International Journal of

Innovative Drug Discovery

e ISSN 2249 - 7609
Print ISSN 2249 - 7617

www.ijidd.com

ANTI CANCER DRUG SUBMISSION PROCESS IN EUROPEAN UNION & THE UNITED STATES OF AMERICA

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ABSTRACT

The Regulatory Affairs section guarantees that their businesses are in compliance with all applicable rules and legislation. Internally, it communicates throughout the development, manufacturing, marketing, and clinical research phases of a medication. It serves as the company's primary contact with regulatory authorities on the outside. Cancer is the uncontrolled and abnormal development of bodily cells. The chemotherapeutic drug must be able to kill or limit the development of cancerous cells selectively. As a result, the approval procedures for these medicines must be consolidated. The current research intends to conduct a comparative analysis of the dossier preparation and submission procedure in the United States and European Union countries, as well as to comprehend regulatory rules in the medication approval process. Although there were major changes in the approval applications, the process for applying for approval in the US and the EU remained the same. The approval procedure took about the same amount of time. In the United States, new anticancer medicines were authorised at a rate of more than 90%, while in the European Union, it was more than 80%. The majority of the new anticancer medicines were approved first in the United States, while the European Union lagged after.

KEY WORDS: Teratology, Pregnancy, Quality Of Life.

INTRODUCTION

Medicinal products, pharmaceuticals, veterinary medicines, medical devices, and food supplements - all these products are subject to regulations designed by governments to protect public health. The Regulatory Affairs department ensures that their companies comply with all of the regulations and laws concerning their business. Internally it liaises at the interphase of drug development, manufacturing, marketing and clinical research. Externally it is the key interface between the company and the regulatory authorities. Cancer is defined as abnormal and uncontrolled growth of body cells. The chemotherapeutic agent must be able to selectively kill or inhibit growth of neoplastic cells leaving normal cells unharmed. But currently available drugs damage DNA or interfere with DNA synthesis there by killing all rapidly dividing cells, both normal and cancerous. In addition, all approaches to cancer chemotherapy are ideally required to eradicate all tumor (cancer) cells completely. The present study aims towards the Comparative study of Dossier compilation and submission process in USA & European Union Countries and to understand the regulatory guidelines in drug approval process and regulatory guidelines.

Major Differences Noticed In Various Arenas

Common Technical Document (CTD) format

It is a harmonized format for presenting the data in ICH regions (International Conference on Harmonization). It is divided into 5 modules. They are as follows.

Module 1 - Regional Administrative Information - Not a part of CTD; Module 2 - Clinical, Nonclinical overview & summary - Common to all countries; Module 3 - Quality - Common to all countries; Module 4 - Non clinical study reports - Common to all countries; Module 5 -

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Clinical study reports - Common to all countries. There is a lot of difference seen only in the first module and all the other modules remain the same.

Approval Processes:

Anticancer drug submission process in USA:

USFDA (United States Food and Drug Administration) is a regulatory agency within the Department of Health and Human Services in United States. FDA follows four steps to approve a new drug for marketing into United States [1].

- Investigational New Drug (IND) Application
- Clinical development
- New Drug Application (NDA)
- FDA review

The FDA review process consists of five phases:

1. Filing determination and review planning
2. Review
3. Advisory committee preparation and conduct (where applicable)
4. Action phase
5. Post-action phase

FDA has 180 days to review an NDA. If it finds deficiencies, such as missing information, the clock stops until the manufacturer submits the additional information. If the manufacturer cannot respond to FDA's request (e.g., if a required study has not been done, making it impossible to evaluate safety or effectiveness of the drug), the manufacturer may voluntarily withdraw the application. If and when the manufacturer is able to provide the information, the clock resumes and FDA continues the review [2].

Special Mechanisms to Expedite the Development and Review Process

Not all reviews and applications follow the standard procedures. For drugs that address unmet needs or serious diseases or conditions, FDA regularly uses three formal mechanisms to expedite the development and review process.

Accelerated Approval Process

FDA regulations allow "accelerated approval" of a drug or biologic product that provides a "Meaningful therapeutic benefit over existing treatments." The rule covers two situations. The first allows approval to be based on clinical trials that, rather than using standard outcome measures such as survival or disease progression, use "a surrogate endpoint that is reasonably likely ... to predict clinical benefit." The second situation addresses drugs whose use FDA considers safe and effective only under set restrictions that could include limited prescribing or dispensing. FDA usually requires post marketing studies of products approved this way.

Fast track. The Food and Drug Administration Modernization Act of 1997 (FDAMA, P.L. 105-115) directed the Secretary to create a mechanism whereby FDA could designate as "Fast Track" certain products that meet two criteria.

- First, the product must concern a serious or life-threatening condition;
- Second, it must have the potential to address an unmet medical need.

Once FDA grants a Fast Track designation, it encourages the manufacturer to meet with the agency to discuss development plans and strategies before the formal submission of an NDA. Such early interaction can help clarify elements of clinical study design and presentation that if absent at NDA submission could delay approval decisions. However, FDA makes similar interactions available to any sponsor who seeks FDA consultation throughout the stages of drug development.

As noted above, the outcome of the review of an NDA can be either an Approval Letter or a Complete Response Letter. With an Approval Letter, the sponsor receives authorization from the FDA to commercialize a drug with the approved labelling. The Complete Response Letter indicates that the review is complete and the application cannot be approved in its current form. It provides information to the sponsor on changes that must be made before an application can be approved, and lists all the deficiencies identified by the FDA. The deficiencies may be major (e.g., additional clinical trials are required) or minor (e.g., labeling changes are required). Where possible, the letter may also outline actions the sponsor may take to prepare the application for approval. Following the receipt of a Complete Response Letter, the sponsor may elect to prepare a response, withdraw the submission from further review, or request an opportunity for a hearing. If a response is submitted, it is categorized as either class 1 or class 2, depending on the data submitted.

Class 1 Resubmission: A class 1 resubmission starts a new two-month review cycle. The following items are classified as class 1:

- Final printed labeling
- Draft labeling
- Safety updates in the same format (including tabulations) as the original safety submissions, with new data and changes highlighted
- Stability updates to support provisional or final dating periods
- Commitments to perform phase IV studies including proposals for such studies
- Assay validation data.
- Final-release testing on the last one to two lots used to support approval
- A minor reanalysis of data previously submitted to the application

Class 2 Resubmission: A class 2 resubmission includes any other information not listed above. Any submission that warrants a re-inspection of facilities is classified as class 2.

Anticancer drug submission process in EU:

Application Form

The application form is to be used for an application for a marketing authorization of a medicinal product for human use submitted to (a) the European Medicines Agency under the centralized procedure or (b) a Member State (as well as Iceland, Liechtenstein and Norway) under either a national, mutual recognition procedure or decentralized procedure [3].

Pre submission

At least seven months before submission, applicants should notify the EMEA of their intention to submit an application and give a realistic estimate of the month of submission [4]. In that notification applicants should include:

- A draft summary of product characteristics;
- A justification of the product's eligibility for evaluation under the centralized procedure (if not already requested at an earlier stage)
- In case of 'generic' or 'bio-similar' applications, details of the proposed

Selection of rapporteur/co-rapporteur

The rapporteur is a country-specific regulatory authority within the EU. The rapporteur (reviewer) and co-rapporteur (if needed) are identified from the CHMP members. The selection of the rapporteur is based on objective criteria, to ensure objective scientific opinion and the best use of available expertise at the EMA. The role of the rapporteur is to perform the scientific evaluation and prepare an assessment report to the CHMP. If a co-rapporteur is involved, the co-rapporteur will prepare an independent assessment report, or provide a critique of the rapporteur's report, at the discretion of the CHMP [5].

Requesting the appointment of CHMP/PRAC/CAT Rapporteurs/Co-Rapporteurs and their assessment teams

Applicants shall request the appointment of CHMP/PRAC/CAT Rapporteurs/Co-Rapporteurs (in the following only described as (Co-) Rapporteurs) by sending a completed Pre-submission request form (selecting the indent "Intent to submit MA") to pa-bus@ema.europa.eu. The pre-submission request form can be accompanied by a cover letter. This notification is also called the "letter of intent" [5].

SOPs and WIN

1. SOP/H/3004 on Tasks of product team on handling of initial Marketing Authorization Application.
2. SOP/H/3101 on Determination of Fees (Medicinal products for Human Use).
3. SOP/H/3106 on Core master files of medicinal products for human and veterinary use following the centralized procedure.
4. SOP/H/3181 on Assessment of similarity of medicinal products.
5. SOP/H/3271 Handling of the compliance check with an agreed pediatric investigation plan
6. WIN/ADM/7009 on Hard copy files pharmaceutical industry.
7. WIN/H/3251 on Handling of Electronic-only submissions, including eCTDs
8. European Review System (EURS).
9. WIN/PDM/1702 on Processing of incoming submissions related to medicinal products
10. Human use.

Timelines of the initial marketing authorization procedure

Timelines of the initial marketing authorization procedure are defined for the purpose of this article as follows

- **Active time**: Is the time needed for scientific evaluation by the CPMP as given in the Annual Reports of the EMEA.
- **Clock-stop time**: Is the time needed by the applicant to answer the objections raised by the authorities as given in the Annual Reports of the EMEA.
- **Scientific time:** Is the time needed for scientific evaluation by the CPMP plus the time needed by the applicant for answering the authority objections; it was calculated as the interval between the start of the procedure and the CPMP opinion as given in the Annual Reports of the EMEA.
- **Administrative time:** The administrative time was calculated as the interval between the CPMP Opinion and the Date of Decision of the European Commission as given in the Annual Reports of the EMEA.
- **Total time:** Is the time needed for the overall duration of the marketing authorization procedure and was calculated as the interval between the start of the procedure and the Date of Decision of the European Commission as given in the Annual Reports of the EMEA, i.e., the sum of the scientific time and the administrative time.

Accelerated evaluation procedure

The EMEA first provided guidance6 on an accelerated evaluation of products in 1996. This guidance foresaw a scientific review time of 120 d instead of the standard 210 d for drugs that meet the following three cumulative criteria:

- Indicated for treatment of a heavily disabling or life-threatening disease and
- Absence of an appropriate alternative therapeutic approach, and

- Anticipation of exceptionally high therapeutic benefit.
- Only one of the oncology drugs investigated has been authorized using an accelerated evaluation procedure.

Withdrawal of the application:

Where an applicant decides to withdraw their application before an Opinion has been adopted by the CHMP or during the appeal process, the applicant shall communicate its reasons for doing so to the EMEA. Further guidance on the withdrawal information to be published is provided in the EMEA "Reflection paper on publication of withdrawals", as published on the EMEA website.

The Committee's Opinion

On or before Day 210, the CHMP adopts its opinion in the light of the final recommendation of the Rapporteur and Co-Rapporteur and further evidence presented at the oral explanation. In case of an oral explanation and where the procedural timetable allows, the CHMP Opinion will be adopted at the following CHMP meeting, allowing applicant, (Co-) Rapporteur and CHMP members to finalize the product information and Assessment Report as appropriate. The applicant should liaise with the PTL on the practical arrangements in connection with the adoption of the opinion.

The draft opinion is prepared by the EMEA and then adopted by the CHMP. The CHMP opinion, which may be favorable or unfavorable, is, wherever possible, reached by scientific consensus. The Rapporteur and the Co-Rapporteur, in co-ordination with the PTL, taking account of the full scientific debate within the CHMP and the conclusions reached, prepares the final assessment report, which, once adopted by the CHMP, becomes the CHMP assessment report and is appended to the CHMP opinion.

Types of Marketing Authorization in EU Countries

Different types of marketing authorization are available when seeking approval to market a new drug in European market. They are as follows

1. National authorization procedure.
2. Decentralized procedure.
3. Mutual recognition procedure.
4. Centralized procedure.

National authorization procedure.

This type of authorisation is granted on country-by-country basis by competent authorities, in each member state. Products only intended for one market will follow this procedure

Decentralized procedure:

By this process, a sponsor can apply for simultaneous authorization in more than one EU country for products that have not yet been authorized in any EU country

Mutual recognition procedure:

A product is first authorized by one country in the EU in accordance with the national procedures of that country. Later, further marketing authorizations can be sought from other EU countries, who, rather than conducting their own review, agree to recognize the decision of the first country.

Centralized 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.

Table 1: Comparative study of dossier submission in Europe &US.

S.NO	Requirements	USA	Europe
A. Administrative			
1	Application	NDA/ANDA	MAA
2	Debarment certification	Required	Not required
3	No. of copies	3	1
4	Approval time line	11Month	12 Month
5	Fees	125 US $ per product	10-20 lakhs
6	presentation	eCTD & paper	eCTD
B. Finished Product Control			
1	Justification	ICHQ6A	ICHQ6A
2	Assay	90%-100%	95%-105%
3	Disintegration	Not required	Required
4	Color Identification	Not required	Required
5	Water content	Required	Not required
C. Manufacturing & Controls			
1	No. of batches	01	03

2	Packaging	A minimum of 1,00,000units	Not required
3	Process validation	Not required at the time of submission.	Required
4	Batch size	A minimum of 1,00,000 units	A minimum of 1,00,000 Units
D. Stability			
1	No. of batches	01	02
2	Condition	25/60:40/75	25/60:40/75
3	Date &Time of submission	3 Month accelerated & 3Month long term	6 Month accelerated & 6Month long term
4	Container Orientation	Inverted upright	Not address
5	Clause	21CFR part 210& 211	Volume 4 European guidelines for medicinal products
6	Qp certification	Not required	Required
E. Bioequivalence			
1	CRO	Audited by FDA	Audited by MHRA
2	Reserved sample	5 times the sample required for analysis	No such sample is Required
3	Fasted/Fed	Must be as per OCG recommendation	No such requirement
4	Retention of samples	5 year from the date of filing the application	No such requirement but usually followed

Table 2: Differences between European and USFDA drug agencies.

S.NO	EMEA	USFDA
1.	Multiple agencies a) European Medicines Evaluation Agency b)Committee For Medicinal Products For Human Use. c) National Health Agencies.	One agency.
2.	Multiple registration process a) National b)Centralized procedure c)Decentralized procedure d)Mutual recognition procedure	One registration process
3.	TSE/BSE data is required.	TSE/BSE data is not required.
4.	Braille code is required on labeling.	Braille code is not required on labeling.
5.	Median time for marketing submission to approval is 350 days	Median time for marketing submission to approval is 182 days
6.	The average time taken by EMA to approve a drug product was 366 days	The average time taken by FDA to approve a drug product was 322 days

Analyses of new antineoplastic agents approved in the US and EU:

We identified 95 new antineoplastic agents were approved in the US between 1999 and 2013 [6]. In EU 85 new antineoplastic agents were approved between 1999 and 2013. Antineoplastic agents were approved in the US, with an average of 3.92 antineoplastic agents approved per year and in the EU a total of 44 new antineoplastic agents were approved, with an average of 3.38 antineoplastic agents approved per year.

Conclusion

While total development time for oncology and non-oncology drugs decreased by half a year between 2011 and 21, this was achieved for oncology drugs by process improvements that shortened regulatory review time. Oncology drug development remains difficult due to smaller patient populations for recruitment and longer periods for treatment evaluation. New antineoplastic drugs were approved at a rate of more than 90% in the United States and over 80% in the European Union. The United States was the first to approve the bulk of the new anticancer drugs, while the European Union was somewhat behind.

FUNDING SOURCE

There was no funding for the research

Competing Interests

Authors declare there are no competing interests

Acknowledgement Author's heart fully thanks those who have helped during the work.

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