	NDA #211651	BLA #761092	NDA #211172
Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised
no	yes	no	no	no	no	yes	no	no	no	no	yes	yes
no	yes	yes	yes	yes	no	yes	no	yes	yes	yes	no	yes
no	no	no	yes	no	no	no	no	yes	no	no	no	no
no	no	yes	yes	no	yes	no	no	yes	no	no	no	no
no	yes	yes	yes	yes	yes	no	no	yes	no	no	yes	yes
14.12.18	28.11.18	28.11.18	26.11.18	21.11.18	20.11.18	16.11.18	09.11.18	02.11.18	24.10.18	16.10.18	05.10.18	05.10.18
21.12.17	29.03.18	28.03.18	24.03.18	27.04.18	20.03.18	16.03.18	10.11.17	05.12.17	24.04.18	06.04.18	26.10.17	06.11.17
SHIRE DEV LLC	ASTELLAS	CATALYST PHARMS	BAYER HEALTHCARE	PFIZER INC	NOVIMMUNE S A	REDHILL	MYLAN IRELAND LTD	PFIZER INC	GENENTECH INC	PFIZER INC	LEADIANT BIOSCI INC	ARCEA THERAPS
MOTEGRITYTM is a serotonin-4 (5-HT4) receptor agonist indicated for the treatment of chronic idiopathic constipation (CIC) in adults.	XOSPATA is a kinase inhibitor indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FLT3 mutation as detected by an FDA-approved test.	TRYDMYSE is a potassium channel blocker indicated for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults. (1)	VITRAKVI is a kinase inhibitor indicated for the treatment of adult and pediatric patients with solid tumors that: • have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, • are metastatic or where surgical resection is likely to result in severe morbidity, and • have no satisfactory alternative treatments or that have progressed following treatment.	DAURISMO is a hedgehog pathway inhibitor indicated, in combination with low-dose cytarabine, for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adult patients who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy.	GAMIFANT is a recombinant gamma (IFNγ) blocking antibody indicated for the treatment of adult and pediatric (newborn and older) patients with primary hemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy.	AEMCOLO is an ansamycin antibacterial indicated for the treatment of travelers' diarrhea caused by non-invasive strains of Escherichia coli in adults. To reduce the development of drug-resistant bacteria and maintain the effectiveness of AEMCOLO and other antibacterial drugs, AEMCOLO should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria	YUPELRI (revefenacin) inhalation solution is an anticholinergic indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD)	LORBRENA is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on -crizotinib and at least one other ALK inhibitor for metastatic disease; or -alectinib as the first ALK inhibitor therapy for metastatic disease; or -ceritinib as the first ALK inhibitor therapy for metastatic disease.	XOFLUZA™ is a polymerase acidic (PA) endonuclease inhibitor indicated for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours. (1)	TALZENNA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) HER2-negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for TALZENNA.	REVCOVI is a recombinant adenosine deaminase indicated for the treatment of adenosine deaminase severe combined immune deficiency (ADA-SCID) in pediatric and adult patients.	TEGSEDI is a transthyretin-directed antisense oligonucleotide indicated for treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults
Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	BLA	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	BLA	Type 1 - New Molecular Entity
yes, Complete bowel movement ts (CBM) Spontaneous complete bow el movement (SCBM)	no	yes, S01 (cP) Quantitative Myasthenia Gravis Score (QMG) (cP) - in ePRO MODE classified as PerfO Patient Most Bothersome Symptom (PMBS) Question (E)	yes, Pe diaQL-Core	no	no	no	yes , St George's Respiratory Questionnaire (SGRQ) (S) Treatment Satisfaction Questionna ire mMRC (E) COPD Assessment Test (CAT) (E) Clinical COPD Questionnaire (CCQ) (E) BDI/Transitional dyspnea Index (TDI) (E)	yes , EORTC QLQ-LC13	yes, Influenz a symptom sco re Measurement of temperature EQ-5D- 5L	yes, EORTC QLQ-C30 (E) EORTC-QLQ-BR23 (E)	no	yes, Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) (P) SF-36
no	no	yes, Clinical Global Impression-Improvement (CGI-I)	no	no	no	no	no	no	yes, Influenz a-related complications	no	no	yes, Modified Neur opathy Impairment score +7 (mNIS+7) (P)
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	yes, Triple Timed-Up-and-Go test (3TUG) (not covered by 1-4) (E)	no	no	no	no	no	yes, CNS assessment Response assessme nt Intracranial response assessment	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
yes, Gastrointestinal Drugs Advisory Committee (GIDAC) held on 19OCT2018 **One patient representative** was involved in that meeting co nfirmed in the final meeting ros te	no	no	no	no	no	no	no	no, the Division did not r efer this NDA to the Oncologic Drug Advisory Committee (ODAC) because the safety pr ofile is acc eptable for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on crizotinib and one other ALK inhibitor or on alectinib or ceritinib as the first ALK inhibitor for metastatic disease, and the application did not raise significant public health questions regarding the role of lorlatinib for this indication. Outside expertise was not necessary as there were no controversial issues that could benefit from an Advisory Committee discus sion.	no	no	no	no
no	no	no	no	no	no	no	no	no reference made to existing Voice to Patient for lung cancer dated June 2013	no	no reference made to existing Voice to Patient for breast Cancer dated Apr 2015	no	no, cannot be confirmed (see 1.4)
yes, PRO and Advisory co mmittee	yes, but no patient experience data were submitted in the application	yes, PRO and ClinRO But one PerfO identified in this a ssessment	yes, PRO	yes, but no patient experience data were submitted in the application	yes, but no patient experience data were submitted in the application	yes, but no patient exp erience data w ere submitted in the application	yes , PRO	yes, PRO and PerfO	yes, PRO and ClinRO	yes, PRO	yes, but no patient experience data were submitted in the application	yes, PRO, PFDD, and Other But one ClinRO identified in this assessment - Safety measure
no	no	no	Three special government employees (SGEs) (2016), an adult oncologist with expertise in melanoma and translational scien ce, a pediatric oncologist with expertise in rare pediatric cancers, and a patient representative with expertise in issues relating to development of tre atments to treat rare cancers, were cleared by the Advisory Committee Oversight and Management Staff (ACOMS) to participate in a divisional assignment to consult on these NDAs. A separate teleconfere nce was held with each SGE to discuss the applications. During these telec onferences, the SGEs indicated that the y considered the risk/ benefit assessment favorable for use of larotrectinib in patients with metastatic or unresectable NTRK-fusion solid tu mors that had progressed following standard treatment or who did not have a satisfactory treatment options. The SGEs also stated that they did not have concerns regarding approval of larotrectinib for treatment of this patient	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no

Annex 2: List of Medicinal Products approved during the time period 01 January 2017 - 31 December 2019 by the FDA

VYNDAQEL	RAYSIZ	BALVERSA	VIDENTY	MAVZIENT	SUNOSI	ZULRESSO	HERCEPTIN HYLECTA	CABLIVI	JEUVEAU	SLZONRIS	ULTOMIRIS	ABRAXLAS
TAFAMIDIS MEGLUMINE	RESMANGZUMAB-RZAA	ERDAFITINIB	RALMOSOZUMAB-AQQG	SIPONIMOD FUMARIC ACID	SOLRIAMFETOL HYDROCHLORIDE	BREXANOLONE	TRASTUZUMAB HYALURONIDASE-OYYK	CAPLACIZUMAB-YHDP	PRABOTULINUMTOXINA-XVFS	TAGRAXOFUSP-ERZS	RAVULIZUMAB-CWVZ	CALASPARGASE PEGOL-MKNL
NDA #211996	BLA #761105	NDA #212018	BLA #761062	NDA #209884	NDA #212330	NDA #211371	BLA #761,106	BLA #761112	BLA #761085	BLA #761,116	BLA #761109	BLA #761102
Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised
yes	no	no	no	no	no	no	no	yes	no	no	no	no
yes	no	yes	no	yes	no	yes	no	no	no	no	no	no
no	no	yes	no	no	no	no	no	no	no	no	no	no
yes	no	yes	no	no	no	yes	no	no	no	yes	no	no
yes	no	no	no	no	yes	no	no	yes	no	yes	yes	yes
03.05.19	23.04.19	12.04.19	09.04.19	26.03.19	20.03.19	19.03.19	28.02.19	06.02.19	01.02.19	21.12.18	21.12.18	20.12.18
02.11.18	23.04.18	18.09.18	18.07.16	26.06.18	20.12.17	19.04.18	01.05.18	08.06.18	15.05.17	UNK	18.06.18	22.12.17
FOLDRX PHARMS	ABBVIE INC	JANSSEN BIOTECH	AMGEN INC	NOVARTIS	JAZZ	SAGE THERAP	GENENTECH INC	ABLYNX NV	EVOLUS INC	SYEMUNE THERAPEUTICS INC	ALEXION PHARM	SERVIER PHARMA LLC
WYNDAQEL and WYNDAMAX are transthyretin stabilizers indicated for the treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization.	RAYSIZ is an interleukin-23 antagonis t indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototh erapy.	BALVERSA is a kinase inhibitor indicated for the treatment of adult patients with loc ally advanced or metastatic urothelial carcinoma that has • susceptible FGFR3 or FGFR2 genetic alterations and • progressed during or following at least one line of prior platinum- containing chemotherapy including within 12 months of neoadju vant or adjuvant platinum-containing chemoth erapy.	VIDENTY is a sclerostin inhibitor indicated for the treatment of osteoporosis in postme nopausal women at high risk for fracture, defined as: a hi story of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy .	MAVZIENT is a sphingosine1-phosp hatereceptormo dulator indicate d for the treatment of relapsing forms of multiple sclerosis (MS), to include clinica lly isolatedsyndrome,relapsing-remitting diseas eandactivesecondary progressivedisease, in adults	SUNOSI is a dopamine and norepinep hrine reuptake inhibitor (DNRI) indicated to improve wakefulness in adult patients with exce ssive daytime sleepiness associated wit narcolepsy or obstructive sleep apnea (OSA).	ZULRESSO is a neuroactive steroid gamma-aminobuty ric acid (GABA)A receptor p ositive modulator indicated for the treatment of postpar tum depression (PPD) in adults.	HERCEPTIN HYLECTA is a combination of trastuzumab, a HER2/neu receptor antag onist, and hyaluronidase, an endogly cosidase, indicated in adults for: • The treatment of HER2-overexpressin g breast cancer. (1.1, 1.2) Select patients for therapy based on an FDA-approved companion diagnostic for trastuzumab. (1, 2.1)	CABLIVI is a von Willebrand factor (vWF)-directed antibody fragment indicated for the treatment of adult patients with acquired thrombotic thrombocytopenic purpura (aTTP), in combination with plasma exchange and immunosuppressive therapy.	JEUVEAU is an acetylcholine release i nhibitor and a neuromuscular blocking agent indicate d for the temporary improvement in the appear ance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients	SLZONRIS is a CD123-directed cytotoxin for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) in adults and in pediatric patients 2 years and older.	ULTOMIRIS is a complement inhibitor indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH	ABRAXLAS is an asparagine specific enzyme indicated as a compone nt of a multi-ag ent chemotherapeutic regimen for the t reatment of acute lymphoblastic leukemia in p ediatric and yo ung adult patients age 1 month to 21 years.
Type 1 - New Molecular Entity	BLA	Type 1 - New Molecular Entity	BLA	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	BLA	BLA	BLA	BLA	BLA	BLA
yes, Kans as City Cardiomyopathy Questionnaire (KCCQ)(S) EQ-5D-3L Patient Global Assessment (PGA)	yes, Dermatology Life Quality Index (DLQI) PSS	yes, Symptom Measurement Questionnaire (SMQ) Global Impression of Change (Symptoms) Global Impression of Ch ange (Quality of Life)	yes, Osteo porosis Assessment Questionnaire (OPAQ-SV) (E) EuroQoL 5-Dimension 5-Level (EQ-5 D-5L) (E) Limited Activity Days(LAD) survey (E) Brief Pain Inventory (BPI) (E)	no	yes, Epworth Sleepiness Scale (ESS) PSI-C Functio nal Outcomes of Sleep Questionnaire (FO SQ-10) SF-36v 2 EuroQoL 5 Q-5D-5L Work Productivity and Activity Impairment Questio nnaire:Specific Health Problem (WPA:SHP)	yes, Edinburgh Postnatal Depr ession Scale (EPDS) Generalized Anxiety Disorder - 7 (GAD-7) Patient Health Questionna ire (PHQ-9) Barkin Index of Maternal Functioning (BIMF) SF-36 HealthCare Resource Utilization Questionnaire (HCRU) Stanfor Sleepiness Scale (SSS) (Safety)	yes, single-use injection device (SID) satisfaction questionna ire	no	yes, Glabellar Line Scale (GLS) (P-S) Global Aesthetic Improvement Scale (E) Subject Satisfaction Scale (E)	no	no	no
no	yes, PASI sPGA	no	no	yes, Expanded Disability Status Scale (EDSS)	yes, Clinical Global Impressi ons scale (CGI-I and CGI-S) (P)	yes, Hamilton Depression Rating Scale (HAM-D)(Response/Remission) (P) Clinical Global Impression of Improvement (CGI-1)	yes, Health Care Professional Questionnaire	no	yes, IGA Glabellar Line Scale (GLS) (P-S)	no	no	no
no	no	no	no	no	no	no	yes, Patient Interview (factors influencing prefe rence)	no	no	no	no	no
yes, 6-Min ute Walk Test (6-MWT or SMWT) (S)	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	yes, PreHER patient preferen ce study: Results from the patient preferenc e study (PreHER) suggest patients preferred the SC route due to time information about PFI ht tps://www.gene.com/media/press-releases/1 47790/2019-02 -28/fda-approves-herceptin-hylecta-for-subcu	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no, observa tional survey study designed to capture patient experien ce data according to 1.4, but cannot be confirmed	no	no	no
no	no, the Agency held no Ad visory Committee Meeting regarding this application because the safety profile was expected to be comparable to that of other biologic products approved for this indication. There were no novel or complex regulatory issues that required public discuss ion at an AC meeting	no, this ND A was not pres ented to an ad visory committe e because e the benefit-ris k profile demonstrated for erdafitinib is clearly favorable for its proposed use. No contro versial issues were identified that would necessitate an ad visory committee meeting	UNK	no	no	yes, Psychoph armacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on November 2, 2018 **One patient representatives** was involved in that meeting c confirmed in the final meeting no ster	no	no	no	no	no	no
no	no	no	no	no	no reference made to existing Voice to Patient for narcolepsy dated Sep 2013	no	no reference made to existing Voice to Patient for breast Cancer dated Apr 2015	no	no	no	no	no
yes, PRO, PerRO, and natural disease history natural disease history cannot be confirmed	no	yes,PRO	yes, PROs ClinPRO s cannot be confirmed, none of the identified PROs are ClinROs as mentioned in p69 Application was submitted before exp iry of transition phase	yes, PROs and natural disease history PRO and natural disease history cannot be confirmed ClinRO identified in this assessment	yes, PRO and ClinRO	yes, PRO and ClinRO	yes, PRO and PPS ClinRO and ObsRO were identified in this assessment	yes, but no patient experienc e data were submitted in the applicatio n	yes, PRO, ClinRO, natural disease his tory and observational study Natural disease history and observation study cannot be confirmed	yes, but no patient experience data were submitted in the application	yes, PRO PRO cannot be confirmed	yes, but no patient experience data were submitte d in the application
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no

Annex 2: List of Medicinal Products approved during the time period 01 January 2017 - 31 December 2019 by the FDA

XENLETA	NRIBBIC	RINVOQ	SOLYTYRBK	PRET OMAND	XAHLY	TUKALIQ	NUBEQA	ACCRUPER	KPOVIO	VYLIESI (AUTOINJECTOR)	POLIVY	RGRAY
LEFAMULIN ACETATE	FEDRATINIB HYDROCHLORIDE	UPADACITINIB	ENTRECTINIB	PRET OMAND	PITOLISANT HYDROCHLORIDE	RESMETIRINIB HYDROCHLORIDE	DAROLUTAMIDE	FERRIC MALTOL	SELINEXOR	BREMELANOTIDE ACETATE	POLATUZUMAB VEDOTIN-PIQ	ALPELISIB
NDA #211672	NDA #212327	NDA #211675	NDA #212725	NDA #21.2992	NDA #2.11150	NDA #211810	NDA #212099	NDA #212320	NDA #212306	NDA #210557	BLA #761121	NDA #212526
Authorised	Authorised	Authorised	Authorised	Authorise d	Authoris ed	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised
yes	no	no	no	no	yes	no	yes	no	no	yes	no	no
yes	yes	yes	yes	yes	yes	yes	yes	no	yes	no	no	yes
no	no	no	yes	no	no	no	no	no	yes	no	yes	no
no	no	no	yes	no	no	yes	no	no	no	no	yes	no
no	yes	no	yes	yes	yes	yes	no	no	yes	no	yes	no
19.08.19	16.08.19	16.08.19	15.08.19	14.08.19	14.08.19	02.08.19	30.07.19	25.07.19	03.07.19	21.06.19	10.06.19	24.05.19
18.12.18	03.01.19	13.12.18	18.12.19	14.12.18	14.12.18	30.11.18	26.02.19	27.09.18	15.08.18	23.03.18	19.12.18	08.12.18
NABRIVA	IMPACT	ABBVIE INC	GENENTECH INC	MYLAN IRELAND LTD	HARMONY	DAIICHI SANKYO INC	BAYER HEALTHCARE	SHIELD TX	KARYOPHARM THERAPS	AMAG PHARMS INC	GENENTECH	NOVARTIS
XENLETA is a pleuromutilin antibacterial in dicated for the treatment of adults with community-a cquired bacterial p neumonia (CABP) caused by susceptible microorganisms. (	NRIBBIC is a kinase inhibitor indicated for the treatment of adult patients with intermediate-2 or high -risk primary or secondary (post-polycythemia vera or p ost-essential thrombocythemia) myelofibrosis (MF)	RINVOQ is a Janus kinase (J AK) inhibitor indicated for the treatment of adults with moderately to sever ely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate .	Adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1-positive, (1.1) Adult and pediatric patients 12 years of age and older with so lid tumors that: - have a neur otrophic tyrosin e receptor kina se (NTRK) gene fusion with ou t a known acquir ed resistance mutation, -are metastatic or where surgical resection is likely to resu lt in severe morbidity, and - have progressed following treatment or ha ve no satisfactory alternative therapy. This indication is approved under accelerated ap proval based on tumor respon se rate and durability of respo nse. Continue d approval for this indication may be contingen t upon verification and description of clinical benefit in the confirmator y trials. (1.2)	Limited Population: Pretomanid Tablet is an antimyco bacterial indicated, as part of a combination regimen with bedaquiline and linezolid for the t reatment of adults with pulmonary extensively drug resistant (XDR) y, treatment-intolerant or nonresponsive multidrug-resis tant (MDR) tuberculosis (TB). Approval of this indication is based on limited clinical safety and efficac y data. This drug is indicated for use in a limited and spec ific population of patients.	WAKIX is a histamine-3 (H3) receptor antagonist/inverse agonist indicated for the treatment of exce ssive daytime sleepiness (EDS) in adult patients with narcolepsy	TUKALIQ is a kinase inhibitor indicated for the treatment of adult patients with symptomatic tenosynov ial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery.	NUBEQA is an androgen receptor inhibitor ind icated for the treatment of patients with non-metastatic castration-resistant prostate cancer.	ACCRUPER is an iron replacement product in dicated for the treatment of iron deficienc y in adults.	KPOVIO is a nuc lear export inhi bitor indicated in combination with dexamethasone for the treatment of adult patients with relapsed or r efractory multiple myeloma (RRMM) who have re ceived at least four prior therapies and w hose disease is refractory to at least two proteasome r inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antib ody	VYLIESI is a melanocortin receptor agonist indicated for the treatment of premenopa usal women with acquired, generalized h ypoactive sexual desire disor der (HSDD) ca racterized by low sexual desire that cau ses marked distress or interpersonal difficulty and is NOT due to: A co-existing medical or psychiatric condition, Problems with the relationship, or The effects of a medication or drug substan ce	POLIVY is a CD79b-directed antibody-drug conjugate indicated in combination with bendamus tine and a rituximab y roduct for the t reatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, after at least two prior therapies.	RGRAY is a kinase inhibitor indicated in combination with fulvestrant for the treatment of postmenop ausal women, and men, with hormone receptor (HR) - positive, human epidermal growth f actor receptor 2 (HER2)-negative, PIK3CA -mutated, a dvanced or m etastatic breast cancer as detected by an FDA-appro ved test, following progression on or after an endocr ine-based regimen
Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	BLA	Type 1 - New Molecular Entity
no	yes, Myelofibrosis -associated Symptoms (Modified MF SAF) Total Symptom Score (TSS)	yes, American College of Rheumatology 20/50/70 criteria (ACR20/50/70) Disease Activity Score - C-Reactive Protein (DAS / DAS-28 CRP) HAQ-DI SF-36 Morning Stiffness	yes, QLQ-C30 QLQ-CR29 EQ-5D	no	yes, Daily/Weekly Cataplexy Attacks (S) Epworth Sleepiness Scale (ESS) (P) Mainten ance of Wakefulness Test (MWT) (S) Sustained Attention to Response Task (SART) (S) Clinical Global Impression of Change (CGI-C) (S) EQ-5D (S Patient Global Opinion on Treatment	yes, Range of Motion PROMIS Physical Function Worst Stiffness MFI-20 EQ-5D-5L PGI-C	yes, EORT C Quality of Life Questionnaire - Prostate Cancer Module (EORT C QLQ -PR25) (E) EQ-5D-3L (E) FACT -P (E) BPI -SF (E)	no	no	yes, Functional Assessment of Cancer Therapy - Multiple Myeloma (FACT -MM) (3 i-E)	yes, Female Sexual Function Index-D (FSFI) (P) Female Sexual Distress Scale (FSDS-DAO Q13) (P)	yes, Therapy-Induced Neuropathy Assessment Scale (TINAS)	yes, EORTC QLQ-C30 (S) EQ-5D-5L (S) BPI-SF (S)
yes, Investigator's Assessment of Clinical Response	no	yes, American College of Rheumatology 20/50/70 criteria (ACR20/50/70) Disease Activity Score - C-Reactive Protein (DAS / DAS-28 CRP)	no	no	no	yes, Surgical As sessment Questionnaire	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
no, no advisory committee meeting was held, and no external c onsultations we re obtained as there were no issues that needed input from external experts	no	no	no, FDA did not refer this NDA to an advisory committee because no review issues were identified that r aised significant public health questions regarding the risk:benefit assessment of entrectinib for the proposed indication.	yes, Antimicrobial Drugs Advisory Committee Meeting held on June 6th, 2019 **One patient representat ives** was inv olved in that meeting confirmed in the final meeting roste	no	yes, Oncologic Drugs Advisory Committee (OD AC); the meeting wa s held on May 14, 2019 **One patient representat ives** was involved in that meeting co nfirmed in the final meeting ros ter	no, the Division did not refer this efficacy supplement to an advisory committee because darolutamide is not the first drug in this class, the safety p rofile is acceptable in this indication, and the clinical trial design is similar to that used previously in this class.	no	yes, Oncologic Drugs Advisory Committee (ODAC) Meeting on 2.6.02.2019; OD AC voted in favor of delaying c onsideration of approval until res ults of the randomized Phase 3 BOSTON trial are available . The final vote was 8 votes Yes, 5 votes No. **One patient represen tatives** was involved in that meeting confirmed in the final meeting ros ter	no	no	no, no advisory committee discussion or consultations external to the F DA were deemed necessary for this NDA
no	no	no	no reference made to existing Voice to Patie nt for lung canc er dated June 2013	no	no reference made to existing Voice to Patient for narcole psy dated Sep 2013	no	no	no	no	yes, FDA Patient-F ocused Drug Development Public Meeting and Scientific Workshop on Female Sexual Dysfunction held on October 28 and 27, 2014, respectively. https://www.federalregister.gov/documents/2014/09/26/20 14-22983/patient-focused-drug-development-public-meeting-and-scientific-workshop-on- female-sexual-dysfunction	no	no reference made to existing Voice to Patient for breast Cancer dated Apr 2015
yes, PRO and ClinRO PRO mentioned in 1.4 can not be confirmed	yes, PRO	yes, PROs and ClinRO	yes, PRO SGE meeting with patient rep resentative identified in this assessment	no	yes, PRO and ClinRO , FDA consider ed input informed from participation in meetings with patient stakeholders - meeting cannot be co nfirmed ClinRO cannot be confirmed as mentioned in 1.4	yes, PRO and ClinRO	yes, PRO	yes, but no patient experience data were sub mitted for this application	yes, PRO	yes, PRO and if PDD	yes, PRO	yes, PRO
no	no	no	yes, Three special government employees (SGEs) [...] Mr. Josh Mallman, a **patient representative** with expertise in issues relating to development of treatments to treat rare cancers, were cleared by the Advisory Committee Oversight and Management Staff (ACOMS) to participate in a divisional assignment to consult on these NDAs. A separate tel econference was held with each SGE on July 11, 2019 to discuss the a pplications. Dur ing these teleconferences, the SGEs indicated that they con sidered the risk :benefit assessment favorable for use of entrectinib in the t reatment of patients with metastatic or unr esectable NTRK-fusion solid tumors that had progressed following standard treatment or who did not have satisfactory available treatment. The SGEs also stated that they did not have concerns regarding approval of entrectinib for	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no

Annex 2: List of Medicinal Products approved during the time period 01 January 2017 - 31 December 2019 by the FDA

XCOPRI	GIVLAARI	ADAKVEO	BRUKINSA	FETROJA	REBLOZYL	TRIKAFTA (COPACKAGED)	RETVOMY	SOENBISSE	BEOVU	AKLIEF	SIRSILA	NOURIANZ
CENOBAMATE	GIVOSIRAN SODIUM	CRIZANLIZUMAB-TMCA	ZANUBRUTINIB	CEFIDEROCOL SULFATE TOSYLATE	LUSPATERCEPT-JAMT	ELEXACAFTOR, IVACAFTOR, TEZACAFTOR, IVACAFTOR	LASMIDITAN SUCCINATE	AFAMELANOTIDE	brolucizumab-dbll	TRIFAROTENE	TRIAMINOHYDROCHLORIDE	ISTRADEFYLLINE
NDA #212839	NDA #212914	BLA #761139	NDA #213217	NDA #209445	BLA #761136	NDA #212272	NDA #212280	NDA #210797	BLA # 761125	NDA #211527	NDA #211801	NDA #022075
Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised
yes	no	no	no	yes	yes	yes	no	yes	no	no	no	no
yes	yes	no	yes	no	no	yes	no	yes	no	no	no	no
yes	no	no	yes	no	no	no	no	no	no	no	no	no
yes	yes	yes	yes	no	no	yes	no	no	no	no	no	no
yes	yes	yes	yes	no	yes	yes	no	yes	no	no	no	no
21.11.19	20.11.19	15.11.19	14.11.19	14.11.19	08.11.19	21.10.19	11.10.19	08.10.19	07.10.19	04.10.19	12.09.19	27.08.19
21.11.18	04.06.19	16.05.19	27.06.19	14.12.18	04.04.19	19.07.19	11.10.18	08.11.18	07.02.19	04.10.18	12.09.18	25.04.07
SK LIFE SCIENCE INC	ALNYLAM PHARMS INC	NOVARTIS PHARMS CORP	BEIGENE	SHIONOGI INC	CELGENE CORP	VERTEX PHARMS INC	ELI LILLY AND CO	CLOVIS NEL INC	NOVARTIS PHARMS CORP	GALDERMA R AND D	ARDELYX INC	KYOWA KIRIN
XCOPRI is indicated for the treatment of partial-onset seizures in adult patients.	GIVLAARI is an aminoketulinate synthase 1- directed small interfering RNA indicated for the treatment of adults with acute hepatic porphyria (AHP).	ADAKVEO is a selectin blocker indicated to reduce the frequency of vasoocclusive crises in adults and pediatric patients aged 16 years and older with sickle cell disease.	BRUKINSA is a kinase inhibitor indicated for the treatment of adult patients with mantle cell lymphoma (MCL), who have received at least one prior therapy.	FETROJA is a cephalosporin antibacterial indicated in patients 18 years of age or older who have limited or no alternative treatment options, for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis caused by susceptible Gram-negative microorganisms. (1.1) Approval of this indication is based on limited clinical safety and efficacy data for FETROJA.	REBLOZYL is an erythroid maturation agent indicated for the treatment of anemia in: - Adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions	TRIKAFTA is a combination of ivacaftor, a CFTR potentiator, lumacaftor, and elexacaftor indicated for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one F508del mutation in the CFTR gene. • If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one F508 del mutation.	RETVOMY M is a serotonin (5-HT) 1F receptor agonist indicated for the acute treatment of migraine with or without aura in adults.	SOENBISSE is a melanocortin 1 receptor (MC1-R) agonist indicated to increase pain free light exposure in adult patients with a history of phototoxic reactions from erythropoietic protoporphyria (EPP).	BEOVU is a human vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of Neovascular (Wet) Age-Related Macular Degeneration (AMD)	AKLIEF Cream is a retinoid indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.	SIRSILA is a sodium hydrogen exchanger 3 (NHE3) inhibitor indicated for treatment of irritable bowel syndrome with constipation (IBS-C) in adults.	NOURIANZ is an adenosine receptor antagonist indicated as adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease (PD) experiencing "off" episodes
Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	BLA	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	BLA	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	BLA	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity
no	yes, SF-12 (E) EQ-5D-5L (E) Days of miss ed work/school PGIC (E) Porphyria Patient Experience Questionnaire (PPEQ) (E)	yes, SF-36 BPI	no	yes, Symptoms reporting according to a assessor	yes, SF-36 TransQoL (There were no prespecified statistical hypotheses in regar d to comparison of the HRQoL endpoints and study was not powered to detect any differences in these assessments and thus all analyses are descriptive.) Healthcare Resource Utilization (HRUQ)	yes, CFQ-R (S) TSAQ: global satisfaction scores (o)	yes, MDAS PGIC	yes, erythropoietic protoporphyria quality of life (EPP-QoL) Daily Diary	yes, Visual Function Questionnaire-25 (VFQ-25)	no	yes, Pain and sto of frequencies (P) IBS-eDiary Irritable Bowel Syndrome - Quality Of Life (IBS-QOL)	yes, Global Impression -Improvement (PGI-i) scores Parkinson's Disease Questionnaire (PDQ) Medical Outcomes Study 36- item Short Form (SF-36)
no	no	no	no	no	yes, Eastern Cooperative Oncology Group Performance Status scale (ECOG Performance Status)	no	no	no	no	no	no	yes, UPDRS Clinical Global Impressions scale (CGI)
no	no	no	no	no	no	no	no	no	no	yes, Physician Global Assessment (PGA) Investigator Global Assessment (IGA)	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	yes, Cystic Fibrosis Foundation Patient Registry, Annual Data Report 2017	no	no	no	no	no	no
no	no, no Oncology Drug Advisory Committee (ODAC) Meeting or other external consultants are required for the current application for givosiran for the treatment of AHP.	no, this application was not presented at an Advisory Committee or to any other external consultants. Presentation was not needed because the Division is familiar with the endpoints, trial design, and control arms.	no, this application was not presented to the Oncologic Drug Advisory Committee or other external consultants because zanubrutinib is not first-in-class, and the application did not raise new efficacy or safety issues for the recommended indications.	yes, Antimicrobial Drugs Advisory Committee was held on October 16, 2019 **One patient representatives** was involved in that meeting confirmed in the final meeting roster	no	no, a pulmonary allergy drug Advisory Committee meeting was considered for this supplement. However, given the persuasiveness of the clinical trial results, the Division decided that the evidence supporting approval for the indicated populations were sufficiently robust that discussion by an Advisory Committee was not necessary	no	no, no advisory committee was held for this NDA because the applicatio n did not raise significant safety or efficacy is sues in the intended population.	no	no, the Agency conducted no Advisory Committee Meeting regarding this application because there were no major safety issu es and the adverse event profile was expected to be similar to other topical retinoids.	UNK	no
no	no	yes, Voice of Patient Report OCT2014: 2/7/2014 FDA Sickle Cell disease PFDD Meeting Patient Report that the health effects of SCD, including excruciating and incapacitating effects of episodic pain crisis and acute c hest syndrome affects all aspects of their lives. The debilitating symptoms and complex treatment needs limit their ability to perform in s chol, pursue career s, have a family, and maintain relationships. Patient also reports that the disease takes an emotional toll as patients face challenges with the healthcare system, stigma with society, financial hardships, and worry about their future. Both young and old live with constant reminders that they are not able to live a normal life.	no	no	no	no	no	no	no	no	no to reliance made to existing Voice to Patient for parkinson 's disease date Sep 2015
no	yes, PRO	yes, PRO sub mitted by MAH; FDA consider in the Review PFDD voice of Patient report SCD	yes, but no patient e xperience data were submitted for this application	yes, PRO	yes, PRO s ClinRO identified in th is assessment	yes, PR O; other: Cystic Fibrosis Foundation Patient Registry, Annual Data Report 2017 FDA co nsidered input informed from participation in meetings with patient stakeholder , but this cannot be confirmed	yes, PROs	yes, PR O submitted by MAH, FDA con sidered 1) input informed from participation in meetings with patient stakeholder and 2) PROD or other stake holder meeting summary reports - see "FDA other"	no	yes, PRO and ClinROs PRO mentioned in 1.4 cannot be confirmed	Yes, PROs	yes, PRO and ClinRO
no	no	no	no	no	no	no	no	no	no	no	no	no
no	no	no	no	no	no	no	no	FDA Scientific Workshop on Erythropoietic Protoporphyria: October 24, 2016 The Division sponsored a Scientific Wo rkshop on EPP that combined patients with EPP sharing th eir perspectives on living with EPP, an overview of the FD As regulatory role and process, and EPP expert panel discussion on scientific aspects of clinical trial design for EPP drug. https://ar ww.fda.gov/drugs/news-events-human-drugs/sc ientific-workshop-erythropoietic-protoporphyr ia-epp	no	no	no	no

Annex 2: List of Medicinal Products approved during the time period 01 January 2017 - 31 December 2019 by the FDA

UBRELVY	ENHERTU	DAYVIGO	CAPLYTA	RADCEV	VYONDYS 53	QUBRYTA
UBROGEPANT	FAM-TRASTUZUMAB DERUXTECAN-NXKI	LEMBOREXANT	LUMATEPERONE TOSYLATE	ENFORTUMAB VEDOTIN-EJPV	GOLODIRSEN	VOXELOTOR
NDA #211765	BLA #761139	NDA #212028	NDA #209500	BLA #761137	NDA #211970	NDA #213137
Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised
no	yes	no	yes	no	yes	yes
no	no	no	no	no	yes	yes
no	yes	no	no	yes	yes	yes
no	yes	no	no	yes	no	yes
no	no	no	no	no	yes	yes
23.12.19	20.12.19	20.12.19	20.12.19	16.12.19	12.12.19	25.11.19
26.12.18	29.08.19	27.12.18	27.09.18	15.09.19	19.12.18	26.06.19
ALLERGAN	DAICHI SANKYO	ESAI INC	INTRA-CELLULAR	ASTELLAS	SAREPTA THERAPS INC	GLOBAL BLOOD THERAPS
UBRELVY is a calcitonin gene-related peptide receptor antagonist indicated for the acute treatment of migraine with or without aura in adults.	ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.	DAYVIGO is an orexin receptor antagonist indicated for the treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.	CAPLYTA is an atypical antipsychotic indicated for the treatment of schizophrenia in adults.	RADCEV is a Nectin-4-directed antibody and microtubule inhibitor conjugate indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting.	VYONDYS 53 is an antisense oligonucleotide indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with VYONDYS 53. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.	QUBRYTA is a hemoglobin S polymerization inhibitor indicated for the treatment of sickle cell disease in adults and pediatric patients 12 years of age and older.
Type 1 - New Molecular Entity	BLA	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity	BLA	Type 1 - New Molecular Entity	Type 1 - New Molecular Entity
no	no	yes, eC-SBRS Sleep diary EQ-5D-3L WPAI:GH PGI-I insomnia (E) Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) (T-BWSQ) ISTC/PBerg Sleep Apnea Questionnaire, International Restless Legs Scale, Epworth Sleepiness Scale, and Munich Parasomnia Scale	yes, WHO (Five) Well-Being Index (WHO-5) Calgary Depression Scale for Schizophrenia (CDSS) Starkstein Apathy Scale (SAS) Brief Adherence Rating Scale (BARS)	yes, EORTC QLQ-C30 EQ-5D	no	yes, Sickle Cell Disease Severity measure (SCDSM) total symptom score (E) EuroQOL 5- dimension 5-level (EQ-5D-5L) (E)
no	no	yes, eC-SBRS	yes, CGI-S PANAS Personal and Social Performance Scale (PSP) Brief Adherence Rating Scale (BARS) Abnormal Involuntary Movement Scale (AIMS)	no	no	yes, Clinical Global Impression of Change (CGIC)
no	no	no	no	no	no	no
no	no	no	no	no	yes, 6- Minute Walk Test (6MWT)	no
no	no	no	no	no	no	no
no	no	no	no	no	no	no
no	no	no	no	no	no	no
no	no, no advisory committee discussion or consultations external to the FDA were deemed necessary for this BLA application.	no, the Division did not identify questions or concerns requiring discussion by external consultants, the Psychopharmacologic Drugs Advisory Committee, or the Drug Safety and Risk Management Advisory Committee.	no, cancelled	no, the BLA was not presented to an advisory committee because the benefit-risk profile demonstrated for enfortumab is clearly favorable for its proposed use. No controversial issues were identified that would necessitate an advisory committee meeting.	no, an advisory committee was not felt to be necessary for consideration of issues related to substantial evidence, safety, or risk: benefit considerations for the use of this drug in the DMD population.	no, this application was not referred to an Advisory Committee meeting as there were no major concerns regarding the safety or efficacy findings from the trials.
no	no reference made to existing 'Voice to Patient for breast Cancer' dated Apr 2015	no	no	no	no	no
yes, but no patient experience data were submitted for this application	yes, but no patient experience data were submitted with this application	yes, PRO and PerfO PerfO cannot be confirmed as mentioned in 1.4 ClinRO identified in this assesment	yes, ClinRO PROs were also identified in this assessment	yes, PROs and ClinROs ClinRO cannot be confirmed as mentioned in 1.4 (NCI-CTCAE or AECOT)	yes, PerfO provided by MAH. FDA included input informed from participation in meetings with patient stakeholder and PFDD or other stakeholder meeting summary reports - Not further specified and cannot be confirmed	yes, PROs and ClinRO
no	no	no	no	no	no	no
no	no	no	no	no	no	no

Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

_____ _____

Ort, Datum Unterschrift