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Research

RISKS AND OPPORTUNITIES IN DEVELOPMENT OF NEW DRUG

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Abstract

Drug Regulatory Affairs refers to all aspects within the pharmaceutical process on drug discovery and research which also deals with many risks and opportunities of drug development and they have subject to different degrees of regulations of different countries such as India, USA, Europe. The pharmaceutical law frame is used as guidelines on covering Quality, Safety and Efficacy of a drug as well as Health Authorities' attitudes and requirements are employed for the correct pathway of pharmaceutical needs and have a great influence on the drug development process and had success through it. The role of Regulatory affairs professionals deals with all these aspects to get a desired result of drug development. The health authorities are framed to guide and analyse the drug which fulfils the appropriate quality and efficacy.

Keywords: Drug Regulatory Affairs, drug development.

INTRODUCTION

Enhancing quality could be very frequently regarded as an interest that is going to increase value. Upgrading the quality of a product is simply the utilization firstgrade raw materials and good strategies in the production of a product. The main aim of enhancing quality is not an easy task although it can be achieved by investing more funds in activities that are designed to prevent manufacture of low quality products like quality assurance instead of funding activities that aid in detection of faulty products after manufacturing. (Poornima, 2017)

An effective regulatory system that achieves good quality is simply a regulatory system that enhances the ability of individuals and establishments to ensure and deal with all safety and quality issues that may arise. This system would involve both he establishment or company and the national regulatory body. For multinational companies the governing regulatory body could be the effective regulatory body in the country where the company is established or it could be governed by the regulatory body from the headquarters of the company.

In recent years, quality has risen to play a big role in the consumer confidence in a products and further influences the consumers choices in using a product especially in the pharmaceutical industry. Also in the past few decades the need has arisen to improve the medicinal products manufactured in Nigerian by way of enhancing the Nigerian regulatory system. However, no notable changes have come up due to different factors especially poor response from the regulators as regards implementation of changes to enhance the system.

OVERVIEW OF THE REGULATORY AUTHORITIES

Falsified and substandard drugs have always been world problem (WHO.int, 2017) and Nigeria are not excluded as they suffer from the effects till date. This is partially as a result of poor regulation of the production and marketing of medicinal products and partially because of the socio-economic state of the country. People are still found to be self-medicating due to lack of funds and getting the drugs from unlicensed marketers who in turn give them poor quality medicine at a cheap price. Overall, use of substandard drugs are one of the major causes of death in Nigeria. As per research by (Adebayo, 2017) up to one hundred and fifty children died by using wrong formulated medicinal product. In 1995 the use of a particular brand of meningitis vaccine during an epidemic lead to the death of over 2,500 people because the vaccine was reported to have contained impurities This high number of deaths as an issue in Nigeria was what made the pharmaceutical society oof Nigeria to push the government into reacting. Their reaction was the setting up of the Decree no.21 of 1998 banning the manufacture and marketing of fake, adulterated, unlicensed and counterfeit medicines in the open market.

Since the inception of NAFDAC in 1994 however, the situation has gotten better. As of 2001 Dora Akunyili was the director general of the agency and she instituted a great reform. Her aim was to rejuvenate the system and redirect their aim to ensure the safeguarding of the health of the nation. During her time, sale of fake drugs fell to about 16% as of 2006 and marketing of counterfeit and substandard medicine was reduced by up to 80% and the system was seen to effective. (Adebayo, 2017).

Before 1906 when the Pure Food and Drug act was passed, America faced the same problem as patent medicines were being sold in catalogues. Due to this the only information available about the medicinal product was the label and over hyped slogans for products made available by the marketers. Due to this fact the producers started to exploit the market by using increase levels of cocaine and morphine in the drugs to give users a high as opposed to treating illnesses. Harvey Wiley was the head of the USDA's Bureau of Chemistry was very passionate about ensuring the safety of American food and drugs and so he worked with activist Alice lakey and together they were able to convince the public about the "Pure Food Bill" and soon after, in the year 1906, the bill was signed into the law. This bill is what has grown to become todays Food and Drug Administration. Since then, the FDA has been a very reputable regulatory authority. One of their most notable achievement is the rejection a drug used to combat morning sickness in pregnancy knows as "thalidomide". A drug very well sold in Europe. At the time the safety and efficacy of the medication was not properly tested because it was believed that the drug did not affect the foetus in any way. However, when the drug was given to the FDA for approval to be sold in the US, the FDA required that the company carry out more safety tests. These tests went on to show that pregnant women who used the drug give birth to babies with severe birth defects. This even gave the FDA an upper hand in the world regulatory authorities. (Ben Panko, 2017).

Pharmaceutical companies world-wide have increasingly become more competitive over the years and so different countries have come to the realization of the need to establish regulatory authorities to oversee the activities of these companies. The task of these regulatory authorises are very important and cannot be over emphasized as they ensure that all products meet up to the set requirements as regards the drug development process in that country. All countries with licensed pharmaceutical companies have an established regulatory authority in charge of implementing 16 guidance and regulations to control the medicine production process. Some of the countries and their regulatory bodies have been listed in the table below.

ICH (International Conference on Harmonization)

The ICH is an international organisation started up in 1990's by the European community (EC) which is now referred to as the European Union (EU) in a bid to unite the pharmaceutical market and bolster public health by way of realizing harmonisation by the establishment of technical guidelines, specifications and stipulations for the registration process associated with new products. By creating tis harmonisation, they hope to create a more rationed use of resources and get rid of needless delays as regards development and availability of new medicines.

There are 4 divisions of the ICH topics, they include

• Q – quality guidelines

• S – safety Guidelines

• E – Efficacy guidelines

• M – Multidisciplinary Guidelines

This research will focus on the Q – Quality guidelines and the Good manufacturing practice (GMP) guidance for active pharmaceutical ingredients under a certified and suitable scheme for managing quality. The ICH guidelines have been adopted for use by up to 10 countries including ANVISA, Brazil, EC, Europe, FDA, United States, HAS, Singapore, Health Canada, Canada, MFDS, Republic of Korea, MHLW/PMDA, Japan, NMPA, China, Swiss medic, Switzerland, TFDA, Chinese Taipei. (ICH.ORG, 2021).

QUALITY REGULATION AND MANAGEMENT SYSTEM

The main aim of Emzor is to ensure wellness if their consumers. To achieve this they provide world-class healthcare services and manufacture medical products that very cost effective. This creates value for their consumers. Emzor has also managed to set up a business model that is very much in line with the set regulatory requirements. Their business model also aids and encourages innovation and excellence. the company set up a QMS with a framework that is constantly reviewed for possible updates and are properly communicated throughout the company after every update. (EmzorPharma, 2021b).

HEALTH SAFETY AND ENVIRONMENTAL (HSE) REGULATION AND MANAGEMENT SYSTEM

Emzor maintains high health, safety, and environmental standard which involve risk management. Emzor trains its employees to work in the safest conditions and to act based on risk reduction efficiency in seeking opportunities to reduce risks and errors involved in manufacturing. The company encourages effective communication of health, safety and environmental(HSE) related matters to make the workplace free from hazards associated with an ability to run a safe and environmentally responsible operation. (EmzorPharma, 2021a)

WHISTLEBLOWING REGULATION AND MANAGEMENT SYSTEM

The QMS operated by Emzor encourages employees to report any form of wrongdoings that breach the company policy. The report in this case, is expected to be made, not on personal gains but in the best interest of the company and the potential consumers. Any report made will be properly examined. During the process of investigation, the company will do its best to maintain anonymity for the employee to prevent victimisation. (EmzorPharma, 2021d).

ENVIRONMENTAL REGULATION AND MANAGEMENT EMZOR SYSTEM

Emzor has emphasized its commitment to environmental safety by establishment of a certain framework that ensures that objectives standards are set that do not fall short of their set Emzor brand policy which is "WELLNESS FOR EVERYBODY". They have also show their commitment to safeguarding the environment as regards pollution from pharmaceutical wastes by implantation the an Environmental Management System (EMS). They strive to create an environment that is favourable to everybody by from consumers to employees to stakeholders. They do their best to carry out activities in accordance to local and international standards the best they can, prevent pollution from pharmaceutical waste and mage resources properly. Emzor assesses the environmental outcome of the activities they engage in terms of the socio-economic aspects of operation and make sure that they provide an adequate means of training for all their staff employees and contractors so that they can follow the set guidelines by either the federal, state, or local government in the environment in which they carry out their operations. (EmzorPharma, 2021c).

The above stated regulations are the ones that Emzor pharmaceutical limited claim to have put in place to ensure quality in their production process. However, there is no further information on the impact of these regulations on the products they manufacture or any proof that these systems are utilized. There is no publication about the quality management system developed in Emzor and other information concerning the quality management system of the company. As per the regulatory body that is supposed to control Emzor which is NAFDAC, there is no information about internal or external audits carried out in the company or in their manufacturing site.

QUALITY MANAGEMENT SYSTEMS AND REGULATIONS IN GLAXOSMITHKLINE PLC (GSK PLC)

This is a UK based global healthcare company that has established various offices in different countries around the world including Nigeria. They came into Nigeria in the year 1971 and started the manufacturing process in 1972. With the goal of becoming one of the world's most innovative and trusted health care companies, GSK has set high ethical standards and ensure compliance to them as their production process is governed by the Medicine and Healthcare Products Regulatory Agency (MHRA) and they utilize the good manufacturing practice guidelines of the ICH in their production process.

THE GSK CODE OF CONDUCT

In GSK, the general belief is believes "it's not just what we achieve that count but also how we achieve it". They believe in taking responsibility or over making profit. The strive make favourable and proper decisions, so that if any issues arise that can take accountability for their actions. All these to achieved they end goal which is to be one of the world's best operating, credible and dependable healthcare organizations, that is innovative and continuously impact the lives of their consumers.

The values that GSK has set for themselves is the driver of their decision making process. They constantly asceses and review their values to ensure that they are always in the right position as regards their goals and aims. They have also set up standards for themselves to that are aimed at solving certain risk problems that are anticipated bearing in mind the following factors during the decision making. Strick adherence to set guidance and regulations, assess to the tools that aid risk assessment, monitoring and fixing and finally the impact of the decisive decision they have made on their consumers. (Policies, codes and standards, GSK, 2013).

The GSK code of conduct is very strict and there are repercussions to not following this code of conduct as an employee. The set standards and policies apply to everyone and failure to abide by them results in disciplinary action against the faulter. Disciplinary action in this case may include but is not limited to suspension, complete dismissal, suspension or rescission of the contract. If the faulter in this case occupies a managerial position, disciplinary action in this case maybe financial recoupment depending on the misconduct and the extent of the misconduct.

Managers at GSK have greater responsibilities as they are in charge of ensuring that the other employees properly understand the code of conduct and work according to it. If for any reason, workers under them violate the set conduct codes, the mangers are required to report them without hesitation. (Policies, codes and standards, GSK, 2013).

According to (Policies, codes and standards, GSK, 2013), it is important to the company to gain the trust of their consumers and the best way to do this was to target the needs of the people. They were able to achieve this by constantly looking at issues form the through the eye of the patient or consumers. Considering their safety, and giving them all the information they needed to feel safe. GSK has made sure that all the marketing activities are carried out ethically and fulfil all set standards and so all medicinal product promotion that is carried out is legal and comes with proof of functionality. They ensure that all scientific activity carried out is evidenced based and ensure that possible underlying issues are not camouflaged in such a way that it is misleading to the healthcare professionals or the consumers. They strive to ensure that all information made available for public consumption is up to date and valid. They achieve this by constantly working with authorised and licensed scientists and experts. Any concern about GSK products such as information about adverse reactions, side effects, or any safety issues like effectiveness of medicinal product is to be reported to the "Central Safety Department" (CSD).

GSK is totally aware of the counterfeit medicines issues that plague the country. The company understands that these counterfeit products do not contain the active ingredients that fight the illness in the human body and some of

them of contain harmful ingredients that have the ability to even worsen a medical condition and so they have taken it upon themselves to report any counterfeit or suspected counterfeit of the GSK products.

GSK does everything possible to ensure the quality, safety, and efficacy of their products for their patients and consumers. This is achieved buy following the GMP regulations and ensuring proper documentation of processes with the Quality Management System.

In order to maintain their integrity, they ensure that all data collected is up to date and accurate. They make sure not to take part in any form of corruption or fraud. If any form of illegal action is carried out with their knowledge, it is immediately reported. GSK established the Anti-bribery and corruption (ABAC) foundation principle for their company to establish transparency in all their activities. The system aids in discovery or determent of bribery and corruption. (Policies, codes and standards, GSK, 2013).

Further research into GSK showed that even with their full proof quality management system, they had still experienced some quality issues. An example can be seen in the GSK consumer healthcare recall of two lots of "children's Robiussin Honey cough and Chest Congestion DM" and "one lot of children's Dimetapp cough and cold". This was a voluntary recall by the company due to incorrect dosing cups in the children's medication. The company consumer healthcare department was concerned about possible overdose due to the incorrect calibration on the drug delivery cup. The company also put out notifications about the possible symptoms of overdose and other side effects in any case where the product couldn't be gotten back. This report was made in February of 2020 and as of June 2020, there had been no reports about adverse events. (GSK, 2020).

The above example highlighted transparency in the system and the effort of the company to ensure quality by setting up a consumer healthcare department that carried out the recall despite the possible loss that they may have to deal with. It is an outright impact of an effective quality system.

Medicinal products are highly regulated in the European Union (EU) and are subject to a separate, complicated system of approvals that governs how, when, where, and in what form such products will be allowed to be sold within the borders of the EU.

The presented marketing authorisation procedures applicable to European Economic Area (EEA country), which included 27 EU member states and the three EEA European Free Trade Association (EFTA) states (Iceland, Liechtenstein and Norway). Hence, European Economic Area constitutes total 30 countries (figure 1).

The regulation of medicinal products is governed in the EU/ EEA by Directive 2001/ 83/ EC relating to medicinal products (the "Directive"). Also known as the Consolidated Directive, it brings many years of separate legislation together into one, detailed document [1] .

GLANCE OF EUROPEAN ECONOM IC AREA

EEA constitutes total 30 countries, with 26 different languages and 14 types of currencies existing in the region. The total population is about 500 millions.

EEA Languages

Shown different languages were existing in the European Economic Area. Among all the languages most commonly used language is English, German and French. In the below figure 3 we can find the other most commonly used languages in the European Union.

EEA Population

The total population of EEA is about 500 millions. illustrated the top 5 highest populated and also lowest populated countries of EEA region. These top 5 highest populated countries population constitutes 60% of total population of EEA. Considering the total population of EEA it stood above the USA population (Around 310 M).

MARKETING AUTHORISATION PROCEDURES[5-9]

Procedures for application for a marketing authorisation

Centralised procedure

National procedure

Mutual recognition procedure

Decentralised procedure

. Centralised Procedure (CP)

European drug approvals are overseen by the European Medicines Agency. It is responsible for the scientific evaluation of applications for authorization to market medicinal products in Europe (via the centralized procedure).

In order to obtain a Community Authorization, an application is made to the EM A – The European Medicines Agency. The application is scientifically evaluated by the Committee for Medicinal Products for Human Use (CHM P). A M A granted under the CP is valid for the entire EU/ EEA market.

The centralised procedure laid down in Regulation 724/ 2004 and Directive 2004/ 27/ EC. Applications are made directly to the EM A and lead to a grant of a European marketing authorization by the EU Commission within 7 months after application (210 days). One M ember State is assigned Rapporteur for an application and takes the lead in the evaluation process of the CHM P. The decision of the Commission is binding on all EU Member States. The product may be marketed in all Member States with one common Summary of Product Characteristics (SPC). [4]

Mandatory for the Centralised Procedure

• Biotechnological medicinal products,

• Orphan medicinal products

• New active substances for which the therapeutic indication is the treatment of

– Diabetes

– Cancer

– Acquired immune deficiency syndrome (HIV)

– Neurodegenerative disorder (Alzheimer …)

– Auto-immune diseases and other immune dysfunctions

– Viral diseases

Optional for the Centralised Procedure

• New active substances

• Innovative medicinal products

• in the interests of patients at Community level

– Pandemic

– Generic medicinal products of nationally authorized reference medicinal products

– OTC medicinal products

• Generic medicinal products of reference medicinal products authorised by the CP

Products authorised pursuant to the centralised procedure are granted marketing authorisations that cover all EU Member States and the EEA. A further distinguishing feature of this route includes the requirement for the marketing holder to secure also a single EU-wide trademark for the product. However, the convenience of the centralised procedure is also accompanied by fees that are significantly higher than the national procedure. The flow of centralised procedure was illustrated in figure 2 & 3.

National Procedure (NP)

If an applicant wishes to obtain a license in one Member State (MS) an application must be made to the national Competent Authority (CA) which then issues a national license.

With the exception of products granted a marketing authorisation under the centralised procedure as set out above, all products are granted marketing authorisations on a country-by-country basis by the competent authorities in each Member State. Such marketing authorisations permit the holder to market the product in question in the Member State concerned, subject to any restrictions or requirements that accompany the authorisation.

Mutual Recognition Procedure (MRP)

The mutual recognition procedure (MRP) laid down in Council Directive 2004/ 27/ EC. Pre-requisite to enter in this procedure is a marketing authorization in one of the EU Member States (reference Member State, RMS). To obtain such initial national marketing authorisation may take 6 to 9 months. An application for mutual recognition may be addressed to any number of Member States (Concerned Member States, CM S). The RM S compiles an assessment report within 90 days and sends this report to all CM S who have 90 days to recognize the decision of the RM S by granting a marketing authorization with an identical SPC. Concerned Member States have additional 30 days for granting the national licenses. The total MR procedure takes 9 months for the first national Marketing Authorisation plus 7 months for the mutual recognition part. 4

For products to be registered in more than one Member State (M S) and which do not qualify for the Centralised Procedure (CP) applicants must use either the Decentralised Procedure (DP) or the Mutual Recognition Procedure (MRP). The MRP is to be used if the aim is to register in more than one M ember State and the medicinal product in question has already received a Marketing Authorisation (MA) in any M S at the time of application.

The MRP is based on the idea that a national license approved in one EU Member State (Reference Member State – RMS) should be mutually recognised in other EU countries (Concerned Member States – CMS). This is based on the assumption that the evaluation criteria in the EU member states are sufficiently harmonised and are of the same standard. At the end of a M RP national licenses are issued in the CMSs involved in the procedure.

Medicines legislation also foresees the possibility that most pharmaceutical companies will wish to market their products in more than one EU country, and provides two mechanisms to applicants that avoid the need to submit full marketing authorisation applications in each country.

The mutual recognition procedure, enables pharmaceutical companies who already hold a marketing authorisation in one EU Member State to ask additional Member States to recognize the marketing authorisation that has already been granted. The procedure involves the preparation of an assessment report by the original M ember State that is forwarded to the additional Member States for its consideration. Assuming the other Member States agree with the report, a marketing authorisation will then be issued for the product in the Member States concerned.

However, the Mutual Recognition procedure often sees disagreements between Member States that can hold up the procedure and lead to delays. For such occasions, there is a detailed disputes procedure that must be followed. Flow of MRP is illustrated in figure 4 & 5

AIM AND OBJECTIVE

AIM

The aim of the study was to provide an understanding of the scientific information required for granting the Marketing authorization for various dosage forms in Europe by EMA/EU National competent authority.

OBJECTIVE

¬ Brief explanation on marketing authorization and its types.

¬ To collect entire scientific information required to grant the marketing authorization for different dosages forms in European medicinal agency and its member states.

¬ General scientific information required to grant the marketing authorization for different dosages.

¬ Compilation of data for European Union and detailed investigation on it.

DISCUSSION

Marketing authorization is the process of reviewing and assessing the evidence to support a medicinal product, such as a drug, in relation to its marketing, finalized by granting of a license to be sold. This process is performed within a legal framework defining the requirements necessary for successful application to the regulatory authority, details on the assessment procedure (based on quality, efficacy and safety criteria), and also the circumstances where a marketing authorization already granted may be withdrawn, suspended or revoked.

The application dossier for marketing authorization is called a Marketing Authorization Application (MAA) in the European Union and other countries, or simply registration dossier. Authorization processes follow either a purely national procedure, with rules and requirements as per national legislation in force, as it occurs in most of countries worldwide, or should follow a centrally approval or a mutual recognition or decentralized procedure within the European Union. Thus, if the application concerns a new active ingredient (new active substance, new chemical entity, new molecular entity), one talks about a full application.

Once a new active ingredient authorized, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations (changes to the existing marketing authorization) and extensions shall also be granted an authorization or be included in the initial marketing authorization, being subject of an abridged application.

Special consideration is to be given to application for authorization of biological products and biotechnology products, homeopathic products, herbal drugs, radionuclide generators, kits, radionuclide precursor radiopharmaceuticals and industrially prepared radiopharmaceuticals; in such instances, requirements are specific, in the meaning that they are special, more or less detailed, as per the nature of active ingredient.

The European medicines regulatory system is based on a network of medicines regulatory authorities from the 30 EEA Member States, the European Commission and the European Medicines Agency (EMA). This network is what makes the EU regulatory system unique.

1. EUROPEAN MEDICINES AGENCY

2. HEADS OF MEDICINES AGENCIES

EMA (EUROPEAN MEDICINES AGENCY)

European Medicines Agency (EMA) has worked across the European Union (EU) and globally to protect public and animal health by assessing medicines to rigorous scientific standards and by providing partners and stakeholders with independent, science-based information on medicines which was founded in 1995. EMA ensures efficacy and safety of human and veterinary medicines across Europe, and promoting research and innovation in the development of medicines. EMA's success is based on cooperation within the European medicines regulatory network – a unique partnership between the European Commission, the medicines regulatory authorities in the European Economic Area countries, and EMA.

HMA (HEADS OF MEDICINES AGENCY)

The Heads of Medicines Agencies (HMA) is a network of the heads of the National Competent Authorities (NCA) whose organizations are responsible for the regulation of medicinal products for human and veterinary use in the European Economic Area.

MARKETING AUTHORIZATION

A medicinal product may only be placed on the market in the European Economic Area (EEA) when a marketing authorization has been issued by the competent authority of a Member State for its own territory (national authorization) or when an authorization has been granted in accordance with Regulation (EC) No 726/2004 for the entire Union (an Union authorization). The marketing authorization holder must be established within the EEA.

A marketing authorization lays down the terms under which the marketing of a medicinal product is authorized in the EU. A marketing authorization is composed of: (I) A decision granting the marketing authorization issued by the relevant authority; and (ii) a technical dossier with the data submitted by the applicant in accordance with Articles

8(3) to 11 of Directive 2001/83/EC and Annex I thereto, Articles 6(2) and 31(2) of Regulation (EC) No 726/2004, or Article 7 of Regulation (EC) No 1394/2007.

The method begins with the scope and objective of the various dosage forms for granting the MA in European Union. Accordingly, information was collected from regulatory authorities, their guidelines and expert opinion. From the entire study, results were obtained and discussion was made on the results and finally conclusion was drawn. Research methodology is a way to systematically achieve the study objectives. In this section a short explanation of following is given:

ϖ Data collection

ϖ Sources of data

ϖ Literature review

ϖ Study parameters

ϖ Internet using the web page content

GRANTING THE MA FOR VARIOUS DOSAGE FORMS IN EU

The European Medicines Agency (EMA) is responsible for the scientific evaluation of centralized marketing authorization applications (MAA). Once granted by the European Commission, the centralized marketing authorization is valid in all European Union (EU) Member States. The EMA main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. The registration of pharmaceuticals in EU is referred as marketing authorization (MA).

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. MARKETING AUTHORIZATION PROCEDURES

In the European Union (EU), medicines can be authorized by the centralized authorization procedure or national authorization procedures. The European system for the authorization of medicinal products for human and animal use was introduced in January 1995 with the objective of ensuring that safe, effective and high quality medicines could quickly be made available to citizens across the European Union.

Until the end of December 1997, it was still possible for companies to make separate applications for licensure of a new active substance to some or all of the national licensing authorities in individual EU Member State (MS). Since each national assessment was conducted in isolation, the Summary of Product Characteristics (SPC) in use in each country was usually different in at least some respects from those of other MS in which the same active substance was licensed. According to European Generic Medicines Association (EGA), the marketing authorization for a pharmaceutical product in more than one country in the European Union must currently be applied for through one of two procedures. A major and important step was taken in 1995 for the evaluation of medicinal products by forming the European Medicines Evaluation Agency, EMEA and the establishment of a centralized procedure, leading to a single EU wide evaluation and approval of new medicines.

In general there are 4 types of marketing authorization for the drug product to enter into European Union drug market. They are as follows,

1. Centralized procedure

2. Mutual recognition procedure

3. National procedure

4. Decentralized procedure

VALIDITY OF MARKETING AUTHORIZATION

In most countries, a marketing authorization is valid for a period of 5 years. After this period, one should apply for renewal of the marketing authorization, usually by providing minimal data proving that quality, efficacy and safety characteristics are maintained and the risk- benefit ratio of the medicinal product is still favorable. However, in the European Union, after one renewal, the marketing authorization shall remain valid for an unlimited period, unless the competent regulatory authority decides otherwise.

If the marketing authorization is not renewed in due time as requested by the local legislation, in order to maintain the pharmaceutical product on a market, one can apply for reauthorization (re-registration). In such situations, the applicant may be requested to submit the whole items necessary for a full application.

Marketing authorization may be withdrawn, suspended, revoked or varied by regulatory authorities if under normal conditions of use the benefit over risk ratio is no more favorable, the product is harmful, or if it lacks therapeutic efficacy; also, one of the above actions can be taken if the qualitative and quantitative composition or other qualitative aspects (control) are not as currently declared.

Marketing authorization may be also withdrawn, suspended or revoked if the marketing authorization holder or its representative does not fulfill other legal or regulatory obligations necessary to maintaining of product on the market, as per the legislation in force.

Also, the marketing authorization is withdrawn in the EU if the product is not placed on the market within next 3 consecutive years after granting of authorization or if it is no more marketed for 3 consecutive years (so-called "sunset clause").

MAA is part of the official procedure before the Medicines and Healthcare products Regulatory Agency in the United Kingdom and the Committee for Medicinal Products for Human Use of the European Medicines Agency, a specialized agency of the European Commission. In the United States, the equivalent process is called New Drug Application.

CENTRALISED PROCEDURE

A marketing authorization granted under the centralized procedure is valid for the entire Community market, which means the medicinal product may be put on the market in all Member States. The Regulation (EC) 726/2004 lays down a centralized Community procedure for the authorization of medicinal products, for which there is a single application, a single evaluation and a single authorization allowing direct access to the single market of the Community.

The centralized procedure, which is compulsory for products derived from biotechnology, for orphan medicinal products and for medicinal products for human use which contain an active substance authorized in the Community after 20 May 2004 (date of entry into force of Regulation (EC) No 726/2004) and which are intended for the treatment of AIDS, cancer, neurodegenerative disorders or diabetes.

MUTUAL RECOGNITION PROCEDURE

The Regulation for the mutual recognition procedure is laid down in Directive 2001/83/EC. The mutual recognition procedure is mandatory for all medicinal products to be marketed in a Member State other than they were first authorized, since 1 January 1998. The mutual recognition procedure is used in order to obtain marketing authorizations in several Member States where the medicinal product in question has received a marketing authorization in any of the Member State at the time of application.

Under this a product registered in one country is mutually recognized by the other country. The application is required to make application only once for initial registration. The same application with some regional changes is accepted by another member country. Assessment Report of medicinal Product by Member Countries in EU: During Mutual recognition process the assessment report of Reference member state is reviewed before granting approval. The submission can be made to any number of the other member states and the RMS sends a copy of the assessment report to the CMSs, who can raise any objections within 90 days. Each CMS issues a national marketing authorization with an identical SPC. Under this scheme following product cannot be registered: Orphans Medicinal Product, All biotechnology based product, Specified Aids and cancer Medicines, Specified Antiviral Medicines, Specified Medicines for Neurodegenerative Disorder including diabetes and Specified Medicines for Auto immune Diseases/ dysfunctions.

The mutual recognition procedure is divided in the following steps:

- National validation by the reference Member State (not further described here)
- Preparation or update of assessment report by reference Member State (90days)
- Validation by the concerned Member States
- Approval by the concerned Member States (90 days), Discussion at the coordination group level, if needed
- National Marketing Authorization step

NATIONAL PROCEDURE

In Europe each nations has its own regulatory body. National procedure is procedure adopted by each nation independently of other nations. The fees are affordable even for small firms. It saves on translation cost to English or regional languages. It creates a base for Mutual recognition Procedure Biotechnical procedures cannot be registered through national procedure. The Centralized filing through EMA is compulsory for the same.

The application, submitted by the sponsor under the national rules to the national competent authority, is reviewed and a marketing authorization is granted. Under this scheme also following product cannot be registered: Orphans Medicinal Product, All Biotechnology Based Product, Specified Aids and Cancer Medicines, Specified Antiviral Medicines, Specified Medicines for Neurodegenerative Disorder including diabetes and Specified Medicines for Auto immune Diseases/dysfunctions.

DECENTRALISED PROCEDURE

The new Decentralized procedure came into effect in the European Union in 2005 and is regulated by Directive 2004/27/EC. The main purpose of this procedure is to acquire marketing authorizations in several Member States, even though there are no marketing authorization has been granted in the European area. Under this, a product is recognized by a group of member's countries simultaneously.

VARIATIONS

Variations are nothing but the modifications requested by the applicant after the grant of a marketing authorization. The submission of variation applications makes sure that the dossier and the Summary of Product Characteristics (SPC) are always kept up to date. During the life cycle of a medicinal product, the modifications are repeatedly made to the dossier, which may be simple changes, such as a change in the manufacturing method or a change in a manufacturer (Type 1 variations) and also can be quite complex, such as the application for a new indication, where new clinical and pre-clinical data has to be presented (Type 2 variations).

EXTENSION OF A MARKETING AUTHORIZATION

A line extension is a change to a marketing authorization that cannot be classified as a variation. Line extension applications are examined in accordance with the procedure for the granting of a new marketing authorization. Examples of a line extension are:

¬ Application for a product with a new strength

¬ Application for a product with a new pharmaceutical form.

¬ The dossier of the line extension can partially refer to the dossier of the initial product.

Level I

Basic fee (Level I)	80 300 EURO
Additional fee Add. Strength/Potency	+ 20 100 EURO
Add Pharm Form	+ 6 700 EURO

Level II

Basic fee (Level II)	60 200 EURO
Additional fee Add.Strength/Potency	+20 100 EURO
Add Pharm Form	+ 6 700 EURO

Level III

Basic fee (Level III) Extension in Pediatric	80 300 EURO
Additional fee Add. Strength/Potency	+ 20 100 EURO
Add Pharm Form	+ 6 700 EURO

In general, our study indicates that CDx accompanying a medicine are critically considered by the EMA in scientific advice provided to companies and during the registration process. Therefore, it can be stated that the EMA and the national agencies in EU member states have gained experience with critically assessing the CDx, as they will be formally required to do when the EU regulation on IVDs, Regulation (EU) 2017/746, becomes effective in 2022.

With respect to the pharmacological classes of medicines that were identified in our study, it is clear that CDx are mostly used in the oncological setting, with 85% and 92% of the CDx identified in the EPARs and scientific advice reports, respectively, belonging to this therapeutic class. This is in line with the known major involvement of specific molecular targets that are critical to be present in a patient's tumor for effective treatment by such oncological medicines. Therefore, it is understandable that oncological medicines represent the majority of medicines involving a CDx.

The relative number of medicines with a CDx involved remained relatively constant in 2017–2019, suggesting a stable proportion of medicines for which biomarker-based patient selection is relevant. At this stage, it is uncertain whether the proportion of medicines with a CDx involved will increase in the future. As such, the new IVDR is not specifically aiming to increase this proportion, however, it is in place to provide more robustness on the quality of the CDx that are marketed in the EU.

Four main topics are considered critical in relation to CDx and are discussed in many cases in scientific advice reports as well as during the registration process of a medicine encompassing a CDx. These can include 1) analytical performance of the CDx; 2) clinical performance of the CDx; 3) interchangeability of CDx assays, including concordance testing and bridging studies and tests for the same PBM; and 4) testing of stored or fresh patient samples, the latter encompassing both the appropriate preservation of the sample, e.g., fresh, frozen, or various

fixations, as well the liquid biopsy or tumor biopsy. Of these topics, the clinical performance of the CDx is discussed most extensively both in the (public) ARs as well as in the scientific advice reports, followed by the analytical performance. In the ARs the category that had the most questions was "suitability of biomarker as PBM". These findings are in line with a recent in which the biomarker qualification procedure of the EMA was studied. They found that issues related to the rationale behind the suggested biomarker, as well as the suggested context of use were raised in >50% of the procedures.

When further examining EPARs and ARs, the discussions of CDx-related topics largely overlapped. In the standard registration process at the EMA, questions are often raised in the day 80 and day 120 ARs, which are responded to by the applicant in the course of the registration procedure. This was also apparent for CDx, and a significant number of specific CDx-related issues were discussed for the majority of medicines involving a CDx in the day 80 and day 120 ARs. In contrast, the EPAR is a more global summary of the assessment details for a medicine, focusing on the final outcome of the assessment. Therefore, information on the performance of the CDx in the EPAR provides somewhat less detail than the original ARs, since, in principle, only the conclusion of the discussion on CDx is provided in the EPAR. Furthermore, due to the known condensing effect in the proces, if no major CDx-related issues were discussed during the registration process of the medicine, little to no information about the CDx may be provided in the EPAR. In fact, the EPAR should be read with the assumption in mind that if there is no information on the CDx in the EPAR, this means that no issues about the CDx were remaining at time of registration.

The types of CDx-related questions raised in scientific advice reports and during the registration process (as described in the ARs and EPARS) largely overlapped. However, regarding scientific advice, relatively more questions focused on the usefulness of a biomarker with a CDx for that biomarker which was not yet validated. Still, also in scientific advice, most CDx discussed were already analytically validated and, therefore, were developed to a reasonable extent for use during the clinical trials ongoing at the time of the scientific advice.

In the EU in general, no brand name of a CDx to be used for patient selection is indicated in the SmPC Sections 4.1–4.3. Instead, a statement is often included that an adequately validated CDx should be used. However, for transparency purposes and in order not to hinder the development of follow-on CDx, i.e., a CDx developed separately from the accompanying medicine, in many cases the brand name used in the clinical studies in support of registration of the medicine is indicated in Section 5.1 (pharmacodynamic properties) of the SmPC and is also mentioned in the EPAR. Of note, Food and Drug Administration-approved CDx are mentioned frequently. Transparency on the identity of used CDx in the SmPC or EPAR is not complete at this stage, with half of the SmPCs or EPARs (i.e., 10 out of 20) not providing such information, and improvement is needed. This is in line with recent observations.

The strength of this research is the access of the authors to all regulatory information of the EMA, allowing an extensive overview of the aspects related to scientific advice and assessment of CDx. As a weakness, relevant assessment reports and scientific advice reports were retrieved by text search. It cannot be excluded that relevant procedures have been missed in case none of the keywords used was indicated in relation to the CDx. Still, we are confident that our results form a relevant representation of the experience at the EMA toward assessment of and scientific advice on CDx.

Overall, our study reveals that the EMA and the individual EU member states have gained relevant experience with critically assessing the CDx as part of registration procedures for medicines. This experience is expected to be of use in in the future, as formal consultation of the EMA or national medicines agencies regarding the performance and safety of a CDx will be required upon implementation of the EU regulation on IVDs, Regulation (EU) 2017/746, the first part related to new CDx becoming effective in 2022. In addition, the issues raised in the EPARs, ARs and scientific advice reports provide insight for applicants on aspects of CDx that need careful consideration.

DMF is a submission to the FDA of information, usually concerning the Chemistry, Manufacturing and Controls (CMC) of a component of a drug product, to permit the FDA to review this information in support of a third party‟s submission. Drug product information or other non-CMC information may be filed in a DMF. (Or) DMF is a submission to the Food and Drug Administration (FDA) that may be used to provide confidential detailed information about facilities, processes or articles used in the manufacturing processing, packaging and storing of one or more human drug.

Generally DMF's have two parts

(1) Applicant‟s Part: This contains non confidential information that the license holder needs to assess for the marketing.

(2) Restricted Part: This contains confidential information about the manufacturing procedure that only needs to be disclosed to the authorities.

DMF in Europe

The content and the format for drug master file used in United states differ from that used in European countries to obtain market authorization (MA). The main objective of the EDMF is to support regulatory requirements of a medicinal product to prove its quality, safety and efficacy. This helps to obtain a Marketing Authorization grant.

Established in 1989-1991Revised in 2005 and became ASMF (Active Substance Master File) after implementation of CTD in EU Applicable only to active substances has been divided into 2 parts.

An applicant‟s part and an ASM Restricted Part. The applicant‟s part of a DMF is Provided by the ASM (Active Substance Manufacturer) to the applicant directly and becomes part of the application for marketing authorization. Both the applicant‟s part and the ASM Restricted Part of the DMF are submitted to the authorities. Applicant‟s part of a DMF – opening part Established in 1989-1991.

The applicant must be supplied by the ASM with sufficient information to be able to take responsibility for an evaluation of the suitability of the active substance specification to control the quality of the substance. This normally includes a brief outline of manufacturing method, information on potential impurities originating from the manufacturing method, from the isolation procedure (natural products) or from degradation and, where applicable, information on the toxicity of specific impurities.

ASM Restricted Part of DMF – Closing part Detailed information on the individual steps of the manufacturing method such as reaction conditions, temperature, validation and evaluation data for certain critical steps of the manufacturing method, etc. and on quality control during manufacture may contain valuable know-how. Such information may therefore be supplied to the authorities only.

Types of drug master file

Type I - Manufacturing site, Facilities, Operating Procedures and personnel (no longer applicable) Recommended for a person outside of the United States to assist FDA in conducting onsite inspections of their manufacturing facilities.

Type II- Drug substance, Drug substance Intermediate, and Material used in their preparation, or Drug product manufacturing section.

1. Quality controls

i. Inputs (raw/packaging Materials)

ii. Intermediates and in-process

iii. Finished drug substance

2. Validations

3. Stability data

4. Impurities

5. Packaging and labelling

In general, be limited to a single drug intermediate, drug substance, drug product or type of material used in their preparation. Detailed guidance on what should be included in a Type II DMF for Drug Substances and intermediates may be found in the following guidelines:

i. Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances.

ii. Guideline for the Format and Content of Chemistry, Manufacturing and Controls selection of an Application.

Type III- Packing material Should be identified by the intended use, components, composition and controls for its release. The name of the suppliers or fabricators of the components used in preparing the packing material and the acceptance specifications should also be given. Data supporting the acceptability of the packing material for its intended use should also be submitted as outlined in the "Guideline for Submitting Documentation for Packing for Human Drugs and Biologics."

Type IV -Excipient, Colorant, Flavor, Essence, or Material used in their preparation. Each additive should be identified and characterized by its method of manufacture, release specifications, and testing methods. Usually the official compendia and FDA regulations for color additives (21 CFR parts 70 through 82), direct food additives (21 CFR parts 170 through 173), indirect food additives (21 CFR parts 174 through 178) and food substances (21 CFR parts 181 through 186) may be used as sources for release tests, specifications and safety. Guidelines suggested for Type II DMF may be helpful for preparing a Type IV DMF.

Type V- FDA Accepted Reference Information, Other Sterile Manufacturing Plants, Biotech Contract facilities.

DMF PROCEDURE

Module-1 REGIONAL & ADMINISTRATIVE INFORMATION

Module-2 QUALITY OVERALL SUMMARY(QOS)

Module-3 QUALITY

Content of the european drug master file

Overall content

Detailed information should be provided as indicated under the various headings of the relevant "Notice to applicants for marketing authorizations for medicinal products in the member states of the European union"– Part II C, Control of starting materials– active substances and part II F, Stability – stability tests on active substances.

Applicant's part and ASM restricted part of a European DMF

The DMF contains information which includes valuable know-how which should be kept confidential and submitted to the authorities only.

Therefore, it should be divided into 2 parts

- An APPLICANT"S part and
- An ACTIVE SUBSTANCE MANUFACTURER RESTRICTED part.

The applicant"s part of a DMF is provided by the ASM to the applicant directly and becomes part of the application for marketing authorization. Both the applicant"s part and the ASM restricted part of the DMF are submitted to the competent authorities. The applicant"s part of the DMF is still a confidential document which cannot be submitted to third parties without the written agreement of the ASM.

a) Applicant's part of a DMF

The applicant must be supplied by the ASM with sufficient information to be able to take responsibility for an evaluation of the active substance specification to control the quality of the substance. [4] This normally includes a brief outline of the manufacturing method, information on potential impurities originating from the manufacturing method, from the isolation procedure (natural products) or from degradation and, where applicable, information on the toxicity of specific impurities.

b) ASM Restricted part of DMF

Detailed information on the individual steps of the manufacturing method such as reaction conditions, temperature and validation and evaluation data for certain critical steps of the manufacturing method, etc. and on quality control during manufacture may contain valuable know-how. Such information may therefore be supplied to the authorities

only. However, the type of information should always be adapted to the manufacturing method and the characteristics of the individual active substance.

Discussion of potential toxicology of impurities

The ASM should include in the applicant‟s part of the DMF available information on the potential toxicology of impurities by reference to literature or by the presentation of data to justify the proposed limits. If the information is incomplete, the applicant for the marketing authorization needs to supply additional information.

. **Information accompanying an edmf**

The ASM should give permission to the competent authorities to assess the data in the DMF on behalf of a specified applicant in the form of a „Letter of accesses. Such a letter should include the following information:

- Name and address of the applicant;
- Name of product and, if possible, date of application;
- Name and address of the ASM;
- Name and address of the importer of the active substance, where applicable;
- Name and address of the distributor (agent or broker), where applicable.

A written assurance that is a formal agreement between the ASM and the applicant which ensures that if there is a significant change in the manufacturing method (likely to alter the quality or safety of the product) or in active substance specification, this information will be communicated to the applicant and to the authorities. It is the responsibility of the applicant to consider any necessary changes in his specification and to inform the competent authorities accordingly. A letter of accesses must be lodged by the ASM for every application for marketing authorization.

Critical appraisal of documentation of the edmf

The applicant for the product marketing authorization has the full responsibility for the inclusion in the expert report of the required critical evaluation of the dossier. However, as information in the ASM restricted part of the DMF is not available to the applicant, a critical appraisal should be included in the ASM substance. In particular this section should consider: The manufacturing method and discuss how it will consistently guarantee material of the desired quality;

Batch analysis and whether these show consistency of manufacture;

Demonstration of how the specification and routine tests in the applicant‟s part are justified in relation to the ASM restricted part.

Use of the european drug master file (edmf) procedure

The possibility of submitting confidential data to the competent authorities directly from an Active Substance Manufacturer (ASM), who is different from the applicant for the marketing authorization, is provided for in Directives 75/318/EEC as amended and 81/852/EEC as mentioned.

If there is no problem of confidentiality between the ASM and the applicant for marketing authorization or if the ASM and the applicant can come to an agreement safeguarding confidentiality, all of the information on the active substance should be given directly in the application for the marketing authorization.

Submission of EDMF

An EDMF may be submitted if it is referred in a marketing application for a medicinal product. It should be submitted shortly after the submission of the application, so that the reference number given by the competent authority to the application for marketing authorization can be given in the letter of access. The EDMF may be submitted at the same time as the application, provided an unambiguous reference to the application can be given.

Only ASMs and their authorized representatives (e.g importers) may submit an EDMF. If an applicant for a marketing authorization wants to rely on alternative suppliers of the active substance, he should refer to this situation in the application.

- One copy of the complete EDMF, comprising the 2 parts (applicant‟s part and ASM‟s restricted part) should be sent by the ASM directly to each of the competent authorities concerned.

- A copy of the applicant‟s part should be supplied in advance by the ASM to the applicant. This applicant‟s part should be included in the application for marketing authorization.

- Specific quality requirements for certain dosage forms may be included in the application for marketing authorization. Such requirements will not form part of the EDMF. They should be described in a formal contract between the ASM and the applicant and included in the application for marketing authorization.

- If an EDMF has been updated since the previous assessment, the changes should be clearly identified (particularly those in the method of manufacture and in the specifications of the active substance). If a DMF was not presented in accordance with the current guideline on EDMF‟s (prior to 1992 for human medicinal products and prior to May 1993 for veterinary medicinal products), it should be re-arranged into the 2-part format, and the different parts sent to the authorities.

The specification of the active substance should be identical in the application and in the applicant‟s part of the EDMF. Any proposal from the applicant to use a different test procedure for the purity tests must be fully validated in relation to the procedure used by the active substance manufacturer, in particular as regards the precision and accuracy of the results of the tests, including the limits of detection for all impurities.

CONCLUSION

An increase in research dollars for pharmaceutical and toxicological studies in GLP compliant laboratory would improve the drug development process. Universities need to invest in making their research laboratories GLP compliant. A change in university policies is needed to fast track evaluation of projects for patent suitability or for releasing the intellectual properties back to investigators. Other changes include refocusing patent law on new product development, and changing the patent.

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REFRENCES

1. Anthony Warnock-Smith, Bringing a drug to market in the EU using the new decentralised procedure, Euralex, M ay 2007, 14-16.
2. VOLUME 2A, Procedures for marketing authorisation, Chapter 1, M arketing Authorisation, European Commission, November 2005.
3. M atrin Johnston and M endel Goldstein, European Union Development Cooperation Activities in Nicaragua, EU Blue Book 2008.
4. Dr. Ute Krahl, BioReg Consultancy, July 2005, www.bioregadvice.com.
5. Document: Notice to Applicant, Vol 2A, Chapter 1 “ M arketing Authorisation” , 2005.
6. Document: Notice to Applicant, Vol 2A, Chapter 2 - M utual Recognition (updated version - February 2007)
7. Document: Notice to Applicant, Vol 2A, Chapter 4 - Centralised Procedure (updated version - April 2006).
8. Commission Regulation (EC) No 1085/ 2003 of 3 June 2003.
9. Commission Regulation (EC) No 1084/ 2003 of 3 June 2003.