Πρόγραμμα Μεταπτυχιακών Σπουδών (ΠΜΣ): «Μεθοδολογία Βιοϊατρικής Έρευνας, Βιοστατιστική και Κλινική Βιοπληροφορική».

A COMPARISON BETWEEN EMA AND FDA IN THE MARKETING AUTHORIZATION OF MEDICINAL PRODUCTS IN NEUROLOGY AND PSYCHIATRY

ΜΕΤΑΠΤΥΧΙΑΚΗ ΕΡΓΑΣΙΑ

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ΜΕΛΕΤΗ ΣΥΓΚΡΙΣΗΣ ΜΕΤΑΞΥ ΤΩΝ EMA ΚΑΙ FDA ΣΤΗ ΧΟΡΗΓΗΣΗ ΕΓΚΡΙΣΕΩΝ ΣΕ ΝΕΥΡΟΛΟΓΙΚΑ ΚΑΙ ΨΥΧΙΑΤΡΙΚΑ ΦΑΡΜΑΚΕΥΤΙΚΑ ΠΡΟΪΟΝΤΑ

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ΠΕΡΙΕΧΟΜΕΝΑ

ΠΕΡΙΛΗΨΗ

Οι δραστηριότητες και οι αποφάσεις του Οργανισμού Τροφίμων και Φαρμάκων των ΗΠΑ (FDA) και του Ευρωπαϊκού Οργανισμού Φαρμάκων (EMA) συχνά αποτελούν πεδίο συγκρίσεων. Η κατανόηση των διαφορετικών απαιτήσεων των ρυθμιστικών αρχών ως προς την ανάπτυξη φαρμάκων και των προτύπων για την αξιολόγηση της ασφάλειας και της αποτελεσματικότητας, είναι καθοριστικής σημασίας για τη διευκόλυνση της διεθνούς συμφωνίας ενώ ταυτόχρονα λαμβάνονται υπόψιν οι εκάστοτε τοπικές ιδιαιτερότητες. Επιπροσθέτως, η εξέταση και η σύγκριση των αποφάσεων των διαφόρων αιτήσεων, ενδεχομένως να βοηθήσει στην κατανόηση του τρόπου με τον οποίο οι Οργανισμοί εφαρμόζουν την κανονιστική επιστήμη στα φαρμακευτικά προϊόντα [1]. Στην παρούσα μελέτη, χρησιμοποιούνται παραδείγματα φαρμάκων για ψυχιατρικές και νευρολογικές διαταραχές προκειμένου να διερευνηθούν οι κύριες διαφορές των τυπικών αλλά και άτυπων κανόνων που διέπουν τις διαδικασίες άδειας κυκλοφορίας νέων φαρμάκων στην Ευρωπαϊκή Ένωση (ΕΕ) και τις Ηνωμένες Πολιτείες Αμερικής (ΗΠΑ). Για το σκοπό αυτό, αναζητήθηκαν δημόσια διαθέσιμες πληροφορίες από τις ιστοσελίδες του EMA και του FDA καθώς και βιβλιογραφία από βάσεις δεδομένων Βιοϊατρικής. Συμπεραίνεται ότι υπάρχει μια γενική συμφωνία στις εγκρίσεις μεταξύ του EMA και του FDA, ως συνέπεια των προσπαθειών για συνεργασία και εναρμόνιση στην κυκλοφορία των φαρμάκων και παροχή των ίδιων η παρόμοιων θεραπευτικών επιλογών στους ασθενείς. Ωστόσο, παραμένουν ορισμένες δομικές κυρίως διαφορές ανάμεσα στον EMA και στο FDA οι οποίες δημιουργούν διαφορετικές ρυθμιστικές διαδρομές και πιθανώς να οδηγούν σε διαφορετικό αποτέλεσμα αξιολόγησης.

ΛΕΞΕΙΣ-ΚΛΕΙΔΙΑ

Οργανισμός Τροφίμων και Φαρμάκων των ΗΠΑ (FDA), Ευρωπαϊκός Οργανισμός Φαρμάκων (EMA), ρυθμιστικές αρχές, φαρμακευτικά προϊόντα, ψυχιατρικές και νευρολογικές διαταραχές, άδεια κυκλοφορίας, εγκρίσεις.

ABSTRACT

The activities and decisions of the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are often compared. Understanding differences in regulators' expectations for drug development and standards for assessment of safety and efficacy, is critical to facilitate more global alignment while allowing for unique considerations of specific regional needs. Additionally, examination and comparison of decisions on applications for marketing authorizations, may provide an understanding of how agencies consider and apply regulatory science in drugs/medicinal products [1]. In the present study, some examples of drugs for psychiatric and neurological disorders were used to investigate the main differences of current (typical and atypical) rules governing the registration of new medicines in the European Union (EU) and the United States of America (USA). For this purpose, publicly available information was searched for from EMA and FDA websites as well as literature from biomedical databases. It can be concluded that there is a general agreement and consensus approach between EMA and FDA approvals, as a consequence of the efforts for cooperation and harmonization of drug regulation and offer of same or similar therapeutic choices for patients. Despite consistency, there are mainly structural differences between EMA and

FDA which generate various regulatory pathways and may lead to different results in the assessments.

KEYWORDS

US Food and Drug Administration (FDA), European Medicines Agency (EMA), regulators, medicinal products, psychiatric and neurological disorders, marketing authorization, approvals.

1. INTRODUCTION

Efforts to pursue harmonization of drug regulation (including International Council for Harmonisation [2]) have been ongoing but differences in the approval characteristics of drugs by different agencies still persist. It is quite frequent that the same drug can be available without restrictions in one regulatory jurisdiction but with restrictions in another—or not approved and not available at all. Also, discrepancies in drug characteristics have been observed between different markets. These issues are of special concern, particularly when a drug is novel and first in class with no comparable therapeutic alternatives available [3].

The case study of psychiatric and neurological disorders is particularly challenging, as several active treatments are already available on the market, rates of spontaneous remission are high, placebo and active treatment response is erratic and variable, and outcome measures are not clear-cut concepts [4].

1.1. EUROPEAN MEDICINES AGENCY (EMA)

The European Medicines Agency (EMA) is a decentralized agency of the European Union responsible for the scientific evaluation, supervision, and safety monitoring of medicines in the EU. EMA is governed by an independent Management Board. EMA is a networking organization whose activities involve thousands of experts from across Europe.

All medicines must be authorized before they can be marketed and made available to patients. In the European Union, there are two main types of marketing authorizations (licenses) for medicinal products: a centralized one and a national, via four different routes/procedures (national, centralized, mutual recognition and decentralized procedure). Under the centralized authorization procedure, pharmaceutical companies submit a single marketing-authorization application to EMA. This allows the marketing-authorization holder to market the medicine and make it available to patients and healthcare professionals throughout the EU on the basis of a single marketing authorization.

EMA's Committee for Medicinal products for Human Use (CHMP) carry out a scientific assessment of the application and give a recommendation on whether the medicine has a favorable benefit/risk ratio and whether it should be marketed or not. However, under EU law, EMA has no authority to actually permit marketing in the different EU countries. The European Commission is the authorizing body for all

centrally authorized products, and the one that takes a legally binding decision based on EMA's recommendation. This decision is issued within 67 days of receipt of EMA's recommendation. Once granted by the European Commission (EC), the centralized marketing authorization is valid in all EU Member States, as well as, in the European Economic Area (EEA) countries Iceland, Liechtenstein and Norway. This Marketing Authorization is the responsibility of the EC. The legal decision to grant, suspend or revoke a marketing authorization for any nationally authorised medicine falls under the remit of national competent authorities of the EU Member States [5].

1.2. FOOD AND DRUG ADMINISTRATION (FDA)

The Food and Drug Administration (FDA) is an agency within the Department of Health and Human Services and consists of nine Center-level organizations and thirteen Headquarter Offices. It is responsible for protecting the public health by ensuring the safety, efficacy and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of US nation's food supply, cosmetics, and products that emit radiation.

The FDA is responsible for the approval of new drugs and biologics in the USA. The new drug and new biologic applications submitted by pharmaceutical companies provide information that the FDA uses to assess the drug efficacy, safety, and risk/benefit ratio. Furthermore, through the application, the FDA determines if the sponsor drugs' proposed labeling is appropriate. FDA has its own experts who review the results of laboratory, animal, and human clinical testing performed by manufacturers. If FDA grants an approval, it means the agency has determined that the benefits of the product outweigh the known risks for the intended use. This license is the responsibility of FDA throughout USA [6].

2. METHODS

Using publicly available information from the FDA and the EMA websites we identified approved medicines in psychiatry and neurology through their brand name or their active substance. We also searched in FDA and EMA websites for information about the agencies, who they are, what they do, their history and for the procedures they follow.

A search of two electronic databases was completed (PubMed and Science Direct). The search terms were a combination of MESH terms and key words (e.g. differences between FDA and EMA, differences in the approval of psychiatry/neurology medicines).First, all articles were screened based on their titles and abstracts. Second, the full text of all the articles identified in this search process was read in order to select the articles.

Additionally, we searched for news in the press concerning medical issues and authorized drugs in psychiatry and neurology, that have raised social and political awareness. This search was performed from 15 August 2021 until 15 September 2021.

3. RESULTS

In this study, we attempted to evaluate some of the differences in the characteristics and authorization procedures of drugs for psychiatric and neurological disorders, approved by the FDA and the EMA. For this purpose, during the search in literature and published news and articles a few distinctive examples of medicinal products were identified. These are discussed below in order to provide the reader with a background of pivotal commonly used drugs in the field of psychiatry and neurology and to elaborate differences in the processes and the decisions between the two agencies.

3.1. ABILIFY

Abilify is a medicine that contains the active substance aripiprazole. It is available as tablets, orodispersible tablets (tablets that dissolve in the mouth), an oral solution and a solution for injection. Abilify has been authorized in EU since June 2004. On November 2009, Otsuka Pharmaceutical Europe Ltd. officially notified the CHMP that it wishes to withdraw its application for a new indication for Abilify, in the treatment of resistant major depressive disorder.

Abilify was already used to treat schizophrenia, and to treat and prevent manic episodes in patients with bipolar I disorder. It was also expected to be used, in addition to antidepressants, to treat major depressive episodes in patients who had not responded adequately to previous antidepressant treatment. The evaluation was withdrawn after 'day 90'. This means that the CHMP had evaluated the documentation provided by the company and formulated a list of questions. After the CHMP had assessed the company's responses to the questions, there were still some unresolved issues.

The CHMP was concerned over the patients included in the studies, as it was not clear whether they all had resistant depression, defined as failure to respond to at least two previous antidepressants. The Committee was also concerned that there was no long-term information from 'double-blind' studies looking at the maintenance of Abilify's effects and its ability to prevent depression coming back. Therefore, at the time of the withdrawal, the CHMP was of the opinion that the benefits of Abilify in the treatment of major depressive episodes did not outweigh its risks [7].

On the other hand, FDA has approved Abilify as an adjunctive treatment of Major Depressive Disorder (MDD) [8,9].

Furthermore, in 2016, FDA announces that compulsive or uncontrollable urges to gamble, binge eat, shop, and have sex, have been reported with the use of the antipsychotic drug aripiprazole (Abilify, Abilify Maintena, Aristada, and generics). These uncontrollable urges were reported to have stopped when the medicine was discontinued, or the dose was reduced. These impulse-control problems are rare, but they may result in harm to the patient and others if not recognized. A search of the FDA Adverse Event Reporting System (FAERS) database and the medical literature in the 13 years since the approval of Abilify in November 2002, identified a total of 184 case reports in which there was an association between aripiprazole use and impulse-control problems. There were 167 U.S. cases, which included adults and children. Pathological gambling was the most common compulsive behavior (164 cases) [8].

In 2019, hundreds of people have filed lawsuits saying Abilify caused them to compulsive-behavior side-effects. Abilify lawsuits claim the drug's manufacturers failed to warn doctors and consumers that their antipsychotic medication could cause compulsive gambling, eating, sex and shopping. As of June 2019, more than 2,600 Abilify lawsuits had been filed in federal court against Bristol-Myers Squibb Company and Otsuka Pharmaceutical Co, the two companies responsible for Abilify [10]. Such cases have not been identified in Europe.

3.2. SPRAVATO

Spravato is a medicine used to treat adults with major depression that is resistant to treatment. It is used in combination with a Selective serotonin reuptake inhibitors (SSRI) or a Serotonin–norepinephrine reuptake inhibitors (SNRI) medicine (other antidepressants) when at least two other treatments have failed. Spravato contains the active substance esketamine. Spravato is available as a nasal spray to be used by the patient in a clinic or doctor's office, under the direct supervision of a healthcare professional. Studies in around 1,800 patients have shown that Spravato taken with an SSRI or SNRI relieves symptoms of treatment-resistant depression as measured using a standard scoring system known as MADRS (Montgomery-Asberg Depression Rating Scale). In a 4-week study, a clinical important improvement was observed between patients treated with Spravato (plus an SSRI or SNRI) than in those treated with placebo (also with an SSRI or SNRI). Slight improvements were also achieved in two other short-term studies. In a fourth long-term study, Spravato was shown to be effective at preventing relapses of depression. The proportion of patients given Spravato (plus an SSRI or SNRI) who relapsed during the study was 27%, compared with 45% in the placebo group (also given an SSRI or SNRI). A fifth study lasting around 1 year showed that the benefits of Spravato (plus an SSRI or SNRI) were maintained long-term. Furthermore, the safety of Spravato was considered acceptable and its side effects manageable.

The administration of Spravato for treatment resistant depression requires an assessment before, as well as and observation post-administration. After dosing with Spravato, blood pressure should be reassessed at approximately 40 minutes and subsequently as clinically warranted. Because of the possibility of sedation, dissociation and elevated blood pressure, patients must be monitored by a healthcare professional until the patient is considered clinically stable and ready to leave the healthcare setting [7].

In March 2019, FDA also approved Spravato, for treatment-resistant depression. The FDA granted this application Fast Track and Breakthrough Therapy designations, which are processes to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. Because of the risk of serious adverse outcomes resulting from sedation and dissociation caused by Spravato administration, and the potential for abuse and misuse of the drug, it is only available through a restricted distribution system, under a Risk Evaluation and Mitigation Strategy (REMS). Risk Evaluation and Mitigation Strategies is a program of the FDA for the monitoring of medications with a high potential for serious adverse effects. In

USA the administration of Spravato also requires monitoring before and after treatment due to sedation and dissociation. The difference with EMA is the duration of monitoring. In USA, post-administration observation requires at least two hours while in EU, patient is monitored until the patient is considered clinically stable and ready to leave the healthcare setting. i.e. If blood pressure is decreasing and the patient appears clinically stable for at least two hours, the patient may be discharged at the end of the post-dose monitoring period; if not, continue to monitor [8].

The most important difference between FDA and EMA in the case of Spravato is in one additional approved therapeutic indication. FDA label includes the following: Depressive symptoms in adults with Major Depressive Disorder with acute suicidal ideation or behavior. The Summary of Product Characteristics (SmPC) from EMA state the following: Spravato, co-administered with oral antidepressant therapy, is indicated in adults with a moderate to severe episode of Major Depressive Disorder, as acute short-term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency.

The assessment of the same submitted dossier and data (described in the relevant section so the label and the SmPC) led to different wording in the indications between Europe and USA.

3.3. RISPERIDONE

Risperidone, sold under the brand name Risperdal among others, is as an antipsychotic, indicated for the treatment of schizophrenia, manic episodes associated with bipolar disorders, persistent aggression in patients with moderate to severe Alzheimer's dementia and treatment of persistent aggression in conduct disorder in children, across EU. It is on the World Health Organization's List of Essential Medicines [11].

On July 2007 the European Commission requested EMA for a referral under Article 30 of Directive 2001/83/EC, as amended, in order to harmonize the nationally authorized Summaries of Product Characteristics (SPC), Labelling and Package Leaflet of the medicinal product Risperdal and associated names. The basis for referral was that there were divergences in the Summaries of Product Characteristics (SPC) of Risperdal and associated names approved across EU Member States, with respect to the indications, the posology and method of administration, the contra-indications, the special warnings and precautions for use and the interaction with other medicinal products and other forms of interaction. This medicinal product belonged to the list of products identified in 2007 for SPC harmonization [7]. The harmonized therapeutic indications for risperidone after the referral are:

- for the treatment of schizophrenia.
- for the treatment of moderate to severe manic episodes associated with bipolar disorders.
- for the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others.
- for the short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation

diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviors requires pharmacologic treatment. Pharmacological treatment should be an integral part of a more comprehensive treatment program, including psychosocial and educational intervention. It is recommended that risperidone be prescribed by a specialist in child neurology and child and adolescent psychiatry or physicians well familiar with the treatment of conduct disorder of children and adolescents.

Studies of risperidone in USA began in the late 1980s and it was finally approved for the United States' market in 1993. The FDA-approved indications for oral risperidone include the treatment of schizophrenia (in adults and children aged 13 and up), bipolar I acute manic or mixed episodes (in adults and children aged 10 and up) and autism-associated irritability (in children aged 5 and up). There are many varied non-FDA-approved uses for risperidone. It has been used to treat psychotic symptoms when they are present. It has also been used for borderline personality, delusional disorder, delirium, depression, brain injury, pedophilia, PTSD, Lesch-Nyhan, Tourette, trichotillomania, stuttering, movement disorders, and developmental disorders. In addition to psychotic symptoms, risperidone is used for aggression and agitation in patients with dementia [12].

The rate of off-label use of antipsychotics worldwide is still high. Risperidone is reportedly the most commonly prescribed off-label antipsychotic [13]. This can be partly explained by the fact that the FDA has not yet approved any medication for treating Behavioral and Psychological Symptoms of Dementia (BPSD) [14]. Despite clinical evidence supporting the efficacy of antipsychotics in the management of BPSD, so far, safety concerns appear to prevent FDA approval. Despite safety concerns, risperidone remains a popular therapeutic choice for patients with Alzheimer's disease and behavioral symptoms, especially those with more severe agitation and aggressive behaviors, and has been approved for this indication in many countries [15]. Indeed, in 2008, the European Union approved risperidone for the short-term management of persisting and severe aggression in individuals with Alzheimer's disease who have failed nonpharmacological treatment [16].

Another important issue in the differences between FDA and EMA is that the decisions taken from one side of the Atlantic may have more often consequences and legal implications leading to juridical settlements between pharmaceutical companies and patients.

In 2006, the Journal of Clinical Psychopharmacology published a study linking risperidone to gynecomastia, or the development of breasts in young males. The study further asserted that prescriptions of the drug for children should be handed out cautiously, as the long-term effects of the medication were not well-known with regard to growth and puberty [17]. While it has been observed to be effective in treating a variety of medical conditions, it has been linked to both serious and life-threatening side effects. The FDA Office of Criminal Investigations eventually launched an investigation into the company's conduct [18].

In September 2012, a lawsuit was settled with a 21-year-old male who developed gynecomastia upon being treated with Risperdal from ages 9 to 14. On Nov. 4, 2013, Janssen Pharmaceuticals Inc. pled guilty to allegations of introducing Risperdal into

interstate commerce as a misbranded drug. At a total of more than $2.2 billion, this financial penalty represented one of the largest ever issued to a company for health care inappropriate marketing. A 2019 Risperdal lawsuit ended in a $8 billion verdict against the company [19].

3.4. REBOXETINE

Reboxetine sold under the brand name Edronax among others, is the first Selective-norepinephrine reuptake inhibitor (SNRI) drug marketed as an antidepressant by Pfizer. Reboxetine is indicated for use in treatment of major depression and acute depression and for maintenance for people who have responded well in using it. It is also used off-label for panic disorder and attention deficit hyperactivity disorder (ADHD). It is available in many European countries (for examples the United Kingdom and Germany) since 1997. However, the application for approval was ultimately rejected after preliminary acceptance, by FDA [20].

Reboxetine is one of the most controversial drugs to the scientific community. According to a 2009 meta-analysis of 12-second generation antidepressants, reboxetine was no more effective than placebo and was significantly less effective than all the other 11 antidepressants in treating acute-phase of adults with major depression [21]. A systematic review and meta-analysis were conducted by The Institute for Quality and Efficiency in Healthcare (IQWiG), including published and unpublished trials of reboxetine compared with placebo or SSRIs in adults with major depressive disorder. The study indicated that reboxetine is, overall, an ineffective and potentially harmful antidepressant [20]. However, a UK and Europe-wide review of available efficacy and safety data published by the Medicines and Healthcare products Regulatory Agency (MHRA) has shown that reboxetine has benefit over placebo in its authorized indication [22]. In addition, reboxetine's preclinical experiments in animal tests for depression, produced such a robust effect that has since been used as a positive control [23].

Despite the controversy, reboxetine is still available for adults in Europe. In April 2005, the Agency's Committee for Medicinal Products for Human Use (CHMP) completed its review of SNRI and SSRI medicines and concluded that reboxetine should not be used in children and adolescents as antidepressant [7].

3.5. SAFINAMIDE

Safinamide (brand name: Xadago) is a drug, indicated for the treatment of adult patients with idiopathic Parkinson's disease (PD), which is a long-term degenerative disorder of the central nervous system that mainly affects the motor system. Safinamide is used as add-on therapy to a stable dose of Levodopa (L-dopa) alone or in combination with other medicines for PD in mid-to late-stage fluctuating patients [7]. Safinamide, is a monoamine oxidase-B (MAO-B) inhibitor. It blocks the enzyme monoamine oxidase type B (which breaks down dopamine), thereby helping to restore dopamine levels in the brain and improving the patient's symptoms [24].

In 24 February, 2015, the European Commission granted marketing authorization for safinamide throughout the European Union. The Agency's Committee for Medicinal Products for Human Use (CHMP) decided that Xadago's benefits are greater than its risks and recommended that it can be approved for use in the EU. The Committee

concluded that the effect of Xadago on the daily time that patients lived without motor symptoms was of clinical relevance, also taking into account the response reported in the literature for other Parkinson's medicines. This effect was also maintained in the long-term. Regarding safety, in overall, it was considered acceptable [7].

In the same year, 2015, Safinamide New Drug Application (NDA) was submitted to FDA by Newron Pharmaceuticals S.p.A., a research and development company focused on novel CNS and pain therapies. The sponsor received a Refusal to File (RTF) letter. Upon preliminary review, the FDA identified some organization and navigation problems, relating to the hyperlinking of tables, folders and the organization of the table of contents in the submission, as well as the conformation of the Package Insert to FDA guidelines. A stricter approach has been followed this time from FDA, which allowed in the end the re-submission of Xadago. Finally, on March 21, 2017 (two years after EU license), Xadago was approved as an Add-On Treatment for Patients with Parkinson's Disease. Safinamide is the first anti-Parkinson medication to be approved for ten years [8, 25].

3.6. RADICAVA

Amyotrophic lateral sclerosis (ALS) is a progressive disease of the nervous system, where nerve cells in the brain and spinal cord that control voluntary movement gradually deteriorate, causing loss of muscle function and paralysis. Radicava is a medicine that contains the active substance edaravone and was intended to treat patients with amyotrophic lateral sclerosis (ALS). The proposed pharmaceutical form was a solution for infusion (drip) into a vein. It was expected to be used to slow down the worsening of the disease in patients who can still perform normal daily activities. Radicava was designated as an 'orphan medicine' (a medicine to be used in rare diseases) on June 2015 for ALS.

The company presented results from a main study of 137 patients with ALS who received either Radicava or placebo. The study looked at how much patients' symptoms changed over 24 weeks, using a standard rating scale known as 'ALS functional rating scale revised' (ALSFRS-R). Doctors use this scale to rate how well patients with ALS can talk, breath, eat and perform other normal activities. At the time of the withdrawal, the CHMP had some concerns and was of the provisional opinion that Radicava could not have been approved. The concerns of the Committee were mostly related to the small number of patients and the lack of evidence of improvement in important measures, such as those related to survival, breathing and muscle strength. Furthermore, the CHMP noted important differences between the two groups (active treatment and placebo) which could have influenced the final results – such as the fact that a higher number of patients in the Radicava group had less severe disease. The CHMP was also concerned about the duration of any benefits from Radicava, noting that 24 weeks (a cut-off point in the main study) was too short and that data from the extension phase of the study were difficult to interpret. Given the clear need for further evidence of Radicava's effectiveness, the Committee considered the possibility of a conditional approval, which would allow the company to provide more data at a later stage. The company proposed a registry study whereby patients treated with Radicava could be compared with patients who received other treatments for ALS in the past. The

Committee considered the merits of such a study but had some objections, including the fact that the treatment for ALS had changed significantly over the past few years, rendering comparisons difficult. It was also noted that the end-of-life measures (tracheostomy and application of respirator) present significant variability between countries even in the same region. During the evaluation, the CHMP consulted a group of experts in the field to obtain their views on the study results, the proposed registry and the patient population that could potentially benefit from treatment with Radicava. At the time the company withdrew, the Committee was of the opinion that, because of lack of proven effectiveness, the benefits of Radicava did not outweigh its risks [7].

On the other side of the Atlantic, in May 2017, the FDA granted approval of Radicava as orphan drug designation, to Mitsubishi Tanabe Pharma America, Inc. In the benefit-risk summary and assessment, FDA supported that there is substantial evidence of effectiveness applying a high degree of flexibility, which is justified by the great unmet medical need for ALS. Also, there are no significant safety signals of concern with edaravone. However, there are some important questions unanswered by the edaravone development program, such as the effect on survival [8].

3.7. ZOLGENSMA

Zolgensma is a gene therapy medicine for treating spinal muscular atrophy (SMA), a serious condition of the nerves that causes muscle wasting and weakness. It is intended for children less than 2 years old, with inherited mutations affecting genes known as SMN1. Spinal muscular atrophy is rare, and Zolgensma was designated as an 'orphan medicine'. Zolgensma contains the active substance onasemnogene abeparvovec and is given once as an infusion (drip) into a vein lasting about 1 hour. The infusion should take place in a clinic or hospital under the supervision of a doctor experienced in managing SMA.

The main study of Zolgensma, showed that a one-time infusion can improve survival in patients and reduce the need for a permanent ventilator to breathe. It can also help them reach development milestones. In this study, 22 babies were given Zolgensma. As for its safety, the side effects are considered manageable; the most common side effect in the study, raised liver enzymes, resolved after treatment with a steroid. The EMA therefore decided that Zolgensma's benefits are greater than its risks and it can be authorized for use in the EU. Zolgensma has been given 'conditional authorization' valid throughout May 2020. This means that there is more evidence to come about the medicine, which the company is required to provide. Every year, the Agency will review any new information that becomes available and this overview will be updated as necessary [7].

Zolgensma was first approved by FDA (earlier than EU) in May 2019. At the time of approval, the cost of Zolgensma was $2.125 million, making it the world's most expensive drug [25]. The Swiss company's AveXis unit (Novartis Gene Therapies currently) argues that its high price is justified considering the lifetime cost of treating the disease of between $2.5 to 4 million. Pricing and access negotiations with payers in European countries are ongoing. In countries such as France and the UK, AveXis is leveraging existing early access funding pathways. Belgium, Ireland and the Netherlands are conducting a joint Health Technology Assessment (HTA) to negotiate pricing for Zolgensma. Elsewhere in Europe the company hopes to offer flexible pricing

options including early access rebates, deferred payments and installment options, and outcomes-based contracts [26]. Meanwhile in USA, Novartis offers insurers the ability to pay $425,000 a year for five years.

Shortly after the approval, FDA accused the company of data manipulation in their regulatory submission [27].

Zolgensma is another case of a medicine which is under a lot of discussion and debate, affecting also its reimbursement.

3.8. ADUCANUMAB

There are no breakthrough treatments for Alzheimer's disease. Several molecules are being investigated for this disease. Aduhelm (active substance aducanumab) is an amyloid beta-directed antibody indicated to treat Alzheimer's disease. It is the first treatment to modify disease's progression, rather than provide symptomatic relief, as currently authorized medicines do. Very recently (7th July 2021) [28], Aduhelm was approved in USA under the accelerated approval pathway, which provides patients with a serious disease, earlier access to drugs when there is an expectation of clinical benefit, despite some uncertainty about the clinical benefit. As it is required by accelerated approval pathway, FDA has asked the company to conduct a post-approval clinical trial to verify the drug's clinical benefit. If the sponsor cannot verify clinical benefit, FDA may initiate proceedings to withdraw approval of the drug. [8, 29].

In EU the marketing authorization application for aducanumab is still under assessment. Application was submitted to EMA in October 2020. Decisions by European regulators are not expected before the end of the year [30].

One ex-FDA adviser called "probably the worst drug approval decision in recent US history" [31].

4. DISCUSSION

Across EU and US there is a trend towards regulatory harmonization to protect public health. Interaction between EMA and FDA allows the strategic partners to review their ongoing cooperative initiatives, discuss strategic priorities for the coming years and strengthen the continuous close collaboration with specific action in the field of pharmaceuticals. However, discordances between approval decisions of regulatory agencies still exist and are often attributed to differences in approval procedures, evaluation of drug efficacy, approaches to decision-making, and post-marketing approaches. Those discrepancies may be related to a certain extent, to differences between structures of the two agencies or to the different reimbursement policies and the existence or absence of a national healthcare system.

As it is already mentioned, the FDA is a centralized agency that oversees the drug development process and grants Marketing Authorizations in a single country, whereas the EMA is a reviewing body that manages the process and recommends approval in many European countries. In the FDA, drug evaluation applications and the drug development process are monitored by the FDA's reviewers and inspectors. In the

EMA, the assessment is conducted by experts from the national agencies of the European Economic Area (EEA) countries. Once EMA renders an opinion, European Commission is the executive body to grant or deny an approval in EU, on the contrary FDA is completely responsible for authorizations in the USA.

Discrepancies on indications and other drug characteristics (administration route, dosage form, strength, and posology) reflect in part different regulatory policies for review and approval. In addition, the results of clinical studies conducted according to common technical documents and submitted in support of new drug applications can be interpreted differently by the agencies, depending on the significance they attach to the various components in their respective benefit-risk analyses.

Differences in approval timelines persist. The FDA is considered quicker than EMA since EMA timelines formally require two steps, namely (step 1) an opinion from the Committee for Medicinal Products for Human use followed by (step 2) a European Commission decision. FDA also offers a wider range of expedited pathways that can be applied in different situations, which jointly contribute to a lower median review time. Recently, EMA revised its accelerated assessment guideline and launched the Priority Medicines (PRIME) scheme to stimulate the support for the development of medicines [3].

Although the FDA and the EMA have similar evaluative processes, the final outcome of the benefit-risk assessment or the speed that this is delivered is not necessarily the same in all cases. Clinical investigations of new drugs in the United States compare the drug with a placebo. In the EU, the benefit-risk assessment has become increasingly based on comparisons between the new and existing drugs. This is not always the preferred method of benefit-risk assessment, however. For example, a three-armed study using placebo and an active treatment as controls is preferable in the EU, when possible [32]. Another important difference is after submission for authorization, the FDA carries out its own analysis of patient-level data to replicate main analyses or to explore possible bias, sensitivity to assumptions and so on. EMA experts do not do that systematically and if there is a need to explore something, the company is asked to submit more details [33].

Differences in review processes, approval criteria, and approval time may affect sponsoring companies' selection of the first regulatory agency to submit new drugs for review [3]. That can certainly lead to different timing access to patients for a specific medication. Pharmaceutical companies may also submit applications with different drug information and proposed drug labels depending on the regulatory agency and the reimbursement policy. Thus, the observed differences likely reflect different regulatory agency requirements and approval processes and different sponsor marketing strategies tailoring the drug characteristics to each market.

Sponsors are spending time and effort on reconciling divergent requirements before submission. This is a protracted process that can take years to accomplish. Indeed, the significance sponsors put on soliciting input on their development projects from regulators is illustrated by the steadily growing number of Scientific Advice procedures given by EMA and FDA. When scientific advice or guidance cannot bridge differences in regulatory requirements, sponsors have the choice to develop separate data packages [3, 34].

Differences in drug indications and restrictions of use may result in differences in clinical guidelines, clinical practice, public funding, pricing policies, drug utilization and patient outcome or even court cases. Prescribers can also decide to use drugs off-label following the recommendations of a regulatory agency from a different jurisdiction. International drug regulation harmonization efforts are important to eliminate duplication of clinical trials, reducing drug development costs, speeding the dissemination of pharmaceutical innovation, improving coordination among regulatory agencies for the benefit of patients as an ultimate goal. However, each country has its own economic, social, political and cultural characteristics as well as healthcare insurance, financing, and provisions that explain why differences in drug regulation and outcomes still remain [35].

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