ORIGINAL RESEARCH

COMPARISON OF HISTORY AND DRUG APPROVAL PROCESS IN THE UNITED STATES AND EUROPE

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ABSTRACT:

This paper aims at reviewing and comparing the history, drug filling process and different aspects of obtaining drug approval in the United States and European Union (EU). It explains the evolution of the pharmaceutical industry and laws regulating the industry in the United States and Europe. Before any drug product is introduced into the market it must be approved by the respective regulatory agency. All new drug products must be shown to be safe and effective before they are approved for marketing by the respective regulatory authorities. In the U S Food and Drug Administration (USFDA) process for new drug approval starts from filling an Investigational New Drug Application (INDA), followed by submission of New Drug Application (NDA). Abbreviated New Drug Application (ANDA) is submitted for approval of generic drugs. Drug approval process in EU includes three different categories such as, Centralized Procedure, Decentralized Procedure and Mutual Recognition Procedure. Regulatory authorities of both, the United States and Europe work on the same objective, but their process of achieving it varies from one another.

KEY WORDS: U S Food and Drug Administration, European Union, Drug Approval Process, Marketing Authorization

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INTRODUCTION

In today's world, pharmaceutical firms are exploring the global market. Each and every country has its own regulatory body. Globally the most powerful regulatory bodies are USFDA (U S Food and Drug the American and Europe Administration) and EMA (European Medicines Agency). Being the main authorities they set great examples for other countries. The United States is a single country but European Union consists of many countries. So, this paper aims to summarize the history and drug approval process of both the countries for ease of understanding.

BRIEF HISTORY OF THE AMERICAN PHARMACEUTICAL INDUSTRY

The laws in the American Pharmaceutical Industry started in the 20th century. On 30th June 1906 Food and Drugs act was introduced by President Roosevelt, also known as Wiley's Act[1]. During this period selling of misbranded and adulterated drugs was a major issue to public health. This law was mainly to address this issue, and it mandated pre-market approval process for all the drugs. Further on 25th June 1938, Food, Drug and Cosmetic act was signed by FDR. One of the objective of this law was to ensure that the labelling was true and accurate. The differentiation between over-the-counter drugs and prescription drugs was given by the Durham-Humphrey Amendment of 1951. Moreover, Drug Abuse Control Amendment of 1965 and a series of laws addressing pesticide residues (1954), food additives (1958), colour additives (1960) and a provision of 1958 law-Delaney Clause, banned all the carcinogenic additives[2]. Nevertheless, the American pharmaceutical industry grew a lot in the 20th century becoming one of the most looked over pharma industry across the globe for its quality.

BRIEF HISTORY OF EUROPEAN PHARMA INDUSTRY

The laws governing the medicinal products came into force after 1961 across the European Community. The first German Medicines law came into action 1961. In 1964, the first European Medicinal Directive: Council Directive 65/65/EEC was defined. It was made by keeping USFDA as a reference. The directive had been included in to national law for all member states. To make the regulatory environment clear and simplify the existing Medicinal Directives, by the end of 2001, Directives 2001/83/EEC was adopted replacing all the previous directives[3]. The clarifications, terms, definitions that were no longer necessary were removed.

Medicinal Product Directive (Directive 2001/83/EC) consists of:

- Directive 2002/98/EC regarding standards of safety and quality of human blood components
- Directive 2003/63/EC regarding clinical, pharmacological, analytical standards for product testing
- Directive 2004/27/EC regarding medicinal herbal products
- Directive 2004/24/EC regarding Good Manufacturing Process (GMP)
- Regulation (EC) 1901/2006 regarding medicinal products for paediatric use
- Council Regulation (EC) 1394/2007 regarding advanced therapy medicinal products

In 1995, EU executed the pan-European registration system known as "Centralized Procedure". European Medicine Agency (EMA), a decentralized agency of Europe, was established in 1995 in London[4]. Further, four scientific committees that conduct review of all centralized procedure application were established. They were:

- Committee for Medicinal Products for Human Use (CHMP)
- Committee for Medicinal Products for Veterinary Use (CVMP)
- Committee on Orphan Medicinal Products (COMP)
- Committee on Herbal Medicinal Products (HMPC)

DRUG APPROVAL PROCESS IN UNITED STATES

The United States has always been a benchmark when it comes to quality of pharmaceutical products. United States Food and Drug Administration (USFDA) has a set of regulations that emphasizes on quality, safety and efficacy of every drug product marketed in the US. This makes the United States the leader in pharmaceuticals across the globe. Before any drug is marketed it has to undergo a particular drug approval process[5].

There are three types of applications which can be filled for approval of a drug product.

A) Investigational New Drug Application (INDA)
B) New Drug Application (NDA)
C) Abbreviated New Drug Application (ANDA)

Investigational New Drug Application (INDA)

When a new molecule is screened it is checked for its potential use. Once the potential benefits of the molecule are determined, further data is collected to ensure that the product is safe[6]. Pre-clinical studies are required to prove that the new drug is safe for performing further clinical trials in humans. Before moving ahead with the clinical studies, Investigational New Drug Application has to be filed to USFDA to seek permission. After filing INDA, the sponsor has to wait for 30 calendar days before starting clinical studies. The main role of FDA is to ensure that the new molecule is safe to be tested in humans. It also ensures that volunteers will not be exposed to any unreasonable risks[7]. Once an INDA is accepted, the molecule changes its legal status under Federal Food, Drug, and Cosmetic Act and becomes a new drug.

There are three types of INDs

A) Investigator IND:
It is submitted by a physician under whose supervision an investigational drug is either administered or dispensed. Researched IND can be submitted if the physician wants to propose studying an unapproved drug, or an approved drug on a different population to obtain its different therapeutic use or for a new indication.

B) Emergency Use IND:
FDA has the authority to allow clinical testing of an experimental drug in an emergency situation that does not allow time to submit an IND according to 21 CFR, Sec. 312.23 or Sec. 312.20.

C) **Treatment IND:**
Some drugs show promising results in clinical trials. If these drugs are effective on serious or immediately life threatening conditions, FDA review takes place while final data of the trials is collected.

The two main categories of IND are
A) Commercial
B) Research

Clinical trials cannot be conducted before 30 days of submission of an IND.

New Drug Application (NDA)

Since 1983, the sponsor of every drug product has to file an NDA before the drug authorised to be marketed in the US. In other words, any drug product that is marketed after 1983, is approved by USFDA[8]. NDA is a document that tells everything about the drug, starting from raw materials used, manufacturing process, therapeutic use, dosage, stability data, results of pre-clinical trials, results of clinical trials till packaging of the drug product.

There are some goals of NDA that help the FDA reviewer to make the following salient conclusions:

- Whether the benefits of the drug product outweigh its risks, and whether the drug product is safe and effective for its suggested therapeutic use.
- Whether the suggested labelling is appropriate and contains the necessary details
- Whether the manufacturing process used and controls maintained to preserve the drugs quality, safety and efficacy are satisfactory.

The INDA and NDA review process is illustrated in figure 1

Abbreviated New Drug Application (ANDA)

Abbreviated New Drug Applications are for obtaining marketing authorisation for generic drugs. According to USFDA generic drugs are defined as "A drug product that is comparable to a brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use". For approval of generic drugs an Abbreviated New Drug Application is filled[9]. It is known as Abbreviated New Drug Application because, there are no pre-clinical or clinical data needed to establish the safety and efficacy of the drug as they already exist in the market and are proved to be safe and effective. The generic drug has to show similar bioavaibility, bioequivalence, therapeutic effectiveness like that of the innovator drug. Once

an ANDA is approved the sponsor can start manufacturing the generic drug and market it in the US[10]. Generic drugs are cheaper and effective alternatives of high cost branded drugs. The ANDA review process is illustrated in figure 2.

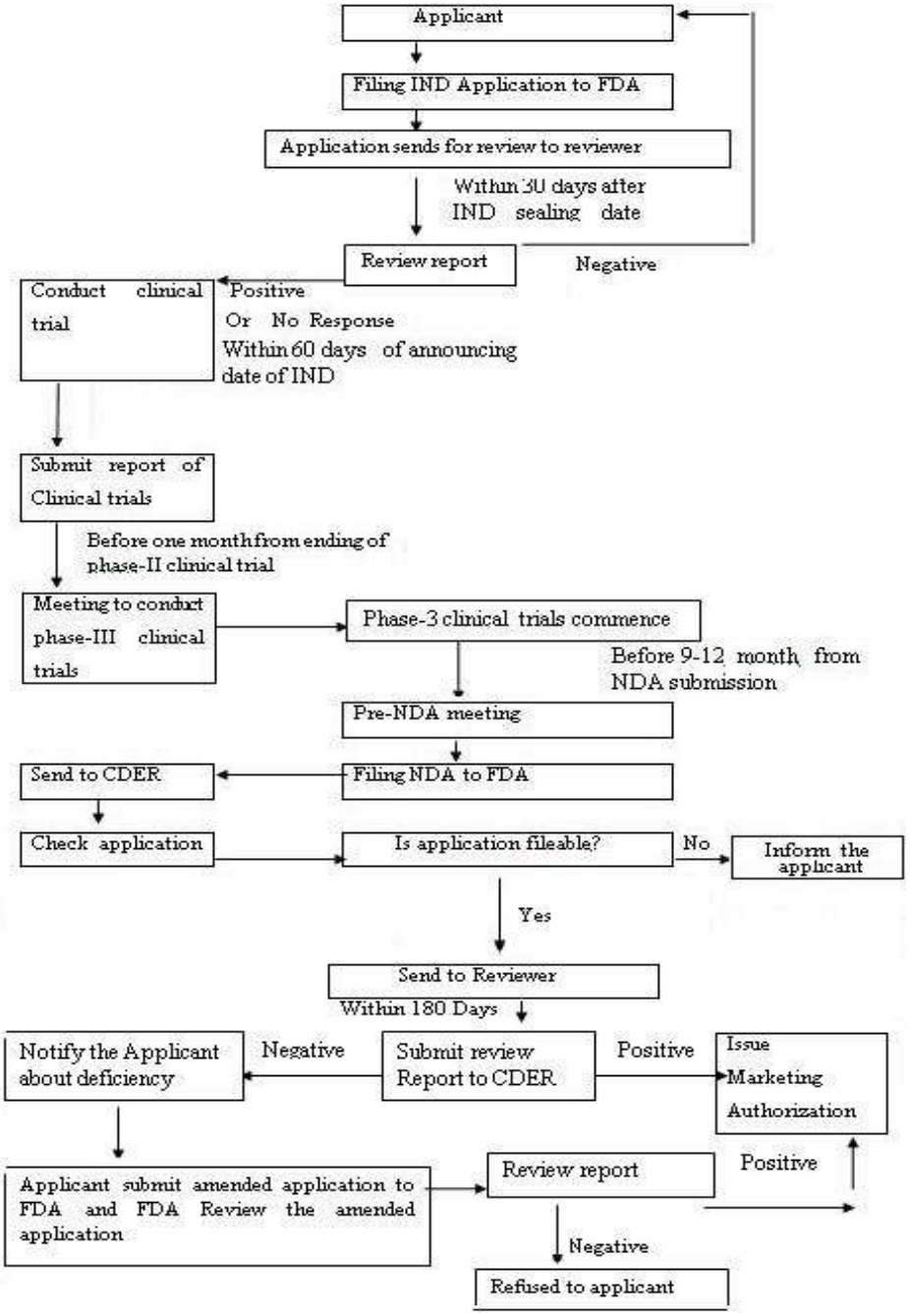

Figure 1: Review process of IND and NDA

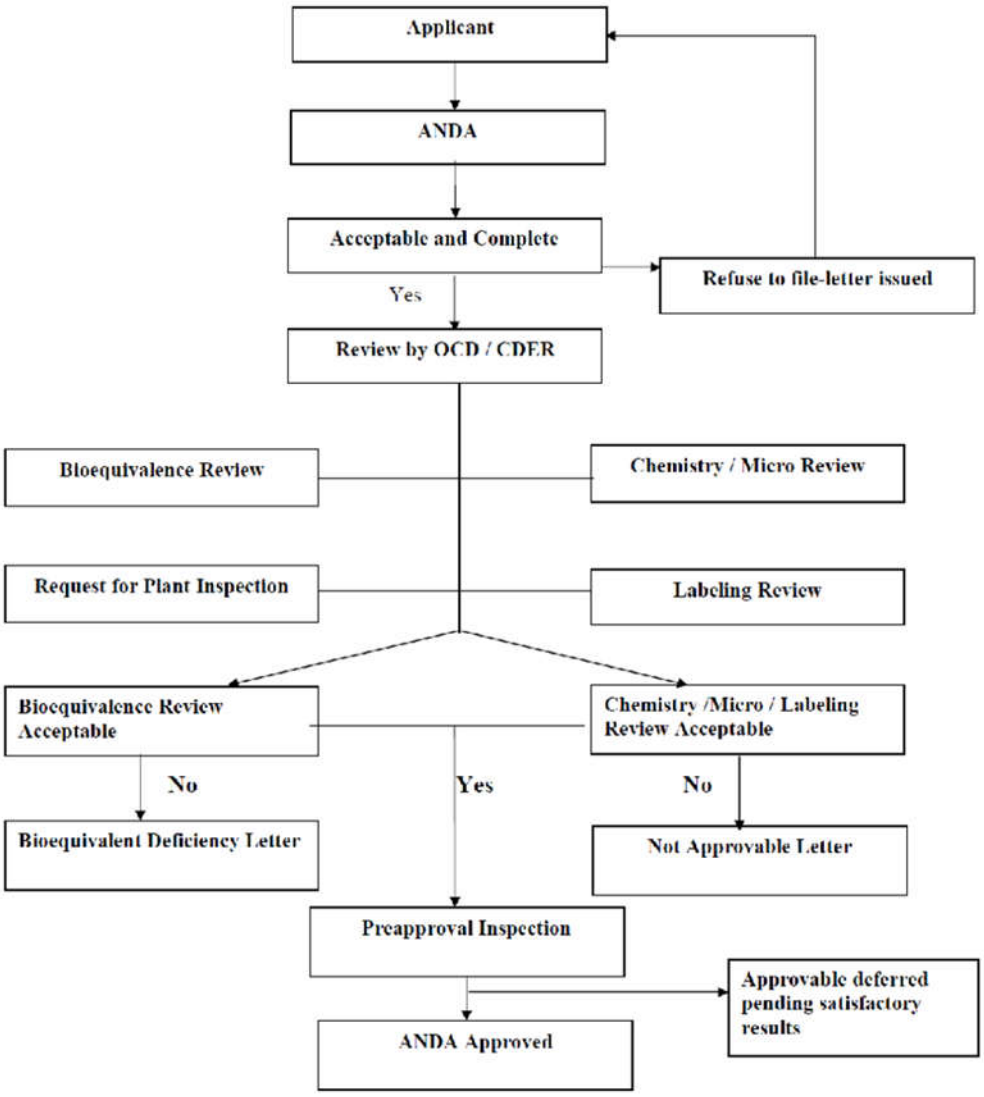

Figure 2: Review process of INDA

DRUG APPROVAL PROCESS IN EUROPEAN UNION (EU)

Medicinal products can be marketed in the EU only after marketing authorization has been obtained either by the regulatory authority of a member state or by the entire community. The European Economic Area (EEA) consists of 28 Member States, as well as Norway, Iceland and Liechtenstein. The Marketing Authorization Holder should be established in EEA. Marketing Authorization Application (MAA) has to be filed by the sponsor. MAA's include significant information that establishes the quality, safety and efficacy of a medicinal product.

Centralized Procedure

This procedure of obtaining marketing authorizations enables the marketing authorization holder to market the product across EU. Marketing authorizations of any member state is not required after obtaining marketing authorization through centralized procedure.

This procedure is laid down in regulation (EC) No 726/2004 and is necessary for:

- Products that are attained from biotechnology
- Orphan products
- All medicinal products that are intended for human use and may contain active

substance authorized in the EU after 20 May 2004 and which are meant for the

- Those that may contain any active substance that is not authorized before 20 May 2004.
- Those that establish a noteworthy therapeutic scientific or technical innovation benefiting the patients.

The review process for Centralized Procedure is illustrated in Table 1.

Mutual Recognition Procedure

In Mutual Recognition Procedure the marketing authorization approved in one Member State has to be approved by the regulatory authorities of other Member States, unless it results as a risk for a particular population. This procedure can be used only if the medicinal product is already authorized in any of the Member States. If not Decentralized

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treatment of Cancer, Neurodegenerative disorders, AIDS or Diabetes.

Procedure should be used. Once marketing authorization is obtained by this procedure, all variations to this medical product have to use Mutual Recognition Procedure. The review process for Mutual Recognition Procedure is illustrated in Table 2.

Decentralized Procedure

This procedure is used for all medicinal products that do not have marketing authorization in any of the EU Member States. So, all medicinal products not authorized in EU have to follow this procedure. Same as in MRP, the applicant is allowed to choose the Reference Member State and list the Concerned Member States. The review process for Decentralized Procedure is illustrated in Table 3.

Table 1: Standard Timeline for Evaluation of a Centralized Application[11]

Day	Action
1	Start of the procedure
80	Receipt of the Assessment Report or critique from Rapporteur and Co-Rapporteur Assessment Report/critique to the applicant making it clear that this only sets out preliminary conclusions, is sent for information only and does not yet present Committee for Medicinal Products for Human Use (CHMP)'s position
100	Rapporteur, Co-Rapporteur, other CHMP members and Europe, Middle East and Africa (EMEA) receive comments from CHMP members (including peer reviewers).
115	Receipt of drafts list of questions (including the CHMP recommendation and scientific discussion) from Rapporteur and Co-Rapporteur by CHMP members and EMEA
120	CHMP adopts the list of questions, as well as the overall conclusions and review of the scientific data to be sent to the applicant by EMEA, Clock stop, At the latest by Day 120, adoption by CHMP of request by Good Manufacturing Practice (GMP)/Good Clinical Practice (GCP) inspection, if necessary (inspection procedure starts)
121*	Submission of the responses, including revised SPC, Labelling and package leaflet texts in 13 languages, and restart of the clock. Submission of mock-ups in color for each strength/form in the smallest pack size covering all EU official languages, Norwegian and Icelandic and language combinations.

Table 2: Timetable for Evaluating Responses[11]

Day	Action
150	Joint response Assessment Report from Rapporteur and Co-Rapporteur received by CHMP members and EMEA. EMEA sends joint Assessment Report to the applicant making it clear that it only sets out preliminary conclusions, is meant for information only, and does not yet represent CHMP's position. Where applicable, inspection to be carried out. EMEA/QRD sub-groups meeting to review English product information with participation of the applicant (optional) around day 165.
170	Deadline for comments from CHMP members to be sent to Rapporteur and Co-Rapporteur, EMEA and other CHMP members.
180	CHMP discussion and decision on the need for adopting a list of "outstanding issues" and/or an oral explanation by the applicant. If an oral examination is needed, the clock is stopped to allow the applicant to prepare it. Submission of final inspection report to EMEA, Rapporteur and Co-Rapporteur by the inspections team (at the latest by Day 180)
181	Restart the clock and oral examination (if needed).
181 to 210	Final draft of English SPC, labelling and package leaflet sent by applicant to the Rapporteur and Co-Rapporteur, EMEA and other CHMP members.
By 210	Adoption of CHMP opinion and CHMP Assessment Report. Adoption of timetable for the provision of revised product information translations.

Table 3: Mutual Recognition Procedure Flowchart[11]

Approx. 90 days before submissions to CMSs	Applicant requests RMS to update Assessment Report (AR) and allocate procedure number
Day 14	Applicant submits the dossier to CMSs; RMS circulates the AR including SPC, PL and labelling to CMSs. Validation of the application in the CMSs.
Day 0	RMS starts the procedure.
Day 50	CMSs send their comments to the RMS and applicant.
Day 60	Applicant sends the response document to CMSs and RMS.
Until Day 68	RMS circulates its assessment of the response document to CMSs.
Day 75	CMSs send their remaining comments to RMS and applicant. A breakout session can be organized between days 73-80.
Day 85	CMSs send any remaining comments to RMS and applicant.
Day 90	CMSs notify RMS and applicant of final position (and, in case of negative position, also EMEA's CMD secretariat); if consensus is reached, the RMS closes the procedure. If consensus is not reached, the points of disagreement submitted by CMS(s) are referred to CMD(h) by the RMS within 7 days after Day 90
Day 15	For procedures referred to CMD (h): If consensus is reached at the level of CMD (h), the RMS closes the procedure. If consensus is not reached at the level of CMD (h), the RMS refers to the matter to CHMP for arbitration.
5 days after close of procedure	Applicant sends high quality national translations of SPC, PL and labelling to CMSs and RMS.
30 days after close of procedure	Granting of national marketing authorizations in the CMSs, subject to submission of acceptable translations.

RESULTS

A brief comparison of both the regulatory authorities is done in order to understand its functioning. They have the same kind of functioning in some aspects but at the same time are totally different in others. The regulatory authority in the US grew by enforcement of various laws and acts. Whereas, in EU various Medicinal Product Directives were established and revised to achieve simplified regulatory functioning. The US learnt and made its Regulations from the heath disasters that happened around the globe. While EU took many of its laws form the USFDA. The US has only one regulatory authority governing the whole pharma industry while in EU there are multiple agencies for each state. This aspect has its own pros and cons. Further, direct comparison of principle differences between USFDA and EU are illustrated in Table 4.

Table 4: Principle differences between USFDA and EU

	USFDA	**EU**
Regulatory Agency	One Agency for approval of drug product throughout United States	Multiple Agencies, for each state in the European Union such as; EMEA, CHMP, National Health Agencies
Registration Process	One single pathway for approval	There are four different pathways for drug approval • Centralized • Decentralized • Mutual Recognition Procedure • National
Application	ANDA/NDA	MAA
Approval Time	18 Months	12 Months
Changes in Approved Drug	By Filing: • PAS • CBE-30/CBE • Annual Report	By Filing: • Type IA Variation • Type IB Variation • Type II Variation
Submission through	eCTD or Paper	eCTD

CONCLUSION:

The United States and Europe have had their own journey in terms of formation of laws and acts in order to ensure public safety. Regulatory authorities of both the countries, aim to ensure that thee pharmaceutical companies bide to the laws and regulations so as to deliver products that are effective and safe for general public. Aim of both the countries is the same but they follow different pathways to achieve them.

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ABBEREVIATIONS:

USFDA U S Food and Drug Administration; **EU** European Union; **EMA** European Medicines Agency; **NDA** New Drug Application; **ANDA** Abbreviated New Drug Application; **INDA** Investigational New Drug Application; **EEA** European Economic Area; **MRP** Mutual Recognition Procedure; **MAA** Marketing Authorization Application; **CHMP** Committee for Medicinal Products for Human Use; **EMEA** Europe, Middle East and Africa; **eCTD** Electronic Common Technical Document

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