

Critical and Comparative Analysis of ANDA Filing of Tablets in India, Europe and US

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ABSTRACT

Abbreviated New Drug Application (ANDA) is an application used for regulatory submission for the authorization of generic drugs and its entry into a brand drug market. Generic drugs are pharmaceutical equivalent to the brand name drugs and distributed without patent protection. Different countries have different requirements for the registration of generic drugs and its own regulatory authority, which are responsible to enforce the rules and regulations, issue the guidelines to regulate the marketing of drugs. Various government agencies in regulating drugs are CDSCO- India, EDQM-Europe, and USFDA-US. Aim of title was to review the generic drug filing and different aspect of obtaining regulatory approval in order to get the marketing authorization in India, Europe & US. Involvement of regulatory in the generic drug development expedites the approval process and they review the queries carefully raised by the regulatory authorities and minimize them. To harmonize the different requirements, CTD format is used for filing the ANDA in respective countries. In this an attempt was made to highlight the difference between the registration requirements for generics drugs in India, Europe & US. The comparison parameters in the generic drug approval among different regions, which gives clear illustration where India lies in its generic drug approval process.

KEYWORDS: ANDA, CDSCO, cGMP CTD, CFR, FDA, ICH

INTRODUCTION

In India the Drug and Cosmetic Act, 1940 and Rules 1945 were passed for regulation of the manufacture, distribution, import, export, sales of cosmetics and drugs. Central Drug Standard Control Organization (CDSCO) was established in India under the Drug and Cosmetic (D&C) Act with an office and its leader Drug Controller General (India) [DCG(I)].

CDSCO is a designated authority for grant marketing license for a generic drug applicant of Abbreviated New Drug Application (ANDA). An ANDA is for those drugs whose patent has been expired and company wishes to market a copy of branded drug. ANDA filing should accompany patent certification, than applicant is able to file an application to Food and Drug Administration (FDA) in Office of Generic Drugs (OGD).

Generic drug products must be harmless, efficient and low cost substitute to the community. The generic drug products "Active Pharmaceutical Ingredient (API), prescribed amount, quality, administration route, strength, use, and performance characteristics must be bio and pharmaceutically equivalent to innovator drugs. The term "abbreviated" is used because clinical and preclinical data is not mandatory to establish safety and efficacy. The reason for reduced cost of generic medicines is they do not require clinical trials and the companies who manufacture generics are not willing to invest in Research and Development (R&D) of new drugs.

FDA's "Approved Drug Products with Therapeutic Equivalence Evaluation" in which they publish a list of innovator and generic drug product, also called as "Orange Book" because of its orange colour cover. It

allows generics to win FDA marketing approval by submitting bioequivalence studies.

GENERIC DRUG MARKETING

To gain regulatory approval for the generic drug, all companies have to prove that its generic version is pharmaceutically equivalent to the original. If the generics chemical makeup is the same, it's assumed that the preclinical, clinical trials and research are as applicable to the generic drug as they were to the original. Regulatory requirements like forms, CTD format whatever is required to the respective country must be compiled by the applicant and submitted to the respective regulatory authority.

REVIEW OF ANDA FILING

INDIA¹

CDSCO is the Centre Drug Authority (CDA) for discharging function assigned to central government under D&C Act. In India issuance of license to manufacture approved drug, to monitor the quality are regulated both at state and central level. At the state level state drug regulatory authorities and at central level CDSCO under the Ministry of Health and Family Welfare (MHFW) are authorized for issuance of license. If innovator drug is already approved within four years of the first authorization and an applicant is seeking authorization for the generic version of that drug, it will be considered as a new drug (see rule 122-E of Drugs and Cosmetics Act 1940 and Rules 1945) and hence, require seeking approval from central regulatory authorities. If innovator drug is already approved and four year time has been expired from the first authorization and applicant wants to manufacture the generic copy then require seeking approval from the state regulatory authorities.

NEW DRUGS ALREADY APPROVED IN THE COUNTRY

FOUR YEARS OLD DRUG:

Applicant submits approved status from CDSCO website of the already approved drug and an application is made directly to the State Licensing Authority (SLA) to receive a permission to manufacture a new drug under:

- Form (24):

Application for the grant of or renewal of a license to manufacture for sale or for distribution of drugs other than those specified in Schedule C, C (1) and X.

For example: Oral Solid Dosage (OSD), Gels, Fluids, and Sprays etc.

- Form (27):

Application for grant or renewal of a [license to manufacture for sale or for distribution of] drugs specified in Schedules C and C (1) [excluding those specified in Schedule X]. For example: Parenteral, Vitamins, Minerals.

LESS THAN FOUR YEARS OLD DRUG:

Applicant submits Form 44 to DCG (I) CDSCO. Recommendation from New Drug Advisory Committee (NDAC) needed, once they give the approval then applicant can apply for Form (46) [Permission/Approval for manufacture of new drug formulation]

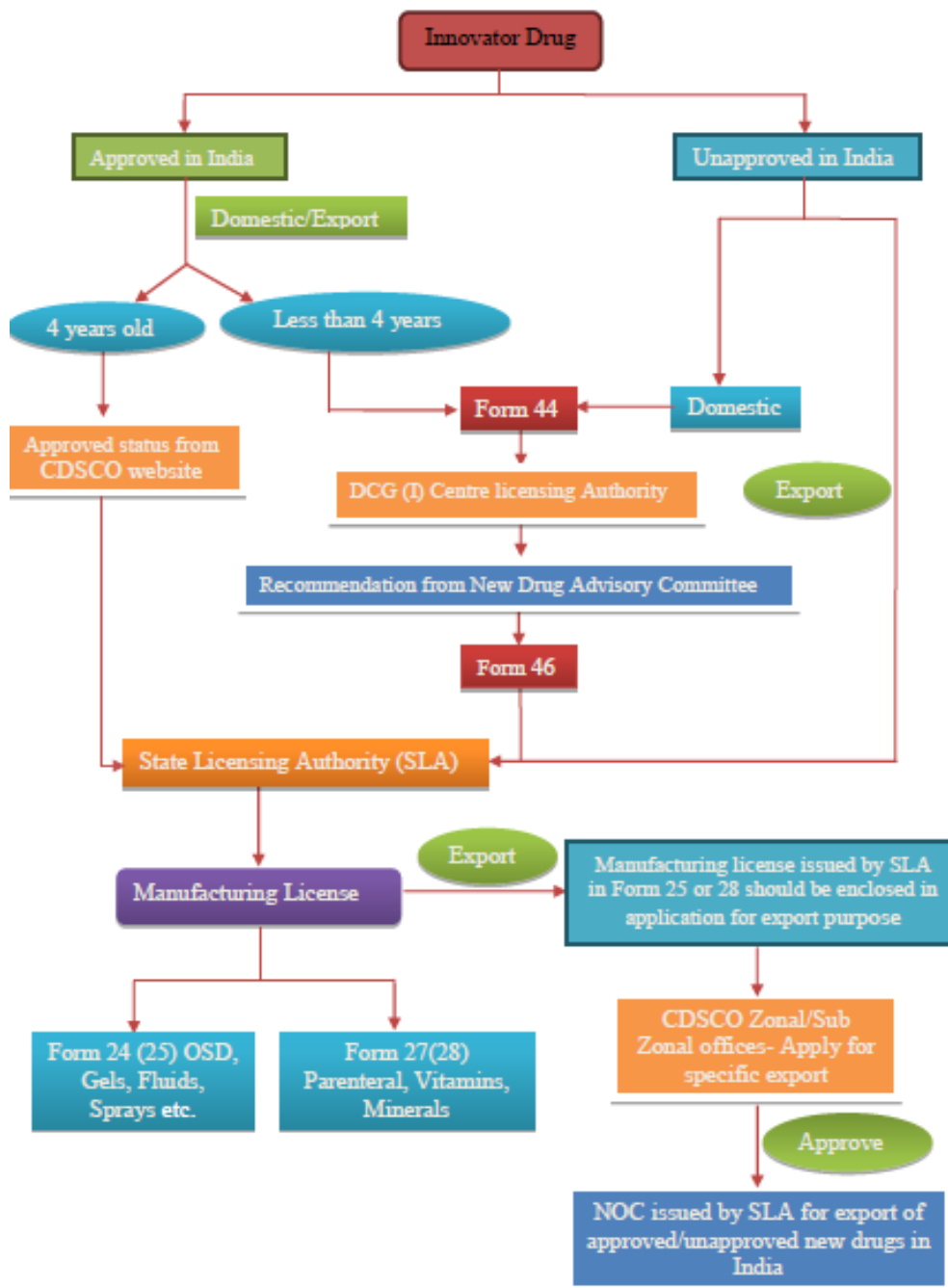
NEW DRUGS UNAPPROVED IN THE COUNTRY (DOMESTIC)

Applicant has to follow the same procedure given as above for approved drug (less than four years old)

NEW DRUGS UNAPPROVED IN THE COUNTRY (EXPORT)

Applicant holding valid license copy in Form (25) and (28) can obtain NOC from CDSCO Zonal/Sub Zonal offices. Applicant applies for export specific permission in their respective CDSCO Zonal/Sub Zonal offices in SLA On approval from SLA, they issue the NOC for export of approved/unapproved new drugs in India.

AUTHORIZATION OF NEW DRUG IN INDIA

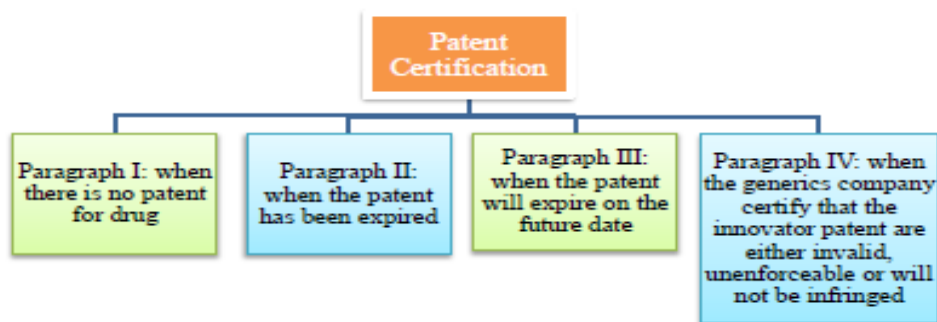
**GENERAL INFORMATION REGARDING CTD SUBMISSION IN INDIA:**

- Type of application: M&M
- CTD is the only format for submission of information to CDSCO
- If applicant has permission for manufacturing of bulk drugs provide copy otherwise can provide consent letter from the approved source regarding supply of material.
- Clear and unmistakable information should be provided
- Text and tables must be printed clearly, left side margin must be kept large and prepared using margin.
- Submitted document printed on both sides of the page, for text Times New Roman and 12 point font and for table context and text 9-10 point font.

- Page numbering must be at the document level and numbered consecutively by page.
- All pages include a unique header or footer and if section contains more than 1 document a specific table of content can be included.
- Submit 1 hard copy and 3 soft copies i.e. Compact Disc (CD) in Portable Document format (PDF).
- Hard copy: Sides and front of file must be labeled with the applicant's company name, drug name, date of submission and the file number.
- Volumes should not be more than 3 inches thick, CD must be marked using a marker pen with applicant's company name, date of submission and drug name.
- Applicant should preserve a duplicate copy of the dossier for further references.
- During cross referencing from module 1 to other specify the volume, page number and tab identifier of the referring document.2
- Send the application to office

UNITED STATES (US): FDA

Pharmaceutical companies may produce a generic drug when patent on the branded drug expires. The expiration of a patent removes the monopoly of the patent holder on the drug. In US generics entry into market begins when manufacturer submits ANDA in US. A generic that can be marketed/produced for the drugs under four certification option:



GENERAL INFORMATION REGARDING CTD SUBMISSION IN US:

- Type of Application: ANDA
- ANDA checklist
- Organizing data: All documents should bind in separate volumes, if documents are combined in volumes they should be separated with named tab identifiers.
- Number of copies: The regulation require for ANDA submission archival, review and field copies.
- Paper size: US letter size paper (8.5 x 11 inches) for all submission
- Paper margins: Margin of at least 0.75 inches from the bound edge of the printed page and other margin can be small as 0.25 inches and print on both side of the paper.
- Fonts: Times New Roman 12 point size, 9-10 point is considered for tables and 10 point for footnotes.
- Binding volumes: Pages should be submitted in 3 holes punch on the left side of the page and bound with fasteners. The front cover of the binder should be 9 x 11.5 inches and back cover 9 x 12 inches.
- Volume size: not more than 2 inches thick
- Volume numbering: Number the volumes by modules
- Volume identification: In the central information of the front cover following information should be print:
 - Name of the applicant
 - Product name
 - Application number
 - Module name and number on the lower right hand corner of each binder print the volume number. For example: x of y volume (6 of 30 volumes)

On the upper right hand corner print "Module__Volume__". For example: Module 3 Volume 1.17.

- Pagination: Page number should be at the document level not at the module and volume level.
- Packing carton: Ship the volumes in boxes measuring 14 x 12 x 19.5 inches and include the information:
 - Name of the applicant
 - Drug name
 - Volume number
 - Number the boxes 1 of n, 2 of n etc.
 - Type of copy should be mentioned (archival, review)^{3,4}
 - For paper submission, postal carrier package must be addressed to the document room and submitted to the Office for generic drug filing.

EUROPE: EUROPEAN UNION (EU)

It is a unique economic and potential partnership between 27 countries of the Europe. There is one single market developed by Europe through a standardized system of laws also known as internal market apply in all member state. On 1st January 1994 the agreement of European Economic Area (EEA) was established between the member states of European Community (EC), the European Free Trade Association (EFTA), later on and the EU.⁵

Marketing Authorization (MA): A medicinal product may only be placed on the market in EEA when MA has been issued by the competent authority for the member state for its own territory.

National authorization: Application must be submitted to the competent authority of the member state.

Union authorization:

Mandatory scope: The drug contain the new active substance, when such substances has not been authorized before 20th November 2005 and drugs for acquired immune deficiency syndrome, cancer, diabetes, neurodegenerative disorder, orphan medicinal products must be authorized via the Centralized Procedure (CP).

Optional scope: The drug containing new active substance and constitute a significant therapeutic, scientific innovation or granting of community authorization medicinal product is in the interest of patients at community level. If drug falls under this criteria than the applicant has a choice of using either the centralized or national (decentralized/ mutual recognition) procedures.⁶

GENERAL INFORMATION REGARDING CTD SUBMISSION IN EUROPE:

- Organizing and preparing the CTD: The information given in CTD must be transparent and definite so it helps the reviewer to facilitate the reviewing of application.
- Font size: Times New Roman 12 point size text, for table it should be large enough to easily readable, even after photocopying.
- In Module 3 product information section it is mandatory to use the (Quality review developments) conventional.
- Pagination and segregation: Each document should be numbered starting from page 1, except for individual literature references and all pages should include header or footer.
- Each document should be prepared in line with the CHMP/ICH/2887/99 revision1 organization CTD recommendation.
- Application is submitted to respective regulatory authority in CTD/ Non eCTD Electronic Submissions (NeeS) or eCTD format.⁷

COMPARATIVE STUDY BETWEEN INDIA, EUROPE AND USTable 4.2: Comparative study of filing generic drugs in India, Europe and US: ^{8,9}

S. No.	General	INDIA	EUROPE	US
1	Regulatory authorities	CDSCO	EMA	USFDA
2	Procedure	Single procedure	Four procedures: a) Centralized b) Decentralized c) Mutual recognition d) National	Single procedure
3	Submission format	Paper CTD	eCTD is not fully mandatory but NeeS is submitted along with the paper submission for MAA	eCTD is mandatory/paper CTD
4	Applicable regulation	Drug and Cosmetics Rules 122A, 122B, Appendix I, IA of Schedule Y	Directive 2001/83/EC-Article 8(j)	USFDA (CFR) documents and FDA section (e.g. 505 (j) for ANDA)
5	Application	M&M	MAA	ANDA
6	Submission requirements	One hard copy and 3 soft copies i.e. CD in (PDF) format)	One Copy	Three copies- (Archival, Review & Field)
7	Approval timeline	One year	One year	One and a half year
8	Data exclusivity	Approved drug in India: · 4 years old · Less than 4 years old Unapproved drug in India	10 years or 8+2+(1)	Patent certification (paragraph I,II,III,&IV)
9	Validity of license	Three years	Five years	Five years
10	Web address	http://www.cdscsco.nic.in/forms/Default.aspx	http://ec.europa.eu/health/documents/eudralex/index_en.htm http://www.ema.europa.eu/ema/	http://www.fda.gov/

Comparative study of CTD requirements for filing of generic drugs in India, Europe and US: 10, 11

MODULE-1				
S.No.	Parameters	INDIA	EUROPE	US
1	General information Covering letter, Table of Components (Module 1 to Module 5)	Required	Required	Required

2 a)	Administrative information: Forms	Form 44 (See Annexure V) (Application for grant of permission to import or manufacture a new drug or to undertake clinical trials) Along with treasury challan of requisite amount Fee- Rs.15,000	Application form Fee- €278,500	Form 356h (See Annexure IX) (Application to market a New or Abbreviated New Drug or Biological for Human Use) Form 3794 (GDUFA Generic drug user fee cover sheet) Fee- \$58,530
b)	Agent authorization	Not required	Not required	Required
c)	Legal and critical document For import and marketing For manufacturing and marketing	Copy of BE/NOC issued by CDSCO Copy of drug sale license (Form20B, & Form 21B), Copy of Free sale certificate, Batch release certificate, Copy of Form 11 Copy of existing manufacturing license in Form 25/28/26 COA	Not Required	Field copy certification, financial certification, debarment certification, patent information
d)	General information of drug product	Required	Required	Required
e)	Product information already approved in the country	Regulatory status in other countries	Required	Required
f)	Labelling	Summary of packaging procedures for Indian shipments Proposed draft labels and cartons: Primary package label Secondary package	Summary of Product Characteristics (SPC) Specimen for labels and cartons Mock-ups for outer and immediate packaging of medicinal product	Package inserts are provided for drug product. Labelling history also provided Proposed draft label for each strength and container including package size
g)	Annotated draft labelling (side by side) compared with RLD	Not Required	No annotation required as such but all information is provided in SPC and package insert	Required
h)	Summary of testing protocol	Required	Not required	Not required
i)	Medicinal product name specify in Braille format	Not required	Required	Not required

j)	Information(curriculum-vitae) about experts	Regarding involvement of expert	Non-clinical and clinical experts name, address, date and signature	Not required
k)	Request for waiver	Not required	Not required	Required
l)	Data/market exclusivity	Not required	Required	Patent certification
m)	Environment Assessment Statement (EAS)	Not required(GMO) or Non-GMO	Environment risk certification is given in the information for Genetically Modified Organism Agreement (EPA) of US.	For categorical exclusion certification in compliance with the law of Environmental Protection
n)	Risk management system	Not Required	Required	Risk management plan for the Policy Management System (PMS) and controlling the adverse effect by proper management (mitigation strategy)
o)	Other Requirements	Brief profile of manufacturer research activity and its business activity in domestic and global market. Samples of drug product is required	Information relating to Pharmacovigilance	Approved suitability petition must be submitted if required

MODULE-2

S. No.	Parameters	INDIA	EUROPE	US
1	(2.3) Quality based review	Not required	Not required	Required

MODULE-3

S. No	Parameters	INDIA	EUROPE	US
1	(3.2.S.1.1) Specified numbers	Chemistry Abstract Number (CAN)	CAN	Central File Number (CFN), Data Universal Numbering System (DUNS), Facility Establishment Identifier (FEI),
2	(3.2.S.4.6) Justification of Specification	Not required	Required	Required
3	(3.2.R) Regional Information	Not applicable	i) Process validation scheme are provided ii) According to ICH limit mention in the Q3C(R3) declaration is impurities given for the residual solvents limits or present in drug	i) Executed batch record and blank master batch record for manufacturing and packaging are provided ii) According to USP declaration is impurities given for the residual solvents limits or present in

			substance and excipient iii) Information on components are generally not provided iv) Comparability protocol not provided v) Methods validation packages are not provided vi) Certificate of suitability obtained from EDQM are attached with this section vii) Bovine Spongiform Encephalopathy (BSE) and Transmissible Spongiform Encephalopathy (TSE) certificate are not attached	drug substance and excipient iii) Information on components including and not limited to applicant and suppliers COA for drug substance lots, package material etc. are provided Comparability protocol are provided iv) Comparability protocol are provided v) Methods validation packages are provided vi) Certificate of suitability are not provided vii) BSE and TSE certificate are to be attached
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MODULE 5[2,12]

S. No.	Parameters: For BE studies	INDIA	EUROPE	US
1	Study design	Two separate (one in fasted state and other in the fed state), Two way cross over design, Parallel design	Randomized, Crossover, Non replicated	Randomized, Crossover, Non replicated
2	Fasting/Fed state studies	Fasting and Fed	Fasting	Fasting and Fed
3	Number of subjects	Minimum number of subjects not less than 16	More than 12 (Min 80% power of acceptance criteria)	Sufficient to achieve adequate power
4	Study dose (test reference)	Made by the manufacturer in or outside India	Made by the manufacturer RLD in Europe	Made by the manufacturer RLD in US
5	Sampling points	12-18 samples to be collected, to be continued upto 3 or more half-lives, atleast 3-4 samples should be collected at T_{max}	3-4 samples during terminal log linear phase	3 samples during absorption phase, 3-4 at T_{max} , 4 points during elimination phase
6	Reserve sample	Not required	Not required	5 times sample required for analysis
7	Analytical method validation parameters	Stability of the drug, Specificity/Selectivity, Sensitivity, Precision, Accuracy, Recovery, Range and Linearity	Precision, Intermediate precision, Accuracy, Repeatability, Detection, Limit of Quantitation (LOQ), and Linearity range	Accuracy, Precision, Sensitivity, Selectivity, Reproducibility, Calibration curve, LOQ and Stability range

8	Moieties to be measured in plasma	Active drug/Metabolite	Active drug/ Metabolite if applicable	Active drug/ Metabolite if applicable
9	Pharmacokinetics Parameters	For plasma-time concentration curve: C_{max} , T_{max} , $AUC_{0-\infty}$, AUC_{0-t} For steady state: $AUC_{0-\tau}$, C_{max} , C_{min}	C_{max} , T_{max} , AUC_{0-t} , $AUC_{0-\infty}$, $t_{1/2}$, λ_z	C_{max} , T_{max} , $AUC_{0-\infty}$, AUC_{0-t} , $t_{1/2}$, λ_z
10	Criteria for BE	90% Confidence index, 80.00-125.00% for C_{max}	90% Confidence index, 80.00-125.00% for C_{max} , AUC_t , $AUC_{0-\infty}$ (For highly variable drugs 75.00- 133.00%)	90% Confidence index, 80.00-125.00% for C_{max} , AUC_t , $AUC_{0-\infty}$
11	Retention of sample followed	As such no requirements but usually 3 years from priority	As such no requirements but usually 3 years from priority date	5 years from priority date
12	Good Clinical Practices (GCP) requirements	CDSCO GCP guidelines	ICH GCP guidelines	ICH GCP guidelines

RESULT

Different countries have their own regulatory framework for the registration of products in their respective countries. In India issuance of license to manufacture approved drug, to monitor the quality are regulated both at state and central level. If innovator drug is already approved within four years of the first authorization and an applicant is seeking authorization for the generic version of that drug, it will be considered as a new drug. If innovator drug is already approved and four year time has been expired from the first authorization and applicant wants to manufacture the generic copy then require seeking approval from the state regulatory authorities. Different forms are being used for obtaining manufacturing approval in India which are already discussed. In US companies may produce a generic drug when patent on the branded drug expires. The expiration of a patent removes the monopoly of the patent holder on the drug by following the method of patent certification through paragraph filing to the concern authority .In Europe medicinal product may only be placed on the market in EEA when MA has been issued by the competent authority for the member state for its own territory. All these authorities required submitting of required documents in prescribed format respective to the territory. Now a days authorities has started electronic submission of documents instead of the

paper submission for the convince of companies as well as authorities.

CONCLUSION

Generic drug companies bring the generic version of the innovator drug product to the market in quick time and a lower cost when compared to innovator drugs, thereby benefiting the public and making healthcare more affordable. These drugs present an equally safe and efficacious alternative to established medicinal products, which contain well known, rigorously tested active ingredients. Generic drugs are well tested high quality drugs which undergo strict regulation by regulatory authority and they are only granted approval through an extensive authorization process. This process ensures the safety and efficacy of the generic drug medicine available in the market. Differences in composition between the generic and RLD are possible, but only regarding the excipients. This includes a discussion on ANDA format, review process, information on launching generic drug into the market, obtaining approval from the regulatory affairs and list of regulatory authorities worldwide responsible to safeguard the public health by ensuring that pharmaceutical company comply with regulation so that safe and effective medication reach in market. Each regulatory authority has its own procedure to review drug submission filed and it can vary

substantially with respect to how the drug submission is handled, the composition of review team, review timelines so on. CTD is a common means of presenting the technical requirements and is an acceptable format in India, Europe and US. The current work describes the differences in the technical regulatory requirements as well as administrative requirements (Module 1) for fittings with Indian, European and US regulatory authorities. Information submitted must be unambiguous and

transparent to facilitate the review, help a reviewer to become quickly oriented. In this work regulatory guidelines are compared on the basis of various parameters involved in the filing of generic drugs. The comparison made is of benefit to fraternity in pharmaceutical companies and academics to understand the filing of generic drugs and the differences in filing requirements in India, Europe and US.

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