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REVIEW ARTICLE

OVERVIEW ON EUROPEAN REGULATORY AFFAIRS AND THE ROLE OF SUBMISSIONS IN REGULATORY AFFAIRS

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ABSTRACT

Regulatory Affairs is the profession which act as a liaison between the Pharmaceutical Industries and Regulatory Authorities. In this Regulatory Affairs Publishing of submissions to the Regulatory Authority is playing crucial role. In this article, I have done analysis on European Regulatory Agency and the types of submissions used for the publishing of documents and finally the role of eCTD in Submissions. We can conclude that eCTD is becoming mandatory for all the countries in Europe mad also all other countries in future.

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INTRODUCTION

European Medical Agency [http://www.ema.europa.eu/ema/] is a body of the European Union (Decentralised body). It is not a part of European commission and has its own legal personality. EMEA suggests the scientific opinions to the European Commission and the commission conveys the decisions to the applicants.

European Regulatory Environment Evolution

EMA and EU Institutions

Being the decentralised agency of the EU, EMA gives opinions on scientific criteria basis and finally commission issues decisions based on that review. Commission must give proper explanation in case of decision against the EMA.

Institutions

1. European Commission (Director General Enterprise, Director General Health and Consumer Protection).
2. European Parliament: Environmental Department, Publics Health Department, Food Safety Committee.
3. Other EU Agencies:

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EMCDDA

The European Monitoring Centre for Drugs and Drug Addiction

ECDC

European Centre for Disease Prevention and Control

EFSA

European Food Safety Authority

Translation Centre.

EMA and National Authorities

EMA conducts Centre for Management Development meetings and elects Secretariat, 11times per year. EMA attends HMA (Heads of Medicines Agency) meetings 4times per year. Maintain regular reports between Heads of Medicines Agency and Management board, 4times per year.

Scope of the EMA responsibilities

Centralised procedure,
Referral Procedure,
Paediatric Medicinal Products,
Orphan Medicinal Products,
Advanced Therapies Medicinal Products

1995 (Birth of EMEA)
↓
2000 (Orphan Drugs Regulation)
↓
2003 (Annexure 1, 2001/83/EC [CTD])
↓
2004 (Part of new legislation comes into force)
↓
2005 (New legislation came fully into force)
↓
2006 (New Legislation on Paediatrics)
↓
2007 (New Legislation on Advanced Therapies)
↓
2008 (Enlargement scope of Centralised Procedure)
↓
2010 (New Legalisation on variation and Pharmacovigilance)
↓
2012 (Implementation of new legislation of PRAC)
↓
2013(Croatia is added on July, 2013)

EMA Organisation chart

Executive Director
Executive support←↓→Legal service
Senior Medical Officer←↓→Internal audit
↓

1. Human medicines special areas Safety and Efficacy of medicines Quality of medicines
2. Pharmacovigilance and risk management Regulatory Procedural and committees Support Medical Information Compliance
3. Veterinary Medicines Product Data Management
4. IT Development IT User and Application support IT infrastructure Operation
5. H.R. Accounting Infrastructure Services Meeting & Conference Management

EMA Structure

- EMA legal representative is Executive Director.
- Management Board supervise the EMA and the scientific activities are carried out by 7 committees and working parties.
- EMA Secretariat supports all the Management Board, Committees and their working parties

Management Board

Management Board is made up of

- 1 representative of each of 28 Member states
- 2 Representatives of the European Commission
- 2 Representatives of the European Parliament
- 2 Representatives of the Patients Organisation
- 1 Representative of Doctor's Organization
- 1 Representative of Veterinarian Organization
- In addition, 1 observer each from the Iceland, Liechtenstein and Norway

Committees of European Medicines Agency

- Committee for Medicinal Products for Human Use [CHMP]
- Pharmacovigilance Risk Assessment Committee [PRAC]
- Committee for Medicinal Products for Veterinary Use [CVMP]
- Committee for Orphan Medicinal Products [COMP]
- Committee for Herbal Medicinal Products [HMPC]
- Committee for Advanced Therapies [CAT]
- Paediatric Committee [PDCO]

Committee for Medicinal Products for Human Use [CHMP]: All questions related to medicines for human use will be answered by CHMP.

It comprises of

- Chair elected by serving CHMP members
- 1 Member and an alternate nominated by Iceland and by Norway
- 1 Member and an alternate nominated by Iceland and by each of 28 Member States
- 5 co-opted members chosen among experts nominated by MS (Or) the agency.

Pharmacovigilance Risk Assessment Committee

The Pharmacovigilance Risk Assessment is for assessing and monitoring safety issues in human medicines.

It is composed of

- A Chair and Co-chair elected by serving PRAC members
- 1 Member and an alternative nominated by each of 28 Member States
- 1 Member and an alternative nominated by Iceland and Norway
- 6 independent scientific experts nominated by the European Commission;
- 1 member and an alternate nominated by the European Commission after consultation of the European Parliament to represent healthcare professionals;

1 member and one alternate nominated by the European Commission after consultation of the European Parliament to represent patient'sorganizations.

Committee for Medicinal Products for Veterinary Use

European Union Member States along with consultation with the Agency's Management Board will nominate the members and alternates of the CVMP.

Based on their qualifications and expertise they are selected. Period is 3 years.

The CVMP is composed of:

- A chair, 1 member and an alternate nominated by each of the 28 Member States;
  1 member and an alternate nominated by Iceland and by Norway;
- 5 co-opted members;

Committee for Orphan Medicinal Products

Applications related to Orphan Medicinal Products are reviewed by Committee for Orphan Medicinal Products.

It is composed of

- A chair
- 1 member nominated by each of the 28 Member States;
- 3 members nominated by the European Commission to represent patient's organisations
- 3 members nominated by the European Commission on the Agency's recommendation;
- 1 member nominated by Iceland and one by Norway.

Committee for Herbal Medicinal Products

The committee on Herbal Medicinal Products is responsible for formulating the Agency's scientific opinions regarding the quality, safety and efficacy of herbal medicinal products. The members in HMPC are experts in the field of herbal medicines. It is composed of

- The Committee has one member and one alternate member nominated by each of the 28 EU Member States and by Iceland and Norway. The chair is elected by serving HMPC members.
- Five additional members who are additional expertise to the HMPC
- Clinical pharmacology;
- Experimental / non-clinical pharmacology;
- Toxicology;
- Pediatrics medicine;
- General and family medicine.

Committee for Advanced Therapies

This Committee is responsible for assessing the quality, safety and efficacy of advanced therapy medicinal products (ATMPs). The CAT is composed of:

- 5 members or co-opted members of the Committee for Medicinal Products for Human Use (CHMP),
- 1 member and one alternate appointed by each European Union (EU) Member State.
- 2 members and two alternates appointed by the European Commission to represent clinicians;
- 2 members and two alternates appointed by the European Commission to represent patient associations.

Paediatric Committee

This committee is responsible for assessing the content of paediatric investigation plans and adopting opinions on them. The PDCO is composed of:

- 5 members of the Committee for Medicinal Products for Human Use (CHMP),
- 1 member and one alternate appointed by each European Union (EU) Member State that is not represented by the members appointed by the CHMP;
- 3 members and alternates representing healthcare professionals; 3 members and alternates representing patient associations.

Role of Submissions in Regulatory Affairs

Regulatory Affairs is a profession in the pharmaceutical industry which is playing a crucial role in the safety and efficacy of Drugs and Drug products [http://ec.europa.eu/health/files/eudralex/vol-2/a/vol2a_chap1_2013-06_en.pdf]. Regulatory affairs acting as a barrier between the Pharmaceutical Industries and Regulatory Bodies, There are different types of Regulatory bodies in different countries like:

USFDA: Food and Drug Administration, USA;

PMDA: Pharmaceuticals and Medical Devices Agency, Japan;
CDSCO: Central Drugs Standard Control Organization, India;
Health Canada;

EMA: European Medical Agency, Europe Countries.

Regulatory Affairs professional will work on the Drug and Drug Products, and prepare the Dossiers for the required application. CMC people will work on the Dossier preparations usually there will be filling of all the Dossier Forms. There will be different types of Forms for the Marketing Authorization Approvals in different Countries. Ex: Form: 21CFR 314.81: NDA, ANDA, AADA; Form: 21CFR 312.32: IND Applications.

Role of Publishing Department

This is the department where the Dossiers will be finalized and submitted. Publishing Department plays a crucial role in the submission of applications to the agencies. Duties of Publishing Department: Identification of Submissions, Description of Submissions, Handling eCTD Software, Preparing the PDFs, Arranging Sequence numbers, giving Bookmarks, Giving Hyperlinks, Technical validation of documents.

Types of Submissions

There are different types of submissions in submitting to the agencies. They are

- eCTD Electronic Submission
- Non eCTD Electronic Submission[Nees]
- Paper Submission

Electronic submission: submitting files in Electronic format.

eCTD

It is a electronic type of registering files (or) submission which is organized according to 3.2 version of ICS eCTD Specifications and EU Module 1 Specifications [http://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/ucm153574.htm; (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm328835.htm#validation; http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm328835.htm#reports; http:// www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM333969.pdf).

It is the submission of PDF (Portable Document Format) usually, and it is stored in the eCTD directory structure and accessed by XML backbone. Integrity of files will be guaranteed by MD5 Checksum.

Advantages of eCTD

- Less space
- Single application format
- Superior technology
- Ease of application

eCTD Technical structure

- Portable Document Format (PDF)
- Sequence Numbers
- Bookmarks and Hypertext links
- XML
- Other file formats
- Validation of eCTD

Checklist of eCTD: There are some points which need to check in eCTD submission. They are:

- eCTD Software checking and Training of Software
- Compiling
- eCTD Bookmark and Hyper linking
- QC of eCTD
- Submitting eCTD on CD/DVD or Use electronic gateway

Life cycle attributes of eCTD:

These are different attributes usually used in the submission

New: Submitting the new files in submission
Append: Adding the additional information to the existing file
Replace: Replacing the existing file with other files
Delete: Deleting the file which is not required by Agency USFDA has started using eCTD by Jan 2008, EU made using by Jan 2010 and made it mandatory.

NeeS

It is a Non eCTD Electronic submission and any information from the applicant will be sent to agency for Marketing Authorization Procedure. It is nearly a collection of electronic files or bunch of files. There should be Text Searchable in documents. Text Searchable should not be there for the Certificates and Signatures.

Contents of NeeS

- PDF
- Hyperlinks between files
- Bookmarks for navigating
- Table of content
- Critical file names

Differences between eCTD and Nees

eCTD	NeeS
Software is needed(eCTD)	No Software needed Adobe Acrobat is enough
XML is back bone	No XML
TOC (Table Of Contents) not there	TOC is backbone
Life cycle management is present	Absent
Can be made in to tool	Bunch of files or folders
Each sequence is unique	It can be used for all countries agencies
If an eCTD Dossier is made and submitted and during the next submission it should be in eCTD format only	In NeeS we can use both eCTD and NeeS format for resubmission of dossiers.

Paper Submission

Paper submission is still accepted but not encouraged. The structure of paper submission should be in accordance with one of the following formats

- XML backbone of eCTD
- Overall TOC of NeeS

The location of each document in the submission dossier must be marked by Tab Identifier.

The name of the Tab Identifier will be the name of the Document.

Validations

Validators will identifies and rates the severity of errors encountered like

- High errors
- Medium errors
- Low errors

Current Status of CTD in Europe

Most of the countries in European Union accepted the eCTD which is most acceptable format for submission of document [http://www.ema.europa.eu/ema].

RESULTS AND CONCLUSION

In the developing stage of Pharmaceutical Industries, all major agencies making mandatory of electronic submissions using different tools and so it is important to know the guidelines of eCTD and NeeS guidelines for the error less submissions andwe can conclude that most of the countries in European Union is accepted the eCTD format for submission.

Region	List of countries	Acceptable format for submission			
		eCTD	NeeS	Paper	Comments
EU	Austria	Accepted	Accepted		
	Belgium	Accepted	Accepted		
	Bulgaria	Accepted	Recommended		
	Croatia	Accepted	Accepted	Recommended	Module 1 and 3 required in paper format
	Cyprus	Accepted	Accepted	Accepted	
	Czech Republic	Accepted			
	Denmark	Accepted			
	Estonia	Accepted	Recommended		
	Finland	Accepted	Accepted		
	France	Accepted	Accepted		
	Germany	Accepted	Recommended	Recommended	
	Greece	Accepted	Accepted	Recommended	For paper filing - Modules 1, 2, and 3 will be accepted in Paper and Modules 4 and 5 must be in eCTD format
	Hungary	Accepted	Accepted		
	Iceland	Accepted	Accepted		
	Ireland	Accepted	Accepted		
	Italy	Accepted	Recommended	Recommended	
	Latvia	Accepted			
	Liechtenstein	Accepted	Accepted		
	Lithuania	Accepted	Accepted		
	Luxembourg	Accepted	Accepted		
	Malta	Accepted	Recommended		
	Netherlands	Accepted	Accepted		
	Norway	Accepted	Accepted	Recommended	
	Poland	Accepted	Accepted	Recommended	Marketing authorization, renewals, variations, MA withdrawal and transfers are only accepted in paper format
	Portugal	Accepted	Accepted		
	Romania	Accepted			
	Slovakia	Accepted	Recommended		
	Slovenia	Accepted	Accepted		
	Spain	Accepted	Accepted	Recommended	
	Sweden	Accepted	Accepted	Recommended	Switch from Paper to eCTD /NeeS are accepted for Variation and Renewal application
	United Kingdom	Accepted	Accepted		

Common Validators are

- EURSValidator
- LORENZ eValidator
- Belgium NeeS checker

Common Errors in Submissions

- Hyperlinks errors
- Bookmarks errors
- Table of content errors
- Missing files
- No filable forms
- More than one form of submission

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