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Master's Thesis

*«**Qualitative** aspects of the various procedures for marketing **authorization of medicinal products in EU and in USA»***

"Ποιοτικά στοιχεία των διαφόρων διαδικασιών έγκρισης φαρμακευτικών προϊόντων σε Ευρώπη και ΗΠΑ"

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Chapter 1: ***Abstract***

The purpose of this Master's thesis is the analysis of the different procedures for marketing authorization of medicinal products in the European Union (EU) and in the United States of America (USA). In that context, in Chapter 2 a short introduction in the approval processes is given. In Chapter 3 the Centralised Procedure in EU will be analytically described, while in Chapter 4 the procedures leading to a national license in EU (Mutual Recognition, Decentralised and National procedures) will be presented. In Chapter 5 a critical comparison of the different procedures in the EU will be given. A description of the authorization processes in the USA will be presented in Chapter 6, while in chapter 7 the procedures for marketing authorisation in EU and USA are compared and discussed. Finally, this thesis ends with the respective references used.

Chapter 2: ***Introduction***

Marketing Authorisation is the outcome of a reviewing and assessing process of the dossier supporting the efficacy and safety of a medicinal product prior to its marketing (also called licensing, registration, approval, etc.). Marketing Authorisation (MA) (equivalent: product license) is an official document granted by the Regulatory Authorities allowing access of medicinal product to a market. It is impossible for a medicinal product to be placed in a market without an MA. This process is performed within a legislative framework which defines the requirements necessary for application to the concerned (competent) regulatory authority, details on the assessment procedure (based on quality, efficacy and safety criteria) and the grounds for approval or rejection of the application, and the circumstances where a marketing authorization already granted may be withdrawn, suspended or revoked[1].

The drugs in the European Union are assessed/approved to be marketed either by the European Medicines Agency (EMA) (Centralised Procedure) or by the National Regulatory Authorities of the Member States (Mutual Recognition, Decentralised and National Procedures) (Figure 1[2]). EMA is a European Union agency for the evaluation of medicinal products, which was set up in 1995 with funding from the European Union and the pharmaceutical industry, as well as indirect

subsidy from member states, in an attempt to harmonize (but not replace) the work of existing national medicine (medicinal products) regulatory bodies[3]. It is worth mentioning that the final approval is granted by the European Commission.

Drugs in United States of America, are approved by the Food and Drug Administration (FDA), which is the regulatory agency responsible for safety regulation of the food and drug products in the US.

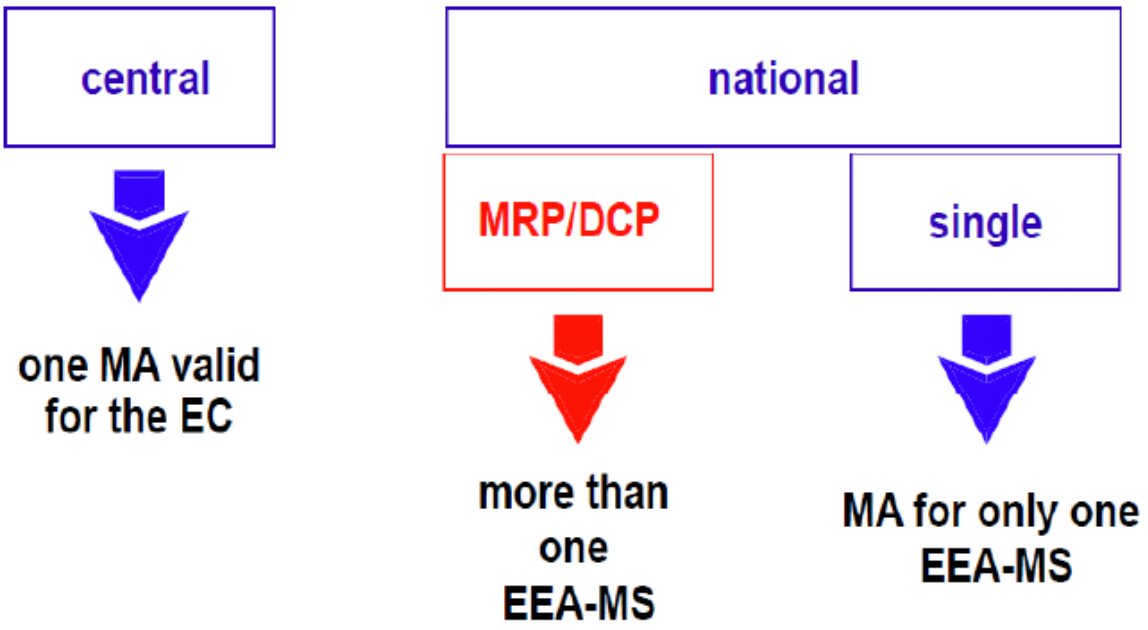

Figure 1: Approval processes in the European Economic Area states[2].

Chapter 3: *Centralised Procedure in the EU*

Only medicines that have been granted a marketing authorisation can be marketed in the European Union. There are two kinds of Marketing Authorisations (licenses) for Medicines in the European Union, as described below, Centralized and National authorization through four procedures (CP, DCP, MRP and NP). In this Chapter the Centralized License through the Centralized Procedure, for which EMA is responsible to make a recommendation and European Commission to issue the approval, will be presented in details.

The Centralised Procedure, which was introduced in 1993 and came into operation in 1995, allows applicants to obtain a Marketing Authorisation that is valid throughout the EU and the European Economic Area (EEA) countries Iceland, Liechtenstein and Norway. It is compulsory for the following therapeutic areas or sectors of medicinal products:

1. human medicines containing a new active substance to treat:
    - human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS);
    - cancer;
    - diabetes;
    - neurodegenerative diseases;
    - auto-immune and other immune dysfunctions;
    - viral diseases.
2. medicines derived from biotechnology processes, such as genetic engineering;
3. advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines;
4. orphan medicines (medicines for rare diseases);
5. veterinary medicines for use as growth or yield enhancers.

It is optional for other medicines in the following cases (the so-called optional scope):

- containing new active substances for indications other than those stated above;
- that are a significant therapeutic, scientific or technical innovation;
- whose authorisation would be in the interest of public at EU level[4,5].

A usual case in the Centralised Procedure for a MAA is briefly presented below.

When a person or a company wishes to place on the market a medicinal product that is eligible for the Centralised Procedure, it sends an application directly to the European Medicines Agency, to be assessed by the Committee for Medicinal Products for Human Use (CHMP).

Full copies of the marketing authorisation application file are sent to a rapporteur and a co-rapporteur designated by the competent EMA scientific committee. They co-ordinate the EMA's

assessment of the medicinal product and prepare draft reports. Once the draft reports are prepared (other experts might be called upon for this purpose), they are sent to the CHMP, whose comments or objections are communicated to the applicant. At that time, the evaluation period clock stops and applicant has up to three months, which can be extended to 6 months, to provide its responses. As soon as the responses have been provided the evaluation period clock starts again and the rapporteur and co-rapporteur assess the applicant's replies, submit them for discussion to the CHMP and, taking into account the conclusions of this debate, prepare a final assessment report. Once the evaluation is completed, the CHMP gives a favourable or unfavourable opinion as to whether to grant the authorisation. When the opinion is favourable, it shall include the draft summary of the product's characteristics, the package leaflet and the texts proposed for the various packaging materials[5].

The whole evaluation process should be completed within 210 on clock days (Figure 2)[6].

The EMA then has fifteen days to forward its opinion to the Commission. This is the start of the second phase of the procedure the so-called decision-making process. The Agency sends to the Commission its opinion and assessment report, together with annexes containing:

- the summary of product characteristics (Annex 1);
- the particulars of the manufacturing authorisation holder responsible for batch release, the particulars of and the manufacturer of the biological active substance and the conditions of the marketing authorisation (Annex 2); and
- the labelling and the package leaflet (Annex 3).

The annexes are translated into the 22 other official languages of the EU. During the decision-making process, the Commission services verify that the Marketing Authorisation complies with Union law.

Upon receiving EMA’s opinion, Commission has another fifteen days to prepare a draft decision. The medicinal product is assigned a Community Registration Number, which will be placed on its packaging if the Marketing Authorisation is granted. The draft decision is then sent to the Standing

Committee on Medicinal Products for Human Use (Member States have one representative each in this committee) for their opinions.

Member States have fifteen days to return their linguistic comments and 22 days for scientific and technical ones. This procedure is conducted in writing but if a duly justified objection is raised by one or more Member States, the committee holds a plenary meeting to discuss it[5].

When the opinion is favorable, the draft decision is adopted via the empowerment procedure and the decision is then published in the Community Register.

Today, the great majority of new, innovative medicines pass through the Centralised authorisation Procedure in order to be marketed in the EU[4].

Below, some new processes under the centralized procedure will be presented, which aim to make innovative drugs available to patients in EU and EEA countries earlier.

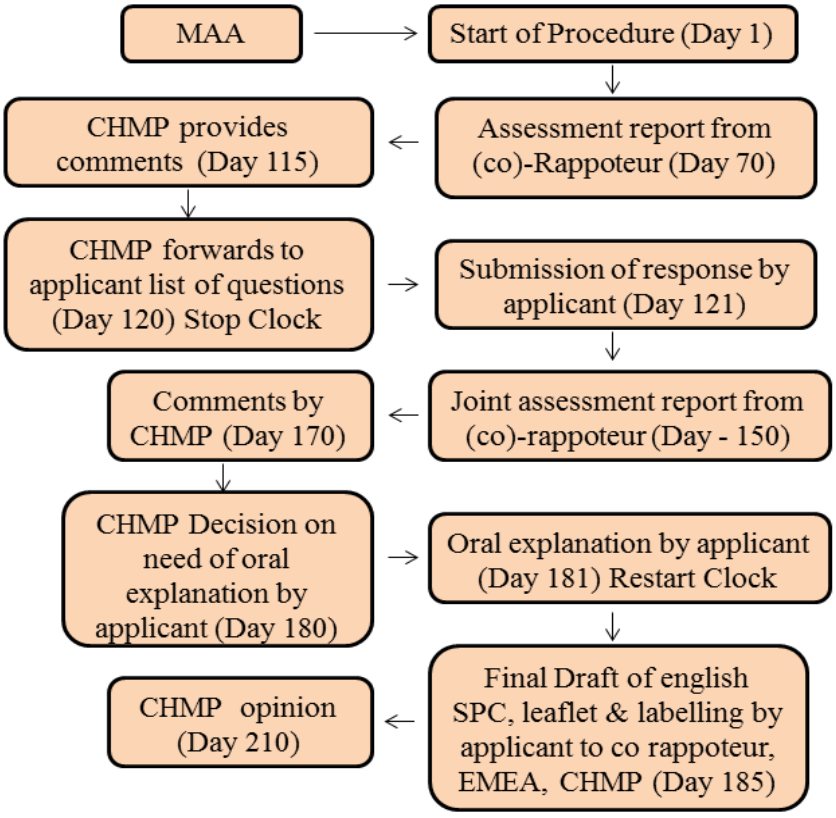

Figure 2: Centralized Procedure Steps and Timelines[6]

Accelerated Assessment

The Accelerated Assessment procedure is provided for by recital 33 and Article 14(9) of Regulation (EC) No 726/2004 and is a rapid assessment of medicines under the Centralised Procedure that are of major interest for public health, especially ones that are therapeutic innovations. Accelerated assessment usually takes 150 evaluation days, rather than 210[7].

Applications may be eligible for accelerated assessment if the CHMP decides the product is of major interest for public health and therapeutic innovation and the applicant provides sufficient justification for an Accelerated Assessment, which should be done at least two to three months before submitting the Marketing Authorisation application[7].

Before submitting a request for accelerated assessment, applicants should seek guidance from the EMA procedure manager to ensure timely submission of their request. Applicants can also request a pre-submission meeting six to seven months before submission to prepare for evaluation under accelerated assessment. In this meeting, they can discuss their proposal for accelerated assessment with the Agency and rapporteurs from the CHMP and any other committees concerned, such as the Pharmacovigilance Risk Assessment Committee, which is the committee that is responsible for assessing all aspects of the risk management of medicines for human use[7].

Under the PRIME scheme, which is described below, launched in March 2016, it is now possible for applicants to receive confirmation during the clinical development phase that their medicine might potentially be eligible for Accelerated Assessment[7].

Assessment procedure

After the rapporteurs have received the request, they will produce a briefing note including their recommendations regarding an Accelerated Assessment.

If necessary, the CHMP may request clarifications from the applicant. The CHMP will make a decision based on the request, the justifications presented and the recommendations of the rapporteurs.

It needs to be clear, that the decision regarding the acceptance or not of an application under the Accelerated Assessment scheme has no impact on the eventual CHMP opinion on whether a Marketing Authorisation should be granted or not. The CHMP conclusions will be communicated to the applicant and the reasons for accepting or rejecting the request will also be summarised in the CHMP assessment report. In case of acceptance, the CHMP will take into consideration the standard timetable agreed for the accelerated assessment procedure[7].

PRIority MEdicines (PRIME)

PRIME is a scheme launched by the European Medicines Agency (EMA) to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimise development plans and speed up evaluation so these medicines can reach patients earlier.

Through PRIME, early and proactive support is offered to medicine developers to optimise the generation of robust data on a medicine's benefits and risks, by improving clinical trial designs and enable accelerated assessment of medicines applications. This will help patients to benefit as early as possible from therapies that may significantly improve their quality of life.

PRIME builds on the existing regulatory framework and tools already available such as scientific advice and accelerated assessment. This means that developers of a medicine that benefitted from PRIME can expect to be eligible for Accelerated Assessment at the time of application for a Marketing Authorisation.

The scheme focuses on medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options. These medicines are considered priority medicines by EMA. To be accepted for PRIME, a medicine has to show its potential to benefit patients with unmet medical needs based on early clinical data. As of the 20th of July 2017, out of 126 requests, 93 have been rejected, 28 have been accepted and 5 were considered as out of scope[8].

Adaptive Pathways

The Adaptive Pathways approach is part of the European Medicines Agency's (EMA) efforts to improve timely access for patients to new medicines. Adaptive Pathways is a scientific concept for medicine development and data generation which allows for early and progressive patient access to a medicine. The approach makes use of the existing European Union (EU) regulatory framework for medicines.

Adaptive Pathways is based on three principles:

- iterative development, which either means:
    1. approval in stages, beginning with a restricted patient population then expanding to wider patient populations;
    2. confirming the benefit-risk balance of a product, following a conditional approval based on early data (using surrogate endpoints) considered predictive of important clinical outcomes;
- gathering evidence through real-life use to supplement clinical trial data;
- early involvement of patients and health-technology-assessment bodies in discussions on a medicine's development

This concept applies primarily to treatments in areas of high medical need where difficulties to collect data via traditional routes exist and where large clinical trials would unnecessarily expose patients who are unlikely to benefit from the medicine.

The approach builds on regulatory processes already in place within the existing EU legal framework, including scientific advice, compassionate use, the conditional approval mechanism (for medicines addressing life-threatening conditions) and patient registries and other pharmacovigilance tools that allow collection of real-life data and development of the risk-management plan for each medicine.

Adaptive Pathways does not change the standards for the evaluation of benefits and risks or the requirement to demonstrate a positive benefit-risk balance to obtain marketing authorisation[9].

***Chapter 4:* National License**

As the majority of medicines authorised in the EU do not fall within the scope of the Centralised Procedure, are authorised by National Competent Authorities (NCAs) in the Member States. EU Member States have three procedures available for the authorisation of medicines within their own territory that fall outside the scope of the Centralised Procedure. The choice of the specific procedure lies with the Applicant.

When an applicant wants to authorise a medicine can use one of the following procedures:

- the Decentralised Procedure (DCP), where applicants can apply for the simultaneous authorisation of a medicine in more than one EU Member States if it has not yet been authorised in any EU country and does not fall within the scope of the centralised procedure;
- the Mutual Recognition Procedure (MRP), where applicants that have a medicine authorised in one EU Member States can apply for this authorisation to be recognised in other EU countries as well.
- National procedure (NP) where the application is submitted in one MS and receives a MA for the specific MS. This is the first step in the MR procedure[10]

Hence, applications for approval in multiple Member States for products that do not fall within the mandatory scope of the Centralised Procedure must follow the Mutual Recognition Procedure (MRP) or the Decentralised Procedure (DCP). In terms of volume, MRP and DCP procedures outnumber the Centralised Procedure and considerable resources are spent by both Marketing Authorisation (MA) holders and national competent authorities on Marketing Authorisation Applications (MAAs) via the MRP/DCP procedures[11].

The two different procedures for granting MA in several EU states outside the Centralized Procedure are outlined below. National Procedure will not be described, as each Member State's Competent Authority approves based on its own Local Regulation and legislative framework.

Mutual Recognition Procedure - MRP

Since January 1, 1998, the MRP is mandatory for any product that is to be marketed in multiple Member States, when a MA exists anywhere in the EU[11], and basic legal arrangements for the implementation of the procedure laid in Directive 2001/83/EC have been made in all Member States. The Mutual Recognition Procedure is based on the principle of the mutual recognition by EU Member States of their respective national Marketing Authorisations. An application for mutual recognition may be addressed to one or more Member States. The applications submitted must be identical and all Member States involved must be notified of them. As soon as one Member State decides to evaluate the medicinal product becomes the "Reference Member State" and has to notify this decision to other Member States, which then become the "Concerned Member States", to whom applications have also been submitted. Concerned Member States will then suspend their own evaluations, and await the Reference Member State's assessment reports on the product.

This evaluation procedure undertaken by the Reference Member State may take up to 210 days, and ends with the granting or not of a Marketing Authorisation in that Member State. It can also occur that a Marketing Authorisation had already been granted by the Reference Member State. In such a case, it shall update the existing assessment report in 90 days. As soon as the assessment is completed, copies of this report are sent to all Member States, together with the approved Summary of Product Characteristics (SPC), labelling and package leaflet. The Concerned Member States then have 90 days to recognise the decision of the Reference Member State and the SPC, labelling and package leaflet as approved by it. National Marketing Authorisations shall be granted within 30 days after acknowledgement of the agreement (Figure 3[6]).

In case any of the Concerned Member States refuse to recognise the original National authorization by the RMS, on the grounds of potential serious risk to public health, the issue will be referred to the coordination group. Within a timeframe of 60 days, Member States shall, within the coordination group, make all efforts to reach a consensus. In case this fails, the procedure is submitted to the appropriate EMA scientific committee (CHMP), for arbitration. The opinion of the EMA Committee is then forwarded to the Commission, for the start of the decision making process.

As in the Centralised Procedure, this process entails consulting various Commission Directorates General and the Standing Committee on Human Medicinal Products[12].

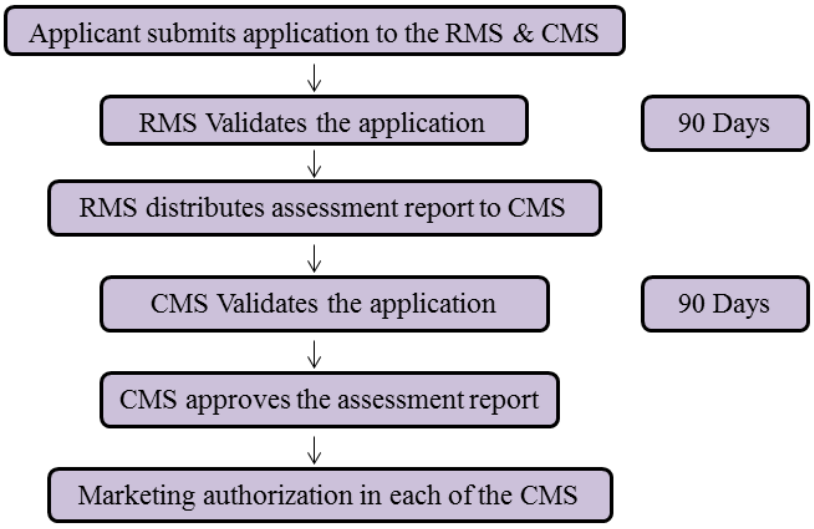

Figure 3: Mutual Recognition Procedure steps and timelines[6]

Decentralised Procedure - DCP

The Decentralised Procedure was introduced by Directive 2004/27/EC. As the Mutual Recognition Procedure, it is also based on recognition by National Authorities of a first assessment performed by one Member State. The difference is that it applies to medicinal products which have not received a Marketing Authorisation at the time of application and of course do not fall into the mandatory scope of Centralised Procedure.

An identical application for Marketing Authorisation is submitted simultaneously to the competent authorities of the Reference Member State and of the Concerned Member States. At the end of the procedure, the draft assessment report, SPC, labelling and package leaflet, as proposed by the Reference Member State, are approved. The subsequent steps are identical to the mutual recognition procedure[13]. Procedure's steps and timelines are shown in Figure 4[6].

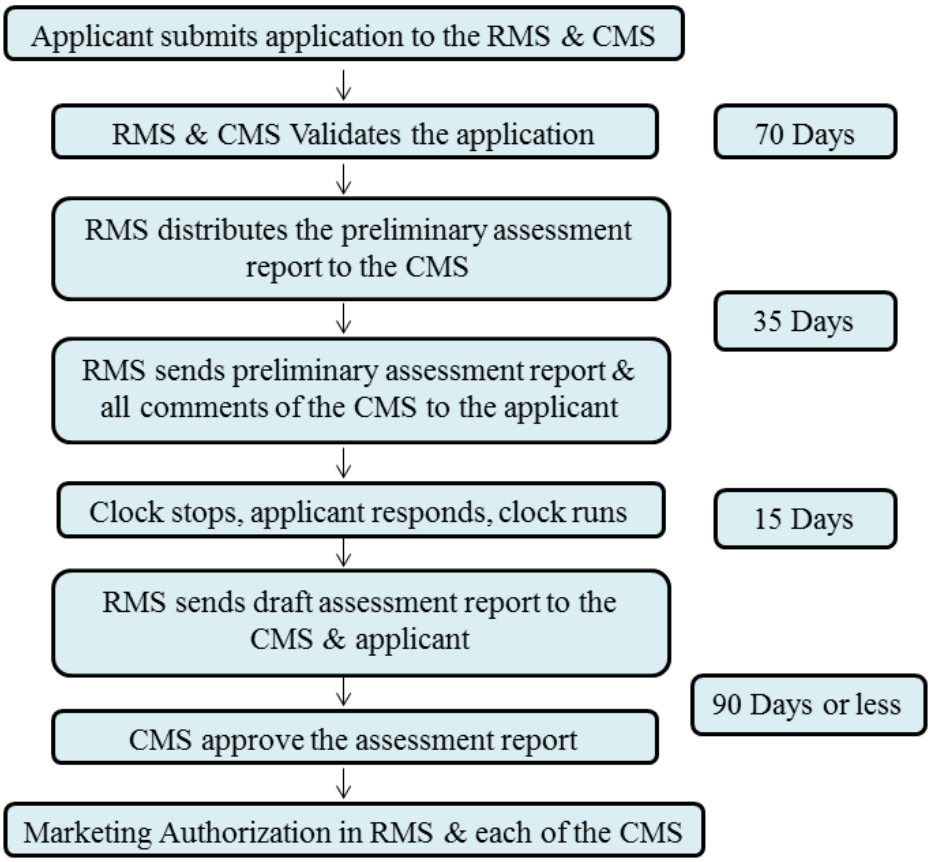

Figure 4: Decentralised Procedure[6]

Chapter 5: Comparison of the marketing authorization procedures in EEA

Based on the data presented above, the basic difference between Centralised Procedure and National License is that the Centralised Procedure is the only option for authorizing in EU and EEA countries the following drug categories:

1. human medicines containing a new active substance to treat:
    - human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS);
    - cancer;
    - diabetes;
    - neurodegenerative diseases;

- auto-immune and other immune dysfunctions;
- viral diseases

2. medicines derived from biotechnology processes, such as genetic engineering;
3. advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines;
4. orphan medicines (medicines for rare diseases);
5. veterinary medicines for use as growth or yield enhancers.

Besides the products falling under the mandatory scope, the centralized procedure is also open for other innovative products. Examples are new active substances or other medicinal products that constitute a significant therapeutic, scientific or technical innovation, or the granting of a Community authorization for the medicinal product is in the interest of patients at Community level. The decision as to whether the product is eligible or not is made by the EMA upon the submission of the corresponding request (letter of eligibility) by the applicant[4,5,14].

With regards to the timelines, according to the Centralised process, 210 on clock days are required for an approval to be granted, with the exception of the accelerated process, while in Decentralized procedure at least 120 on clock days are required, in case no comments are issued, but it might need up to 240 on clock days upon approval issuance. The MRP process requires 90 days (without clock stops) in case an authorization already exists in a EU member state. If not, 210 additional days are required in order to obtain the first approval, form the so called Reference Member State and then within 90days the MRP process can start[15]. The MRP process may need a period up to 390 days[6].

Major advantage of the CP is the fact that one application leads to one assessment and finally to one MA for all EU states.

***Chapter 6:* Marketing Authorisation procedure in the United States of America**

If a drug developer may have evidence from its early tests and preclinical and clinical research that a drug is safe and effective for its intended use, the company can file an application to market the drug, the so called New Drug Application (NDA). Other forms of drug approval applications also exist e.g. Abbreviated New Drug Application (ANDA) for generics, Over The Counter (OTC) and Biologic License Application (BLA), which will not be examined in this Thesis. Upon an NDA submission, the FDA review team thoroughly examines all submitted data on the drug and makes a decision to approve or not based on the submitted data which should demonstrate that a drug is safe and effective for its intended use in the population studied.

A drug developer must include everything about a drug—from preclinical data to Phase 3 trial data—in an NDA and additionally the following:

- Proposed labeling
- Safety updates
- Drug abuse information
- Patent information
- Any data from studies that may have been conducted outside the United States
- Institutional review board compliance information
- Directions for use

Once FDA receives an NDA, the review team decides if it is complete and if not, the review team can refuse to file the NDA. If it is complete, the review team has 6 to 10 months (approximately 180-300 days) to make a decision on whether to approve the drug[16]. According to the Prescription Drug User Fee Act (PDUFA) the FDA is expected to review and act on at least 90% of NDAs for standard drugs no later than 10 months (300 days) after the applications are received[17].

In cases where FDA determines that a drug has been shown to be safe and effective for its intended use, it is then necessary to work with the applicant to develop and refine prescribing information. This is referred to as "labeling", which accurately and objectively describes the basis for approval and how best to use the drug[16].

Speeding Up the Approval Process

As the existing process is quite time-consuming, FDA has developed four distinct approaches (Figure 5) to making drugs that treat serious diseases, especially when the drugs are the first available treatment or if the drug has advantages over existing treatments available as rapidly as possible[18]:

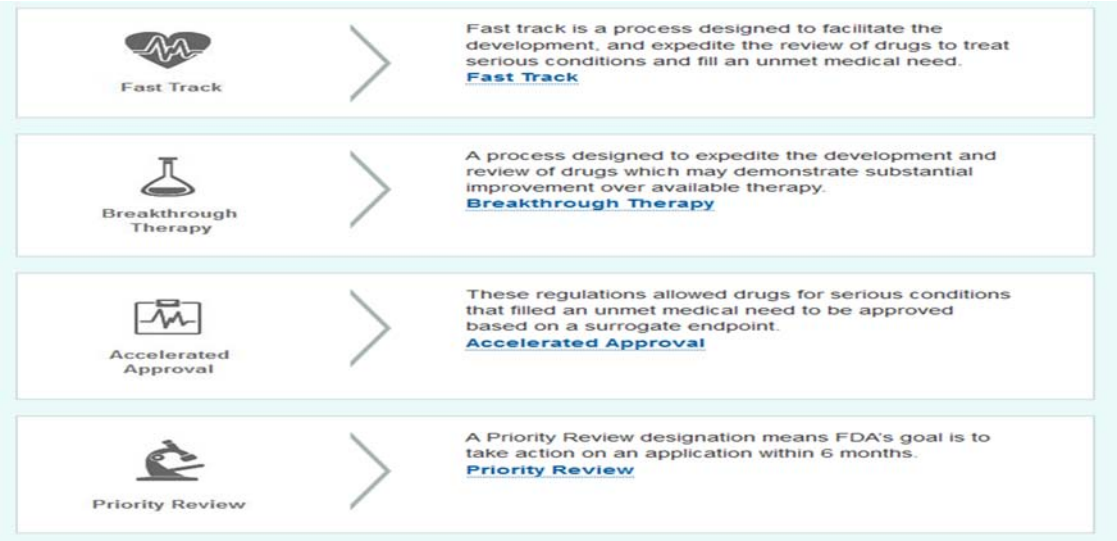

Figure 5: Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review procedures by FDA[18]

- Fast Track
- Breakthrough Therapy
- Accelerated Approval
- Priority Review

Each of these speeding processes is outlined below.

Fast Track

Fast track is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need. The purpose is to get important new drugs

to the patient earlier. Fast Track addresses a broad range of serious conditions.

Any drug being developed to treat or prevent a condition with no current therapy obviously is directed at an unmet need. If there are available therapies, a Fast Track drug must show some advantage over available therapy, such as:

- Showing superior effectiveness, effect on serious outcomes or improved effect on serious outcomes
- Avoiding serious side effects of an available therapy
- Improving the diagnosis of a serious condition where early diagnosis results in an improved outcome
- Decreasing a clinical significant toxicity of an available therapy that is common and causes discontinuation of treatment
- Ability to address emerging or anticipated public health need

A drug that receives Fast Track designation is eligible for some or all of the following:

- More frequent meetings with FDA to discuss the drug's development plan and ensure collection of appropriate data needed to support drug approval
- Eligibility for Accelerated Approval and Priority Review, if relevant criteria are met
- Rolling Review, which means that a drug company can submit the so far completed sections of its New Drug Application (NDA) for review by FDA, rather than waiting until every section of the NDA is completed before the entire application can be reviewed. NDA review, as already described, usually does not begin until the drug company has submitted the entire application to the FDA.

Fast Track designation must be requested by the drug company. The request can be initiated at any time during the drug development process. FDA will review the request and make a decision within sixty days based on whether the drug fills an unmet medical need in a serious condition[19].

Breakthrough Therapy

Breakthrough Therapy designation is a process designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s)[20].

For purposes of Breakthrough Therapy designation, clinically significant endpoint generally refers to an endpoint that measures an effect on irreversible morbidity or mortality (IMM) or on symptoms that represent serious consequences of the disease. A clinically significant endpoint can also refer to findings that suggest an effect on IMM or serious symptoms, including:

- An effect on an established surrogate endpoint
- An effect on a surrogate endpoint or intermediate clinical endpoint considered reasonably likely to predict a clinical benefit (i.e., the accelerated approval standard)
- An effect on a pharmacodynamic biomarker(s) that does not meet criteria for an acceptable surrogate endpoint, but strongly suggests the potential for a clinically meaningful effect on the underlying disease
- A significantly improved safety profile compared to available therapy (e.g., less dose-limiting toxicity for an oncology agent), with evidence of similar efficacy

A drug that receives Breakthrough Therapy designation is eligible for all Fast Track designation features and for intensive guidance on an efficient drug development program, beginning as early as Phase 1.

Breakthrough Therapy designation is requested by the drug company. If a sponsor has not requested breakthrough therapy designation, FDA may suggest that the sponsor consider submitting a request if: (1) after reviewing submitted data and information (including preliminary clinical evidence), the Agency thinks the drug development program may meet the criteria for Breakthrough Therapy designation and (2) the remaining drug development program can benefit from the designation[20].

Ideally, a Breakthrough Therapy designation request should be received by FDA no later than the end-of-phase-2 meetings if any of the features of the designation are to be obtained. FDA will respond to Breakthrough Therapy designation requests within sixty days of receipt of the request[20].

Accelerated Approval

In 1992 FDA instituted the Accelerated Approval regulations which allowed drugs for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint. Using a surrogate endpoint enabled the FDA to approve these drugs faster.

In 2012, Congress passed the Food and Drug Administration Safety Innovations Act (FDASIA). Section 901 of FDASIA amends the Federal Food, Drug, and Cosmetic Act (FD&C Act) to allow the FDA to base Accelerated Approval for drugs for serious conditions that fill an unmet medical need on whether the drug has an effect on a surrogate or an intermediate clinical endpoint[21].

A surrogate endpoint used for Accelerated Approval is a marker - a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Likewise, an intermediate clinical endpoint is a measure of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on irreversible morbidity and mortality (IMM)[21].

The FDA bases its decision on whether to accept the proposed surrogate or intermediate clinical endpoint on the scientific support for that endpoint. Studies that demonstrate a drug's effect on a surrogate or intermediate clinical endpoint must be "adequate and well controlled" as required by the FD&C Act[21].

Using surrogate or intermediate clinical endpoints can save valuable time in the drug approval process. For example, instead of having to wait to learn if a drug actually extends survival for cancer patients, the FDA may approve a drug based on evidence that the drug shrinks tumors, because tumor shrinkage is considered reasonably likely to predict a real clinical benefit. In this example, an approval based upon tumor shrinkage can occur far sooner than waiting to learn whether patients actually lived longer. The drug company will still need to conduct studies to confirm that tumor

shrinkage actually predicts that patients will live longer. These studies are known as phase 4 confirmatory trials[21].

Where confirmatory trials verify clinical benefit, FDA will generally terminate the requirement. Approval of a drug may be withdrawn or the labeled indication of the drug changed if trials fail to verify clinical benefit or do not demonstrate sufficient clinical benefit to justify the risks associated with the drug (e.g., show a significantly smaller magnitude or duration of benefit than was anticipated based on the observed effect on the surrogate)[21].

Priority Review

In 1992, under the Prescription Drug User Act (PDUFA), FDA agreed to specific goals for improving the drug review time and created a two-tiered system of review times – Standard Review and Priority Review. A Priority Review designation means agency has to take action on an application within 6 months (compared to 10 months under standard review) from its submission[22].

A Priority Review designation will direct overall attention and resources to the evaluation of applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications[22].

Significant improvement may be demonstrated by the following examples:

- evidence of increased effectiveness in treatment, prevention, or diagnosis of condition;
- elimination or substantial reduction of a treatment-limiting drug reaction;
- documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes; or
- evidence of safety and effectiveness in a new subpopulation.

FDA informs the applicant of a Priority Review designation within 60 days of the receipt of the original application or efficacy supplement. Designation of a drug as “Priority” does not make the scientific/medical standard for approval or the quality of evidence necessary[22].

It is believed that FDA regulates over 1 trillion dollars worth of products in New Human Drug, Biologics, Biologics, Complex Medical Devices, Food and Color Additives, Infant formulas and Animal Drugs[23].

Chapter 7: *Marketing procedures in EEA and USA – A qualitative comparison of EMA and FDA approaches - Discussion*

Lately, the main concern for regulators across the globe appears to be the timely access of patients to medicines appropriate for their disease or pathological condition. As a result, both EMA and FDA tend to share similar objectives including public health promotion and protection, evaluation and supervision of the medicinal products and to make novel therapies available to patients in a speedy manner[24]. Based on what was described above EMA and FDA approval procedures share a lot of similarities and each Agency has setup flexible procedures. These procedures are more evident in the expedited approval processes where, the priority review by the FDA is equivalent to accelerated assessment by EMA, and the FDA accelerated approval corresponds to EMA conditional approval[17].

The fundamentals of the various prioritization procedures were set by FDA in 1974, Priority Review, Accelerated Approval, Fast Track designation, and Breakthrough Therapy designation[25].

Fast track approval is a relatively old concept established by FDA to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need. The purpose is to get important new drugs to the patient earlier. Fast Track addresses a broad range of serious conditions[19] .

Fast Track was introduced by the FDA Modernization Act of 1997[26] and designations for new drug candidates in that scheme have grown substantially, from an average of 22 per year during 1998-02 to 49 per year during 2003-07[27].

There is also the Breakthrough Therapy of FDA, which is designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s)[20]. The Breakthrough Therapy mechanism originated during a

discussion at a conference co-hosted by Friends of Cancer Research and the Brookings Institute in 2011 regarding potential novel approaches to speed up the FDA approval process for certain promising new drugs[25].

In an analogous manner, EMA recently established PRIME scheme in an effort to bridge fast track approval and breakthrough designation. As it is described in EMA's PRIME website[8]: PRIME is a scheme launched by the European Medicines Agency (EMA) to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimise development plans and speed up evaluation so these medicines can reach patients earlier.

Through PRIME, the Agency offers early and proactive support to medicine developers to optimise the generation of robust data on a medicine's benefits and risks and enable accelerated assessment of medicines applications. By engaging with medicine developers early on, PRIME is aimed at improving clinical trial designs so that the data generated is suitable for evaluating a marketing-authorisation application. Early dialogue and scientific advice also ensure that patients only participate in trials designed to provide the data necessary for an application, making the best use of limited resources[8]

Although both agencies share similar objectives and efforts to harmonize processes are underway, there is a major structural difference. FDA is a federal agency that oversees the drug development in the entire US in 52 states, while EMA is a coordinating agency that manages the processes in the 28 Member States of the EEA. One decision from FDA is immediately applicable to all 52 United States, whilst a guideline needs to be adopted formally or informally by the 28 Member States before it can be implemented. One more point of note is that FDA has the authority to regulate drugs and issue approvals with a field of application the soil of USA, whereas EMA is a reviewing body providing opinions to the European Commission, which is responsible to issue enforceable decisions binding all the Member States[17]. EMA can organize and co-ordinate inspections, but there is no actual field (country) to be able to apply them. The place of inspection will belong to a country and the authorities of this country will be responsible for the any legal actions. Furthermore, FDA has a structural autonomy, meaning that drug development processes and submitted applications

are reviewed and evaluated by FDAs own staff. EMA, as a decentralized agency, has no own resources but brings together scientific resources of the EEA Member States Regulatory Authorities, in order to perform the relevant activities[24]. A summary of the Regulatory Oversight in EU and USA is shown in Figure 6[24].

Regulatory Oversight	
United States	European Union
FDA	**National Authorities**: Each country is responsible for monitoring the safety profile of the product in its territory and and taking action when needed **European Commission**: This body is responsible for the legal framework and authorization. **European Medicines Agency:** This agency evaluates and supervises medicinal products and provides advice on measures to ensure safety and efficacy. **Committee for Medicinal Products for Human Use (CHMP):** This committee prepares opinions for the European Medicines Agency and makes recommendations for human use.

Figure 6: Regulatory Oversight in EU and USA[21]

These structural and legislative differences can justify the empowerment of the expedited procedures with greater easiness by FDA and the delay observed in the case of EMA. Formal and informal consultation periods in Europe take longer time. This cannot be verified by numbers and data. It can only be deducted by the timing of establishing new procedures.

An indirect proof of the above observation is the fact that EMA and FDA present differences in the time to approval new medicinal products and especially innovative medicines. A recently published comparison of the EMA and FDA approval time showed that FDA approves faster than EMA[28].

Moreover, differences are also observed regarding indication approval and the labeling language. Trotta et al found that only half of the oncology indications evaluated by EMA and FDA between 1995 and 2008 were approved by both agencies, while 19 out of 100 were approved by one but not

the other, which of course may have a clinical Impact, as "Differences in access to treatments in such a globalized world, may have several consequences. First, in the countries where the indication is not approved, a growing pressure on regulatory bodies, both from patients and health care professionals, can be expected. This may potentially influence the regulatory review process, possibly leading to a biased evaluation. Second, the off-label use of medicines is fuelled where the indication is not approved. However, if such an indication is approved in another country based on robust data, it can be considered as an off-label use only from a regulatory perspective"[29].

Finally, although some believe that drug approval standards in the United States are considered to be the most demanding in the world[6], the same study by Trotta et all showed that the 69% of the studied oncology indications were first approved by FDA[29].

Finally it is worth mentioning, although it is beyond the scope of this Thesis, that although it is widely believed that early regulatory approval results in early access to care, this seems to be a myth[17], given that apart from time needed for regulatory approval and the Marketing Authorisation, reimbursement is also important and can be a resources demanding and time-consuming process. As payers are more involved and reimbursement does not happen automatically, due to the pharmaceutical policy of each country, it is obvious that time to approval does not mean automatically timely access of patients to innovative medications[30].

In the recent period, with the economic crisis having affected all health/insurance systems all over the globe and especially in Europe[31], medicinal product cost affordability is a key element for systems' sustainability. As a result, discussions arose regarding the strategy that needs to be followed. Some support that strict pricing policies should be followed in order more patients to gain access to novel medicinal products, while some support that pricing regulation and reimbursement constraints should be applied in order to limit health related expenditure.

Timely access to medicines from patients that need them is a multifactorial issue. While in the recent years respectful efforts are being made by regulatory agencies to provide the procedures and the means for the development of an effective and safe medicine that would lead to the grant of a Marketing Authorisation, it appears that these efforts are not sufficient.

However, despite the structural and legislative differences, both agencies have recognized that due to globalization, international collaboration/cooperation is of paramount importance and a regulatory decision in one country may have unavoidably an impact on the others, especially when decisions are taken by worlds' leading agencies such as EMA and FDA[29].

It is well-known that in most instances, patients are not in a position to diagnose their disease/condition or make decisions about which drugs to use, when to use them, how to use them and to weigh potential benefits against risks as no medicine is completely safe. Professional advise from either prescribing doctors or pharmacists are needed in administering the appropriate medication[32].

The regulatory agencies are expected to play a significant role in this chain from the development of a medicine to the administration of the right medication for the right condition. A regulatory authority will have to:

- Ensure that all medicines manufacturing, importation, exportation, wholesale and distribution establishments are licensed. Activities and premises must comply with Good Manufacturing Practices (GMP) and Good Distribution Practice requirements
- Before medicines are marketed, assess their safety, efficacy and quality
- Monitor the quality and safety of medicines on the market to prevent harmful, substandard and counterfeit medicines from reaching the public
- Regularly inspect and control the informal market, including e-commerce, to prevent illegal trade of medicines
- Monitor advertising and promotion of medicines, and provide independent information on their rational use to the public and professionals
- Participate in sub-regional and regional regulatory networks and international meetings of drug regulatory authorities to discuss issues of mutual interest and concern, facilitate timely exchange of information and promote collaboration
- Monitor and evaluate performance to assess if perceived regulatory objectives have been met, to identify weaknesses and take corrective action [32]

The need to make these agency's tasks in an organised and collaborative manner with another agency has increased tremendously over the past few years. To this effect EMA and FDA have significantly increased their level of collaboration and sharing of information to advance regulatory excellence worldwide. There are now daily interactions, most of them structured around scientific and regulatory working groups or "clusters". The focus of the cluster reviews during this bilateral was pharmacovigilance, biosimilars, paediatrics and veterinary medicines. They also agreed to further strengthen their collaboration in inspections and data integrity, safety monitoring of medicines, biosimilars, paediatric medicines, rare diseases, timely access to new medicines and veterinary medicines. This will help EU regulators and FDA increase efficiency on a global level and avoid duplication[33].

It can be safely concluded that despite important qualitative differences, EMA and FDA are recently making continuous efforts to streamline processes and procedures which lead to a Marketing Authorisation without significant delays (where it is considered appropriate) and a subsequent safe periodical monitoring of this license always with a view towards patients' benefit and wellbeing.

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