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RESEARCH ARTICLE

Regulatory Filing In Us and Eu: A Comparative View

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ABSTRACT:
Regulatory Affairs in pharmaceutical industry is dealing with all aspects of government affairs and to fulfill the requirements of Pharma regulatory agency of the concerned nations and deals with obtaining the approval from license, development of a pharmaceutical product to manufacturing,drug approval process and registration of pharmaceutical products for sale and distribution in different regulated markets and for post marketing studies. The pharmaceutical companies must adhere to the legislations that require drugs to be developed, tested, trialed, and manufactured in accordance to the guidelines so that they are safe and patient's well - being is protected. This topic aims at reviewing about the basics of drug regulatory filing in pharmaceutical industry and to gain knowledge about the different aspects of introducing drug product(s) into USFDA/Europe regulated market.

KEYWORDS: Regulatory Affairs,Filing and USFDA/Europe.

1. INTRODUCTION:

Before a new drug or biologic can go to market, a drug submission must be compiled and filed with all relevant regulatory agencies to seek a review and, ultimately, regulatory approval.Each jurisdiction has its own procedures to review drug submissions filed to their regulatory agency. These procedures can vary substantially with respect to how the drug submission will be handled, the composition of the review team, review timelines and so on.[1-4]

Despite the Differences, the Procedures to Reach Regulatory Approval Generally follow these Stages:

Pre-Submission Meeting:

Although optional, a pre-submission meeting[5] is often useful so that any scientific or submission issues can be discussed and resolved prior to the actual submission. This meeting also provides the agency insight into your drug or biologic submission and allows them to organize their internal resources accordingly.

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Pre-Submission Activities:

Review what communication is required prior to submitting your marketing application. In Canada, sponsors (that is, applicants) are requested to send advance requests for Priority Review status and for Requests for Advance Consideration under the NOC/c.[6] In the EU, an applicant should notify the European Medicines Agency (EMA) of its intention to submit via the centralized procedure at least seven months before the drug submission.[7] Any orphan drug designation should also be requested and approved before your drug submission will be reviewed as an orphan product.

Administrative Review:

Once a drug submission is filed, it goes through an administrative review to ensure its acceptability (for example, completeness). A submission number (such as NDS Control Number or NDA number) is assigned and this number must be used in all subsequent communication with the regulatory agency. If the drug submission is found to be acceptable at this stage, it will be accepted for review. If minor deficiencies are identified (for example, missing forms), the agency will normally allow the sponsor time to respond. If the response is satisfactory, then the submission will proceed

to review. If the sponsor fails to provide the requested information within the set timeframe, or if that the response is unsatisfactory, the agency can reject (refuse to file) the submission.

Agency Review and Sponsor Response:
Once a drug submission is accepted, it is evaluated by reviewers with the necessary expertise. In the US, for example, a review team may include clinicians, pharmacokineticists, pharmacologists, toxicologists, statisticians, microbiologists and chemists, as well as a regulatory project manager (RPM). The objective of the review is to confirm and validate the sponsor's conclusion that the drug is safe and effective for its proposed use. Once the technical review is complete, an evaluation report will be generated. If the submission is deemed acceptable, then the technical review of the submission is complete. If deficiencies are identified, then the agency will issue a list of questions for the sponsor to address within a set timeline. This review also evaluates the text in the proposed labelling, which needs to be justified by the data submitted in the submission. If the reviewers question the proposed labelling, they will discuss revised wording with the sponsor.

Tip:
Assemble a response team that can address agency questions and requests for additional information. A quick response by the sponsor facilitates the review process.

Activities Prior to the Agency's Decision:
These may include any necessarypre-approval inspections (for example, of drug manufacturing sites or clinical trial sites). In the US, for example, the Food and Drug Administration (FDA) may decide to convene an advisory committee (AC) meeting and seek input. Based on the discussions at the AC meeting and its recommendations, the FDA may ask for additional data or analyses to review.

Decision:
The decision made at the end of the review process normally results in regulatory approval, an approval with conditions, or a rejection.
*NOC/c = Notice of Compliance with conditions

The above presetting s and regulatory filings are framed to attain the goals to provide enough information to permit reviewer to reach the following key decisions:

- Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.
- Whether the drugs proposed labeling (package insert) is appropriate, and what it should contain.
- Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity

2. MATERIALS AND METHODS

Drug Approval in United States*:*
The United States has perhaps the world's most stringent standards for approving new drugs. Drug approval standards in the United States are considered by many to be the most demanding in the world [8-10]
Following are the some important terms and definition used in the regulatory filings is described below.

FILING:
A document that a company has to send to an official organization that regulates its activities.

DOSSIER :
A document that contains all the technical data (administrative, quality, nonclinical and clinical) of a pharmaceutical product to be approved / registered / marketed in a country

Drug Master File:
A Drug Master File (DMF) is a submission to the 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 drugs.

Type I:
Manufacturing Site, Facilities, Operating Procedures, and Personnel (No longer accepted by FDA).

Type II:
Drug Substance, Drug Substance Intermediate, and Material used in their Preparation, or Drug Product.

Type III:
Packaging Material.

Type IV :
Excipient, Colorant, Flavor, Essence, or Material used in their Preparation.

Type V:
FDA accepted Reference Information (FDA discourages its use)

INDA:
Provides resources to assist drug sponsors with submitting applications for approval to begin new drug experiments on human subjects.

NDA:
Provides resources to assist drug sponsors with submitting applications for approval to market a new drug.

ANDA:
Application for the review and ultimate approval of generic drugs.

Prior Approval Supplement (PAS) :
major change is a change that has a substantial potential to have an adverse effect on the identity, strength, quality or potency of a drug product requires the submission of a supplement and approval by FDA prior to distribution of the drug product made using the change.

CBE 30:
Moderate change requires the submission of a supplement to FDA at least 30 days before the distribution of the drug product made using the change. drug product made using a moderate change cannot be distributed if FDA informs the applicant within 30 days of receipt of the supplement that a prior approval supplement is required.

CBE:
FDA may identify certain moderate changes for which distribution can occur when FDA receives the supplement.

❖ **Annual Report:**
Minor change

Prior Approval Supplement (PAS):
Following are examples of changes considered to have a substantial potential (major changes).

- Move to a different manufacturing site, except one used to manufacture or process a drug substance intermediate, when the new manufacturing site has never been inspected by FDA.
- New manufacturing site does not have a satisfactory CGMP inspection.
- Changes in the sterilization method (e.g., gas, dry heat, irradiation)
- Addition, deletion, or substitution of sterilization steps or procedures for handling sterile materials in an aseptic processing operation

CBE 30: Following are Examples of Changes Considered to have a Moderate Potential:
- Move to a different manufacturing site for the primary packaging of any drug product that is not otherwise listed as a major change modified-release solid oral dosage form drug products.
- For drug products, any change in the process, process parameters, and/or equipment except as otherwise provided for in this guidance.
- Increase or decrease in production scale during finishing steps that involves different equipment
- Changes in dry heat depyrogenation processes for glass container systems for drug substances and drug products
- Changes to filtration parameters for aseptic processing (including flow rate, pressure, time, or volume, but not filter materials or pore size rating)
- Move to a different manufacturing site for the manufacture or processing of the final intermediate
- Change in methods or controls that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency
- Sterile drug products, elimination of in-process filtration performed as part of the manufacture of a terminally sterilized drug product.

Annual Report:
Examples of changes considered to have a minimal potential
- A move to a different manufacturing site for secondary packaging.
- A move to a different manufacturing site for labeling.
- A move to a different manufacturing site for the manufacture or processing of drug substance intermediates other than the final intermediate
- A minor change in an existing code imprint for a dosage form. For example, changing from a numeric to alphanumeric code
- Change in the order of addition of ingredients for solution dosage forms or solutions used in unit operations

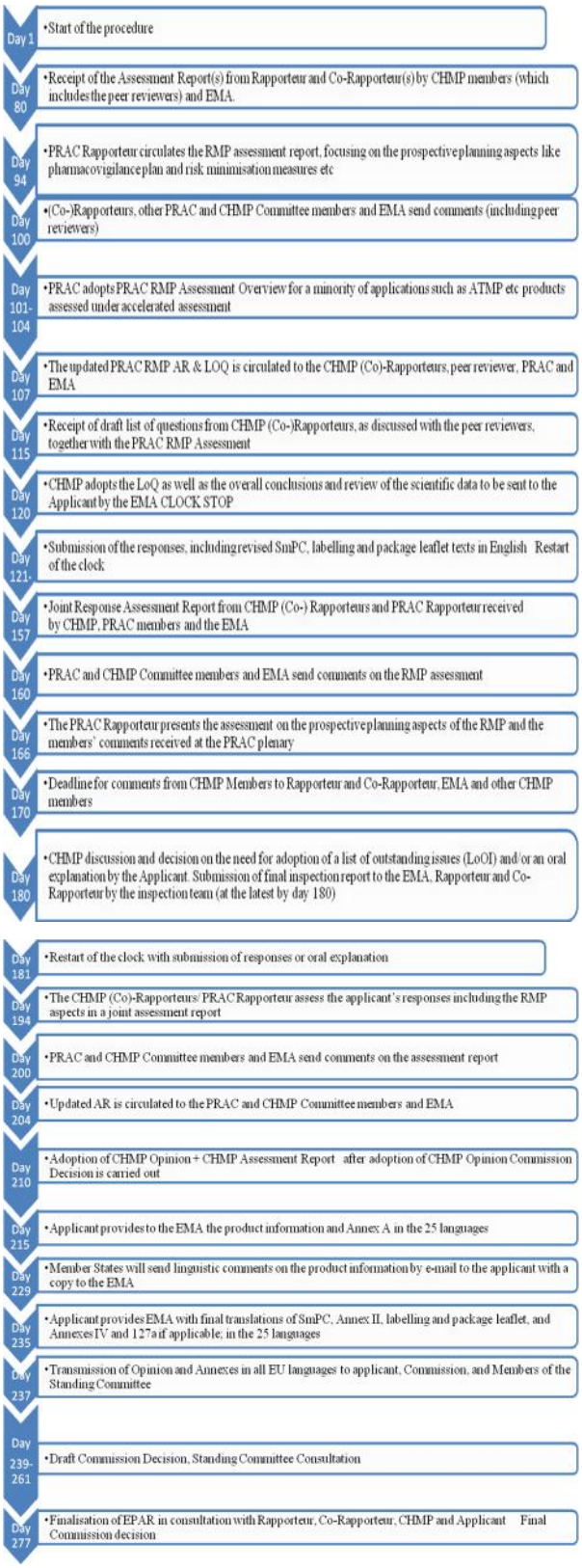
Drug Approval in Europe:
Centralized Procedure :
Single marketing authorization valid in EU.

Mutual Recognition Procedure:
medicine authorized in one EU Member State can apply for this authorization to be recognized in other EU countries.

Nationalized Procedure:
marketing authorization in one member state only.

Decentralized Procedure:
simultaneous authorization of a medicine in more than one EU country if it has not yet been authorized in any EU country and it does not fall within the mandatory scope of the centralized procedure

Centralized Procedure:



Mutual Recognition Procedure:

Approx. 90 days:

Before Submission:

To CMS:

Applicant requests RMS to update Assessment Report (AR) and allocate procedure number.

Day -14:

Applicant submits the dossier to CMS. RMS circulates the AR including SmPC, 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, CMSs and applicant.

Day 60:

Applicant sends the response document to CMSs and RMS

Until Day 68:

RMS evaluates and circulates a report on the applicant's response document to CMSs.

Day 75:

CMSs send their remaining comments to RMS, CMSs and applicant.

Until Day 80:

A break-out session (BOS) can be organised around Day 75 (but may take place between days 73 – 80).

Day 85:

CMSs send any remaining comments to RMS, CMSs and applicant.

Day 90:

CMSs notify RMS and applicant of final position (and in case of negative position also the CMDh secretariat of the EMA). If consensus is reached, the RMS closes the procedure. If consensus is not reached, the points for disagreement submitted by CMSs are referred to CMDh by the RMS within 7 days after Day 90.

Day 150:

Final position adopted by the CMDh If consensus is reached at the level of CMDh, the RMS closes the procedure. If consensus is not reached at the level of CMDh, the RMS refers immediately the matter to EMA for CHMP arbitration.

5 days after Close of Procedure:
Applicant sends high quality national translations of SmPC, PL and labelling to CMSs and RMS.

30 days Afterclose of Procedure:
Granting of national marketing authorizations in the CMSs subject to submission of acceptable translations.

All days mentioned in this document should be regarded as calendar days.

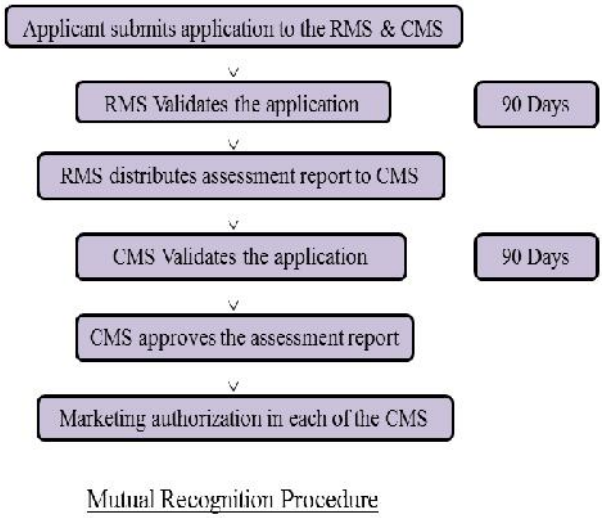


Fig 1: Mutual Recognition procedure

Decentralized procedure:
Pre-procedural Step:
Before Day -14:
Applicant discussions with RMS, RMS allocates procedure number. Creation in CTS.

Day –14:
Submission of the dossier to the RMS and CMSs Validation of the application. Positive validation should only be indicated in CTS, not via e-mail.

Assessment step I
Day 0:
RMS starts the procedure. The CMS are informed via CTS.

Day 70 :
RMS forwards the Preliminary Assessment Report (PrAR) (including comments on SmPC, PL and labelling) on the dossier to the CMSs and theapplicant

Until Day 100:
CMSs send their comments to the RMS, CMSs and applicant. It may also be sufficient for the CMS to indicate in CTS only in case there are no additional comments.

Until Day 105:
Consultation between RMS and CMSs and applicant. If consensus not reached RMS stops the clock to allow applicant to supplement the dossier and respond to the questions.

Clock-off period:
Applicant may send draft responses to the RMS and agrees the date with the RMS for submission of the final response. Applicant sends the final response document to the RMS and CMSs within a period of 3 months, which can be extended by a further 3 months.

Day 106:
RMS restarts the procedure following the receipt of a valid response or expiry of the agreed clock-stop period if a response has not been received. The CMS are informed via e-mail and CTS will be updated accordingly.

Assessment step II:
Day 120 (Day 0):
RMS sends the DAR, draft SmPC, draft labelling and draft PL to CMSs and the applicant

Day 145 (Day 25):
CMSs send comments to RMS, CMSs and the applicant. It may also be sufficient for the CMS to indicate in CTS only in case there are no additional comments.

Day 150 (Day 30):
RMS may close procedure if consensus reached, proceed to national 30 days step for granting MA.

Until 180 (Day 60):
If consensus is not reached by day 150, RMS to communicate outstanding issues with applicant, receive any additional clarification, prepare a short report and forward it to the CMSs and the applicant All days mentioned in this document should be regarded as calendar days.

Day 195 (at the latest):
A Break-Out Session (BOS) may be held at the European Medicines Agency with the involved MSs to reach consensus on the major outstanding issues.

Between Day 195 and Day 210:
RMS consults with the CMSs and the applicant to discuss the remaining comments raised.

Day 210 (Day 90):
Closure of the procedure including CMSs approval of assessment report, SmPC, labelling andPL, or referral to Co-ordination group. Proceed to national 30 days step for granting MA.

Day 210 (at the latest):
If consensus on a positive RMS AR was not reached at day 210, points of disagreementwill be referred to the Co-ordination group for resolution.

Day 270 (at the latest):
Final position adopted by Co-ordination Group with referral to CHMP/CVMP for arbitration in case of unsolved disagreement.

National step:
5 days after close of Procedure:
Applicant sends high quality national translations of SmPC, labelling and PL to CMSs and RMS.

30 days after close of the Procedure:
Granting of national marketing authorization in RMS and CMSs if outcome is positive and there is no referral to the Co-ordination group. (National Agencies will adopt the decision and will issue the marketing authorization subject to submission of acceptable translations).

30 Days After Close of CMD Referral Procedure:
Granting of national marketing authorization in RMS and CMSs if positive conclusion by the Co-ordination group and no referral to the CHMP/CVMP. (National Agencies will adopt the decision and will issue the marketing authorization subject to submission of acceptable translations).The drug filing and different aspects of obtaining United States Food and Drug Administration (USFDA) and European Medicines Agency (EMA) approval for a drug in order to get a Marketing Authorization in US and Europe and their effective role in improving the standards laid down by them and the comparative requirements are listed below.

3. DISCUSSION

Table 1: Principle Difference Between Usa and Eu Submission

Requirements	USA	EU
Agency	One Agency USFDA	Multiple Agencies • EMA • CHMP • National Health Agencies • European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) • European Centre for Disease Prevention and Control (ECDC) • European Food Safety Authority (EFSA) • European Chemicals Agency (ECHA) • European Environmental Agency (EEA)
Registration Process	One Registration Process	Multiple Registration Process • Centralized (European Community) • Decentralized (At least 2 member states) • Mutual Recognition (At least 2 member states) • National (1 member state)
Braille code	Braille code is not required on labelling	Braille code is required on labelling
Post-approval changes	Post-approval changes in the approved drug: • Minor changes – Annual Report • Moderate changes – CBE, CBE 30 • Major changes - PAS	Post-variation in the approved drug: • Type IA Variation • Type IB Variation • Type II Variation

Table 2: Administrative Requirements Between Usa and eu Submission

Requirements	USA	EU
Application	ANDA / NDA	MAA
Approval Timeline	~18 Months (18-21)	~12 Months (210 -277Days)
Fees	• Application w/Clinical - $2,374,200 • Application w/o Clinical and Supplement w/Clinical - $1,187,100 • ANDA Application - $76,030 • PAS application - $38,020 • DMF - $42,170	• Marketing-authorisation application (single strength, one pharmaceutical Form, one presentation) - From €278,200 • Extension of marketing authorisation (level I) and Type-II variation (major variation) - €83,500
Presentation	eCTD	eCTD

Table 3: Manufacturing and Control Requirements Between Usa and Eu Submission

Requirements	USA	EU
Packaging	A minimum of 1,00,000 Units	Not Required
Process Validation	required at the time of submission	Required
Batch Size	1 pilot scale or minimum of 1 lakh units whichever is higher.	2 pilots scale plus 1 lab batch or minimum of 1 lakh units whichever is higher.

Table 4: Stability Requirements Between Usa And Eu Submission

Requirements	USA	EU
Number of batches	3 Pilot Batch or 2 Pilot Batch and 1 Small scale	2 Pilot Scale (If API Stable) - DCP 3 Primary Batches - CP (If API unstable)
Condition: Long term stability, Accelerated stability,	Long term: 25°C/60%RH Accelerated: 40°C/75%RH(0,3,6 months); Intermediate: 30°C/65%RH	Long term: 25°C/60%RH Accelerated: 40°C/75%RH(0,3,6 months) Intermediate: 30°C/65%RH
Minimum time period at Submission	6 Months accelerated and 6 Months long term	6 Months accelerated and 6 Months long term

Table 5: Bioequivalence Requirements Between Usa and Eu Submission

Requirements	USA	EU
CRO (Audits)	Audited by FDA	Audited by MHRA
Reserve Sample	5 times the sample required for analysis	No such requirement
Retention of samples	5 years from date of filing the application	No such requirement

4. CONCLUSION AND SUMMARY:

- Drug approvals in the United States and Europe are the most demanding in the world.
- The primary purpose of the rules governing medicinal products in US and Europe is to safeguard public health.
- It is the role of public regulatory authorities to ensure that pharmaceutical companies comply with regulations.
- There are legislations that require drugs to be developed, tested, trialed, and manufactured in accordance to the guidelines so that they are safe and patient's well - being is protected.

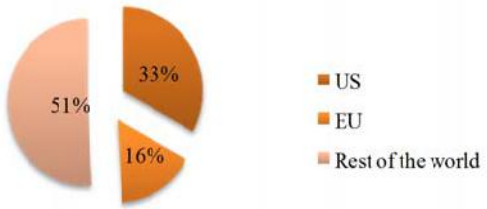


Fig 2: Pharma Market Share

5. ACKNOWLEDGEMENT:

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