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# An overview on comparative study of registration requirements for generics in US, Canada and Europe

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## ABSTRACT

Generic Drug Product approval is most stringent and crucial process for company with different rules and regulation in different country. For the registration of the product company has to follow regulatory rules and requirement of country specific agency. Company should apply product marketing authorization as per norms of country requirements and should manage life cycle of that product throughout market. Need to understand and describe the various regulatory requirements for the generic drug approval process and comparison of regulated country. To understand the technical requirements required to market medicines in regulated pharmaceutical market. To evaluate similarities and differences within regulated market of U.S, Canada, and Europe. To understand and evaluate differences of post approval Changes within regulated market.

Keywords: ANDA; ANDS; EMEA; US; Canada; Europe; Regulatory Registration Requirements.

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Review Article

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## INTRODUCTION

Generic Drug is a pharmaceutical drug product identical, pharmaceutical equivalent and Bioequivalent or comparable to reference listed drug product in dosage form safety, strength, quality, performance characteristics, and route of administration and intended use. An important factor for increasing demand of generics drug is lower as well as decline price of product which attract to customer. This generic drug product manufactures without notification or permission of innovator Drug Company after expiration of patent and exclusivity right.<sup>[2]</sup> Using bioequivalence as a tool to establish therapeutic equivalence between a reference and a generic product certainly forms the basis for market approval of multisource drug products as generic drug is a copy of branded drug. FDA detailed studied indicate that the generic drug request submitted to FDA for sanction must include the next:

- The generic drug 'pharmaceutical equivalent' to the brand.
- The 'active Ingredient' is the same as that of the brand.
- The manufacturer is capable of making the drug in correct process.
- The manufacturer is capable of making the drug consistently.
- The right amount of the ingredient effect on that part of the body on the targeted area.
- The 'inactive ingredient' of the drug is safe.
- The container in which the drug will be shipped as well as sold is appropriate.
- The label is the same as the brand-name drug's label
- Relevant patents or legal exclusivities are expired.<sup>[1]</sup>

#### Patent Protection of Drug

A company that developed a new drug product or drug substance should granted a patent for the drug itself, for usage for manufacturing and for method of administration and releasing the drug into blood stream. Hence a company must have more than one

Regulation as per agencies	US	Canada	Europe	
Agency	Single Agency USFDA	<ol> <li>Health Canada</li> <li>Therapeutic Product Direc- torate of Health Product Food Branch. (HPFB)</li> </ol>	Multiple Agencies 1. EMEA (European Medical Eval- uation Agency) 2. National Health Agency	
Registration process	Single Registration Process	s Single Registration Process	Multiple Registration Process. 1. Centralized Process: (European Community) 2. Decentralized Process: (At least 2 Member State) 3. Mutual Recognition Process: (At least 2 Member State) 4. National (1Member State)	
Application	Abbreviated New Drug Applic tion (ANDA)	a- Abbreviated New Drug submis- sion (ANDS)	Marketing Authorization Applica- tion (MAA)	
Stability data	The Stability data for accele ated Studies are submitted for 3 Months at the time of origin Submission	r- The Stability data for accelerated or Studies are submitted for com- al plete 6 Months at the time of orig- inal Submission	The Stability data for accelerated Studies are submitted for com- plete 6 Months at the time of origi- nal Submission	
Approval time	18 Months	2 Years	12 Months	
Pharmaco- peia	US Pharmacopeia	British Pharmacopeia, European Pharmacopeia, US Pharmacopeia	British Pharmacopeia, European Pharmacopeia	
	Table	e 2: Administration requirements		
Applicati	on Form 356 (h)	HC/SC 3011	eAF Version 1.23.1.0	
Agent	Required	Required	Not Required	
Trend for previous submission non e- CTD)         Archival Copy –BLUE Review Copy –RED Field         Module: 1- RED Module, 2-YELLOW Mod- ule, 3- BLUE Module, 4- GREEN Module, 5- BLACK		LLOW Mod- Not Required EN Module,		
Fees	\$178,799.00	\$37,358.25	Different for different countries Application	
Paper size fo mission	r sub- n Paper size (8.5 x 11 inches 11.69)inches Font 12 (New Times man)	x 11)Paper size (8.5 x 11) inchesPapeches11.Times Ro-Font 12 (New Times Roman)Font 1		
	Table and Figures i.e. 8-10	size Table and Figures s i.e. 9	ize Table and Figures size i.e. 8-10	

Table 1: Regulation

patent for a drug. Patent provides company to exclusive right of a drug for 20 years.<sup>[1]</sup> Usually about 10 years pass between the drug is discovered (when the patent was filed) as well as the time of drug is approved for use, exit the company only about half of the patent life to the new drug.

After a patent has expired, other company can sell as well as produce a generic version of a drug as the agency approved it. These generic drugs are sold at a lower price than the Branded drug the main reason is that the generic manufacture does not have to recover the original cost of the drug development process and hence not much spend on marketing of drug. A generic drug may be sold under its Brand name or its Generic name (A branded generic drug) but not under the brand name used by the original patent holder.

Not all expired patent drugs have generic version. sometimes it's very complex to duplicate or tests are not available to compare the generic drug acts similarly as the branded drug. Eventually the market for the Drug is so small that producing another version is not profitable.<sup>[3]</sup>



		Table 3: Certifica	tions		
Regulation as per agen- cies	US	Car	nada		Europe
Environment assessment	EAS (Environment Assess- ment Statement) for cate- gorical exclusion certificate in compliance with the law of EPA of US is Provided	EAS is required for new Substances in product regulated under the F& D act as per the New Substances Notifica- tion Regulations (NSN) of the Canadian Environmental Protection Act. (CEPA)		Declaration for Environmental Risk Assessment is given with the Information from GMO or Non -GMO. The fresh/New Cer- tificate is Provided	
Department Certificate	Required	Not Such	Required	Ν	ot Such Required
Patent /ex- clusivity statement	Para I /II /III /IV	Pref	erred		Required
Certificate of suitability	It's Not Applicable	Pref	erred	Certifi mono Pharn Europo Quality	cate of Suitability to the graph of the European nacopeia (CEP) for the ean Directorates for the y of Medicines (EDQM) 'ALIDITY: 5 years.
Field copy certificate	Required Not required for biological licensing applica- tion (BLA)	Not Such	Required	N	lot Such Required.
	Tab	ole 4: Raw materia	l controls		
Regulation as per agencies	US		Canada		Europe
Definition of drug mas- ter file	A Drug Master File (DMF) is a Submission to the FDA. The main Objective is to Support regulatory requirement and to prove the quality, Safety, and efficacy.		A DMF is a referen provides information specific process or nents used in the m turing processing Packaging of a d	ce that n about compo- anufac- and rug.	In Europe drug Master File is Known as Ac- tive Substance Master File (ASMF) or Euro- pean Drug Master File (EDMF).
Type of DMF	Five Type of DMF: TYPE I: Man cilities, Operating Procedure and II: Drug Substance, Drug Subst and Material Used in their Prep Packaging, TYPE IV: Excipient Essence or Material used in the TYPE V: FDA Acceptance Refe	ufacturing Site Fa- d Personnel, TYPE ance Intermediate paration, TYPE III: , Colorant, Flavor, neir Preparation, rence Information.	Four Type of DM TYPEI: Substance Intermediates and als Used In their Pr tion, TYPE II: Pack Material, TYPE III: ants, Flavor and Ot ditives, TYPE IV: D Form.	IFs: , Drug Materi- epara- kaging Color- her Ad- losage	Two Type of DMFs of: Drug Substances TYPE I : Applicant Part of DMF – Open Part(Non confiden- tial), Type II: Re- stricted Part of DMF - Closed Part- (confi- dential)
Letter of Authoriza- tion	Required	Required Required			Required
TSE/BSE	TSE and BSE certificate are no section whereas Subr DMF.	e not attached in this submitted in this to be a section whereas Sub- ted in DMF.		ificate n this ubmit-	TSE and BSE certifi- cate are not attached in this section whereas Submitted in DMF.
Spectra Chromato- gram	Required		No Such Require	ment	No Such Requirement
<ul> <li>Module 1:</li> <li>Module 2:</li> <li>Module 3:</li> <li>Module 4:</li> <li>Module 5:</li> </ul>	<b>At: e-CTD format</b> Administrative information CTD Summaries Quality Nonclinical study reports Clinical study reports	Out Eur	line of registration ope Regulation Administration r Certifications Raw material cor	require equiren ntrols	ements of US, Canada

## Table 2. Cortificati

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		Table 5: Comp	osition			
Regulation as per ag cies	en-	US Canada			Europe	
IIG database (Inactive ingredien	t) Must be v	Must be within IIG Limit No such D		se Re- N	o such Database Re- quired	
Iron content	Maximum Daily	Dose Should not be more	No such Reguir	ement N	lo such Reguirement	
	than t	5 mg / Day	· .			
	Tab	le 6: Manufacturii	ng and control			
Regulation as per ag	gen-	US	Canada		Europe	
	A minimum	of 100,000 units	A minimum of 100		A minimum of 100,000 units	
Batch size	10% of Total C	OR ommercial produc-	A minimum of 100	J,000 A		
	1070 01 10101 0	tion	unito			
Packaging	A minimum	of 100,000 units	No Such Requirer	nents No	Such Requirements	
Number of batche (validation batche	es s)	3	2		2	
	Table 7: F	inished product co	ontrol requirement	ts		
	Regulation as per age	ncies US	Canada	Europe		
_	Justification	ICH Q(6A	) ICH Q(6A)	ICH Q(6A)		
_	Assay	95 -105 %	<u> </u>	95 - 105 %	_	
_	Colour Identification	on Not Require	ed Not Required	Required		
_	Water contents	Required	Required	Not Required	<u> </u>	
Regulation as per	911		nada		Europo	
agencies	03	Ca	liaua		Luiope	
Inspection	FDA	Health F Food Bra	Product and nch (HPFB)	MH	IRA /PICS/EMA	
QP certification	No required	No re	equired		Required	
Clause	21 CFR Part 210 &211	Division 2, Part C o lation	of Food & Drug Regu- of HPFB	Guideline	Volume 4,EU es of GMP for Medici- nal Products	
Import distribution site	No Such Re- quired	Rec	quired	No	Such Required	
	Т	able 9: Stability re	quirements			
Regulation as per agencies	ļ	JS	Canada		Europe	
Number of batches	;	3	2		2	
Conditions	25°C 6	60 % RH	25°C 60 % R	Н	25°C 60 % RH	
(standard for room	30°C 6	30°C 65 % RH		H	30°C 65 % RH	
temperature storage	e) 40°C 7	40°C 75 % RH		Н	40°C 75 % RH	
Data at time of Sub	<ul> <li>6 months acceler</li> </ul>	ated and 6 months	6 months accele	rated 6	months accelerated	
IIIISSION	on long term 24 Months and can be extend up to		36 Months based of	on Sta- 36	Months based on Sta-	
Maximum shelf life	36 Months base	d on Stability data	data bility data		bility data	
Container Orientatio	ntainer Orientation Invert &Upright / Horizontal		Invert & Uprig	ht	Invert & Upright	
Photo Stability         Light Sensitive Products         Light Sensitive Prod		oducts Lig	ht Sensitive Products			

Table 5: Composition

- Composition
- Manufacturing and controls
- Finished product control requirements
- Gmp requirements
- Stability requirements

- Labelling requirements
- Bioequivalence requirements
- Outside testing labs
- Post-approval requirements

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## Table 10: Labeling requirements

Regulation as per agen- cies	US	Canada	Europe	
Number	NDC (10 Digit)	DIN (8 Digit)	Not Required	
SPL/PLR	Required	Not Required	Not Required	
Prescription Status	Rx	Pr, N	РОМ	
Braille code	Not Required	Not Required	Required	
Labels	Vial/Cartons/PI	Vial/Cartons/Pl/Product Mono- graph	Vial/Cartons/PI/SPL	
Side by side comparison	Annoted Draft Labeling (Side by Side) for label and carton compared with the RLD with Proper annotation is Provided	Annoted Draft Labeling (Side by Side) for labels and carton com- pared with the RLD with Proper annotation is Provided	No Annotation (Side by Side) for labeling is Provided, Labeling and Package leaflet text as per inno- vator to be Provided.	
Packaging Insert	Packaging insert are provided for drug product in labeling	Packaging insert are provided for drug product in labeling	SPC (Summary of product char- acterization) is provided about drug product in labeling	

Table 11: Generic drug label checkpoint of

Difference Code	US	Canada	Europe
1	Company Name / Logo	Company Name / Logo	Company Name / Logo
2	Braill Code	Drug Identification Number	Braill Code
3	Generic name	Generic name	Generic name
4	Rx/OTC Status	Rx/OTC Status	Rx/OTC Status
5	Strength	Strength	Strength
6	Pack size	Pack size	Pack size
7	Name and Address	Name and Address	Name and Address
8	Barcode	Barcode	Barcode
9	Expiry	Expiry	Expiry
10	Control/Lot No.	Control/Lot No.	Control/Lot No.
11	Label Claim	Label Claim	Label Claim
12	Storage instructions/Conditions	Storage instructions/Conditions	Storage instructions/Conditions
13	Any other text/number	Any other text/number	Any other text/number
14	-	2D Code	-

## Table 12: Bioequivalence study

Regulation as per agencies	US	Canada	Europe	
CRO	Audited by FDA	Audited by FDA/Health Canada	Audited by MHRA/EMEA (Medicine and Healthcare Product Regulatory Agency)	
Fasting/fed state studies	Fasting or Fed/ both Depends on Product mono- graph	Fasting or Fed/ both Depends on Product monograph	Fasting	
Analytical method valida- tion parameters	Accuracy, precision, selectiv- ity, sensitivity, reproducibility, calibration curve, LOQ and stability	Accuracy, precision, selectivity, sensitivity, reproducibility, cali- bration curve, LOQ and stability	Accuracy, precision, selectivity, sensitivity, reproducibility, calibra- tion curve, LOQ and stability	
Study dose	Made by the Manufacturer USA Reference listed drug in (Test Reference)	Made by the manufacturer Ca- nadian reference product (Test Reference)	Made by the manufacturer Euro- pean reference product. (Test Reference)	
Retention of samples	5 years from the date of filing the application	No such requirement, but usu- ally followed	No such requirement., but usually followed	
Sampling points	12–18 samples, more Samples should be collected at Tmax	At least 2 samples before ex- pected Tmax,	12-18 samples per subject/dose	
Study dose	Made by the manufacturer reference listed drug in USA (Test Reference)	Made by the manufacturer refer- ence listed drug in Canada (Test Reference)	Made by the manufacturer refer- ence listed drug in Europe (Test Reference)	

		Table	13. Outside di			
		Regulation as per agencies	US	Canada	Europe	
		GDEA Certificate	Required	Not Required	Not Required	
		c-GLP/c-GMP Certificate	Required	Not Required	Not Required	
		Contractual Agreement	Not Required	Not Required	Required	
		Table 14	4: Post approva	l changes		
Differ-						
ence	ence US		Canada		Europe	
Code						
Guide- lines	SUPA	C (Scale up and Post Ap- proval Changes)	Supplem	Supplements		riations
Туре	Post-ap 1. Mo 2. Mo 3. Majo	pproval changes in the ap- proved drug: Minor changes (CBE 0) derate changes (CBE 30) or changes (Prior Approval Changes)	Post-approval changes in the approved drug: 1. Minor changes 2. Moderate changes 3. Major changes		Post-variation in the approved drug 1. Type IA Variation (Do and tell) 2. Type IB Variation (Tell- Wait and Do Procedure) 3. Type II Variation (Major Changes)	

Table 12: Outside GMB labs



Figure 2: Generic Drug Label as per United States



Figure 3: Generic drug label as per Canada



Figure 4: Generic drug label as per Europe

## CONCLUSION

World Pharmaceutical market is developing very fast but regulatory profile is different for various countries. The primary purpose of the rules governing medicinal products in US, Canada, Europe is to safeguard public health. It is difficult to harmonize and switch the drug product from one country to another Regulatory rules divide world into two parts, one with regulated market like US, Japan, Europe, Australia, Canada while other is semi regulated market such as LATAM Countries, ASEAN Countries, African Countries etc. This is due to the heterogeneity in the regulatory landscape of the various countries. United State is regulated country and it has a well-developed regulation. They developed new guidance for better safety and quality with using different approaches like QbD data integrity and vigilance monitoring FDA gives new guidance day by day. It is always tuff to approved product in US market.

Canada is the 10th largest pharmaceutical market ranked in the world and second largest in North America. Continuous update in regulatory guidelines and rules makes the rules stuff and stringent for Pharma market to approved product in Canada market. The Countries have different standards; there are high registration costs and long timelines for registration of generic drugs. This may account for the low market share of generics in Europe as compared to USA and Canada.

This paper concluded specific requirements, technical Requirements, administration requirements and filling process and Bioequivalence Requirements, labeling requirements conclusion with using comparative study in between United State, Canada and Europe.

## ABBREVIATIONS

ANDA: Abbreviated New Drug Application, CEPA: Canadian Environment Protection Act, CFR: Code of Federal Regulation, c-GMP: Current Good Manufacturing Practices, DIN: Drug Identification Number, DMF: Drug Master File, e-CTD: Electronic – Common Technical Document, EMEA: European Commission and the European Medicines Agency, FDA: Food and Drug Administration, GCP: Good Clinical Practices, GLP: Good Laboratory Practices, GMP: Good Manufacturing Practices, PAS: Prior Approval Changes, QP: Quality of Product, RTR: Refuse to Receive, USFDA: United State Food and Drug Administration, USA: United State of America, WHO: World Health Organization.

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