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Food Drug Administration vs. European Union

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Abstract

This paper describes the differences in food drug administration and European Union on various aspects like Approval Process, Review Board, Inspection, Legal Authorization and Document Request.

Keywords: Food drug administration (FDA); European union (EU); Approval process; Inspection; Legal authorization; Good laboratory practices (GLP); Good manufacturing practice (GMP); Document request; Institutional review board (IRB)

Introduction

In the struggle for survival, the fittest win out at the expense of their rivals because they succeed in adapting themselves best to their environment - Charles Darwin [1]. With the annual growth rate of four percent to six percent, the pharmaceutical market is one of the complex businesses in the world economy. According to IMS, with the augmentation of total sales in emerging markets, which are expected to reach $120 billion $140 billion, the worldwide pharmaceutical sale will reach $1.1 trillion in 2014 [2]. Everyday myriad of applications is submitted in the regulatory bodies all over the world. In 2010, FDA's Center for Drug Evaluation and Research, with an average of 22.9 approvals per year, approved a total of 21 new molecular entities, i.e. 18 drugs and three biologics [3]. In year 2009, there were 9655 submissions for FDA's Center for Devices and Radiological Health (CDRH) [4]. Thirty three new marketing authorization applications were approved by European Medical Agency in 2010. In addition to that in 2009, one hundred new applications, twenty two line extensions and nineteen type II variations were identified to European Medical Agency as pivotal trials [5]. Medicines and Healthcare products Regulatory Agency (MHRA) performed a total of six hundred ninety three GMP inspections, out of which one hundred and fifty three inspections were preformed overseas and thirty nine were EMA inspections. In addition to that Medicines and Healthcare products Regulatory Agency (MHRA) also performed 1755 marketing authorizations [6]. Moreover Pharmaceutical and Medical Device Agency (PMDA), Japan has approved 853 over the counter drugs out of 1086 filed application in 2010.

Today, the giant pharmaceutical firms are exploring drug market in all over the world. Every country in the world has their local regulatory association. The two main regulatory bodies in the world are Food drug Administration (FDA) and European Union (EU). But obvious when they are the main authorities they are the paragon for other countries. In other words, these most powerful and rival authorities have more policy making burden, more submission and approval burden and also more approbation and criticism burden. However, the competition for proving and making their system exemplary and irreproachable these to regulatory bodies are antagonizing each other. Amidst of this, they are endangering public health and human safety. But to come out with a solution how we can truncate and remove the barrier between this to regulatory apex let us first understand and list out the difference associated in food drug administration and European union.

Differences in Food Drug Administration and European Union

Food Drug Administration (FDA)

Food Drug administration's formation can be traced back from 1848 when chemical analysis of agricultural products had been carrying out in the patent office. With the pure food and drug act in 1906 the FDA's modern regulatory functions incepted and in 1930 it is known by its present name i.e. Food Drug administration [7]. Food drug and administration's federal statutes and regulations are followed in all the over United States i.e. in all fifty states in addition to the applicable individual states laws.

The US Food and Drug Administration (FDA) and Pharmaceutical Research and Manufacturers of America (PhRMA) are two main regulatory bodies which control all the regulatory approvals in United States. FDA work on investigating and ensuring the safety for a wide range of products comprising of drugs, biologics, medical devices, cosmetics and radiological products. Further, it is divided into Center for Drug Evaluation and Research (CDER) for evaluating drugs, the Center for Biologics Evaluation and Research (CBER) for evaluating biologics and Center for Drug Evaluation and Research (CDRH) for evaluating the medical devices. FDA is responsible for protecting and promoting public health. The approval process of FDA comprises of two parts i.e. clinical trials and New Drug Application (NDA) approval. This approval process incepts with the submission of investigational new drug application which is composed of all the high quality preclinical and non-clinical data to justify the testing product in/on human body, followed by phase I, Phase II and Phase III clinical trials to ensure the safety and efficacy of product for human use. When the drug successfully passes all three phases of clinical trial a New Drug Application (NDA) is submitted which mainly comprises of clinical and non-clinical studies, data analysis, statistical reports, manufacturing and proposed label of the product. Generally on an average the NDA approval takes a two year time period to get approved and after approval phase IV and post marketing studies are also conducted. This

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FDA approval process (till NDA approval) can be completed in two months (via fast track or accelerated approvals) to several years.

European Union (EU)

European medical agency was set up in 1995 by the funding of EU [8]. The European Union directives are applicable only to all members i.e. in all twenty seven members and in addition to that the national laws are applied. London Headquarter of European Medical Agency, operated under EU, has around 700 employees. The funding of the organization comes from both by company fees from their applications submission (75%) and from the 27 member states (25%).

European Union comprises of multiple agencies like European Medicines Evaluation Agency (EMEA), Committee for Medicinal Products for Human Use (CHMP) of the EMEA and National Health Agencies. However two main associations namely European Commission and European Federation of Pharmaceutical Industries Associations represent EU. European commission comprises of fifteen member countries of European Union whereas European Federation of Pharmaceutical Industries Associations (EFPIA) includes pharmaceutical organizations from sixteen Western Europe countries. EFPIA comprises of all Europe's main pharmaceutical organizations.

The EU approval process also consists of two parts, namely clinical trial and marketing authorization. For initialization of conducting clinical trials within the EU, Clinical Trial Application (CTA) is filed to the competent authority in the state which evaluates the application. After getting the approval three phases of clinical trials are conducted and then the Marketing Authorization Application (MAA) is submitted. MAA is mainly comprised of all clinical and non-clinical data, statistical data, analytical data, manufacturing and proposed label. However, the applicant, after successfully completing the marketing authorization application has a choice to move further by following the respective regulatory procedures, i.e. centralized procedures, decentralized procedures, national procedures or mutual recognition procedure, in accordance to their submission.

Differences in approval process

The figure 1 shows, how the drug approval process in both agencies, i.e. FDA and EU differ from each other. After the completion of preclinical and non-clinical testing the FDA requires the applicant to submit Investigational Drug Application (IND) whereas the EU requires the applicant to submit the Clinical Trial Application (CTA).

In the EU, the applicant cannot start the clinical trials without getting an approval of Clinical Trial Application (CTA) whereas, FDA submit Investigational Drug Application (IND) i.e., FDA form 1571, is a request for an exemption from the federal statute that prohibits an unapproved drug from being shipped in the interstate of commerce [9].

In addition to that, after completing all the three phases of clinical trial FDA needs New drug application whereas the EU needs the Marketing Authorization Application. After getting approval in EU, pharmaceutical organization has two options, i.e. centralized or decentralized, for bringing drugs to the market however, no such option is available for the pharmaceutical organizations seeking approval under FDA.

Differences in review board

The FDA and EU have different review boards to review and investigate the approval of the submitted application in the respective authorities. In Food drug administration, the Institutional Review Board (IRB) is the main authority. IRB approval is required for getting approval of New Drug Application submission in FDA and the registration of the Institutional Review Board (IRB) is necessary. On the contrary side in European Union the ethics committee is responsible for the approval of the Market Authorization Application. These Ethics committees are appointed and/or authorizes by the states in EU.

Differences in inspection

To ensure that the organizations are complying with the required Good Laboratory Practices (GLP) and Good Manufacturing Practice (GMP), there are many inspections conducted by the regulatory authorities. There are many differences in the inspection processes conducted by the FDA and EU which are shown table 1. In FDA there are no prior notifications given for conducting such inspections unless it is specified by the related FDA center whereas in EU prior notifications are given before the inspection is done by the inspectorates of the local regions. In EU, the MAA applicant/holder will not only cover all the inspection expenses but also cover all the expenses coming under inspections e.g. expenses of inspector's travelling arrangement. However, FDA covers all the expenses for the inspection. The FDA inspections are usually done by a single inspector alone whereas in EU, two or three inspectors may together conduct the inspection [10].

The beginning of inspections, conducted by FDA, need the various documents e.g. form 482 with FDA signature, notice of inspection etc. However, on the other side no such formal documentation is required in the beginning of the inspection instead of that in EU, there is an open discussion which comprises of the purpose, expectation and verbal discussions related to the inspection.

After the FDA inspection the regulatory classification of inspectorial finding are classified as:

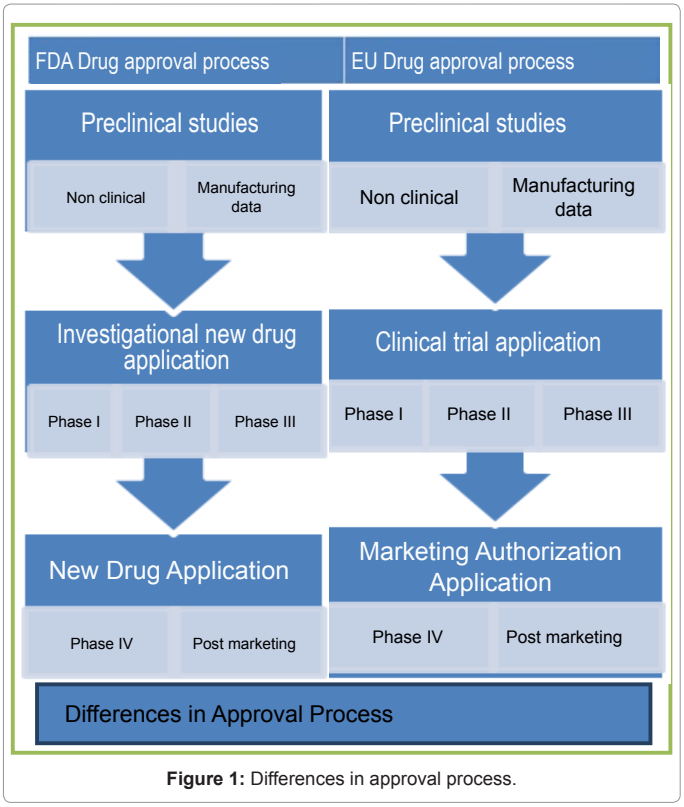

Figure 1: Differences in approval process.

1. NAI-no action indicated
2. VAI-voluntary action indicated
3. OAI-official action indicated

Whereas the regulatory classification of inspectorial finding under EU is classified as:

1. Critical
2. Major
3. Minor
4. Others

In EU, the inspector verbally discusses all the organization's shortcomings, problems etc., if found during the inspection, in the end of the meeting, known as "closeout meeting" whereas, FDA inspectors present/issue all the significant problems, violations, objectionable conditions etc. to the most responsible person in the firm on FDA-483 in writing.

Differences in legal authorization

During and after the inspection, Food Drug administration has myriad of regulatory arsenals to address the violations. As shown in table 2, FDA can take legal actions on the firm, sponsor or monitors by sending the legal letter, notices or by terminating, withdrawing the application [11]. On the contrary side EU does not have such enforcements actions.

Differences in document request

Table 3 shows and compare the document request by the FDA and EU during the regulatory submission.

Generally Food drug administration may need/request all the documents for the regulatory submission prior or during the time of inspection whereas the European Union need/request all the necessary documents prior or during the inspection process.

In addition to this, FDA requires the retention of all the essential documents for two years after the drug approval, whereas EU requires the retention of all the essential documents for at least five years (exceptions in some cases) after the drug approval.

Conclusion

With the above discussed differences we can easily perceive the lack of cooperation between these two gigantic regulatory bodies. There are many solutions for curtailing the difference in Food drug Administration and European Union. The two main solutions can be the transparency in the system and the harmonization between these two systems. FDA and EU are working for the same goal i.e. to protect public health. The Unjustified differences between FDA and EU can be eliminated by making the system transparent. This transparency can be achieved by implementing the global submissions e.g. submission of Electronic Common Technical Document (eCTD) can allow other authorities in the world to check the other authorities submission, their approach, planning etc. and ameliorate the transparency at the same

	Food drug Administration	European Union
Notification Process	Prior notification is not usually given unless specified by the related FDA center.	Formal inspection done by inspectorates of the local regions.
Inspection expense	All expenses are covered by FDA.	All expenses are covered by MAA holder including the travel expense
Number of inspectors	Usually wok alone	Commonly work in a team of two or three members
Regulatory classification of inspectorial findings.	Classifications include: NAI- no action indicated VAI-voluntary action indicated OAI- official action indicated	Classifications include: Critical Major Minor Others

Table 1: Differences in Inspection Process [10].

Warning and untitled Letters.
Re-inspection
Termination of exemption (IND, IDE).
Refusal to approve or license.
Withdrawal of approval (PMA, NDA).
Determination of not substantial equivalent or rescission of 510K
Implementation of the application integrity policy.
Initiation of Stock recovery.
Seizure of test articles.
Injunction.
Prosecution under the FFDCA and other federal statutes e.g. 18 USC 371

Table 2: FDA Legal Authority Actions For Sponsors, Monitors, And CRO'S [11].

	FDA	EU
List of all polies/SOP's/work instructions conduct of clinical trials including AE reporting.	During the inspection	Prior to inspection
Investigator meeting presentation, attendance log, investigator agenda.	During the inspection	Prior to inspection
List of ongoing clinical trials of IMP from previous GCP inspection or minimum of last 3 yrs.	During the inspection	Prior to inspection
Instructions provided to Investigator and monitors.	During inspection	Prior to inspection
Complete study report and Table of contents for Trial Master File (TMF).	During inspection	Prior to inspection

Table 3: Differences in Document Request [10].

time in the system. Global submission will help both the regulatory bodies to work together, to understand the risks and benefits of submissions, to learn from each other and to make the world safer.

Another way of achieving transparency is by globalization of reporting the adverse events. The globalization of adverse event reporting with the help of Pharmacovigilance will not only help the regulatory authorities but also help organizations to learn with past mistakes of other organizations and authorities before incepting or submitting an application to the regulatory bodies. To curtail the differences in the inspection process, an initiative of joint inspection can be a solution. The joint inspection can help in sharing the information, making and designing policies and better understanding the outcome. Adoption of these new or improved technical research and development ameliorate the harmonization between FDA and EU.

At last I want to end where we start, the quote of Charles Darwin that the fittest can only survive by understanding and adapting the change. For the better future and survival of the world the adaptation of above solution by these two paragons, i.e. Food drug administration and European Union, will definitely make the world a better place to live.

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