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Comparison of Regulatory Requirements for Filing of Generic Drug Product in USA and China

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Abstract

Objective: The goal of this study is to understand differences in regulatory requirements, bio-equivalence data, drug registration, approval process and guidelines associated with the generic drug filing in the USA and China and also to provide enough information about the drug safety and efficacy in humans.

Discussion: Generic drugs are identical, indistinguishable with-in an acceptable bio-equivalent level for the innovator product name counterpart esteems to the "Pharmacokinetic and Pharmacodynamics" properties. A generic drug product must meet the standards, established by "United States Food and Drug Administration" in the USA and "National Medical Product Administration" in China to be approved to successfully enter the pharmaceutical market. It must be bioequivalent to the branded medicine. In USA, in Module II there is complete information on the quality overall summary, but in China there is complete information about a Drug substance, whereas in module III in USA there is complete information about Drug Substance and Drug Product, but in China module III contains complete information about drug product only.

Conclusion: This compilation provides a view of harmonizing the Generic Drug submissions in these two countries which may reduce the tedious work that has to be done in altering the submission format.

Key words: Bio-equivalence, CTD, Generic Drugs, Generic Drug Submissions.

INTRODUCTION

A **generic drug** is a drug defined as "a drug product that is comparable to a brand/reference listed drug product in dosage form, strength, quality and Performance characteristics, and intended use". It has also been defined as a term referring to any drug marketed under its chemical name without advertising or to the chemical makeup of a drug rather than to the advertised brand name under which the drug is sold. Although they may not be associated with a particular company, generic drug is subject to the regulations of the governments of countries where they are dispensed. Generic drugs are labelled with the name of the manufacturer and the adopted name (non-proprietary name) of the drug.[1]

USA Market

The U.S. pharmaceutical market is the world's most important national market. Together with Canada and Mexico, it represents the largest continental pharma market worldwide. The US pharmaceutical industry is a highly globalized industry, dominated by multinational companies that engage in significant business activity in many countries and whose products are distributed and marketed worldwide.

The US generic drug market has witnessed a transformation over the last three decades. From less than 20% of the total prescriptions, generic drugs now account for the majority of the total prescriptions dispensed in the United States. During 2011-2018, the US generic drug market grew at a CAGR of 13% and currently represents a multibillion dollar industry US generic drug market reached a value of nearly 4 Million prescriptions, Over the past several years, the United States has undergone a major transformation in the pharmaceutical sector. Nearly, 80% of the total prescription drugs in the US consist of generic drugs. They are low-cost versions of the innovator drugs with same dosage, strength, risks, effects, side-effects and intended usage. Generic drugs assure that the medicines are effective and safe for the consumers. Upcoming patent expiry of branded drugs is projected to boost the market growth.[2]

China Market

China's pharmaceutical market is in great shape. The second largest in the world, next to the US, it is also one of the fastest growing. It is expected to surge from $122bn in 2017 to $573.5bn in 2022, a compound annual growth rate of 30%. The country has a large and diverse domestic drug industry, comprising around 5,000 manufacturers. Many of these are small or medium-sized, and base their businesses on generics, active pharmaceutical ingredients (APIs) or traditional Chinese medicine.

In recent years, these companies have benefited from strong government support for innovation. Spurred by policies such as preferential pricing for innovative drugs, China has become the world leader in API manufacturing and exports, and the second highest investor in R&D. The Chinese generics industry has been growing at an extremely strong rate in recent years, even though there is saturation within the overall pharmaceutical market. Generics now account for 90% of the Chinese pharmaceutical industry and the [pattern of rapid growth is expected to continue well past 2020 also].[3]

The main objective of this study is to understand differences in regulatory requirements and guidelines related to registration and approval process of the generic drug filing in USA and China.

DISCUSSION

Generic Drug Product Registration Requirements in USA

1. The eCTD is mandatory for the submission of the drug applications (NDA/ANDA).
2. US FDA guidance (CFR) documents and FDA sections (e.g. 505 (b) for NDA and 505(j) for ANDA) are followed for the preparation of the dossier for the drug approval applications.
3. The applications are different as follows:
    a. For new drug- NDA
    b. For generic drug – ANDA
    c. For biological application – BLA
4. The applicant himself or a GDEA (Generic Drug Enforcement Act) certified and approved agent may directly submit the application to the FDA.
5. Administrative information is different from a cover letter, forms (356h), application information, field copy certification, debarment certification, financial certification, Patent information, and exclusivity.
6. The paper size for the submission is Letter size (8.5x11 inches) with font size 12 in times new roman format. The tables and figures have small font size i.e. 8 to 10.
7. Package inserts are provided for drug product in labeling.
8. Proposed Labels and cartons with proper dimensions similar to that of the RLD (Reference Listed Drugs) labels are provided.
9. The information about the clinical investigators is provided in Module 5 and in financial disclosure Statement section of this module.
10. Request for waiver of *in-vivo* BE studies is provided in module 1.
11. Annotated draft labeling (side by side) for labels and cartons compared with the RLD with proper annotation is provided.
12. The EAS (Environment Assessment Statement) for categorical exclusion certification in compliance with the law of EPA (Environment Protection Act) of US is provided.
13. Risk management Plans section is for the post-marketing surveillance and controlling the adverse effects of the drugs by proper management. This is the part of Clinical Trial Phase IV.
14. The executed batch records for manufacturing and packaging are provided in Module 3.2.R for only single batch.
15. The declaration is given for the residual solvent's limits used or present in the drug substance and excipients according to the USP.
16. Information on components including the name and address of the supplier or manufacturer of the raw material, package material etc. provided in the 3.2.R format.
17. Letter of Access is not mentioned in 3.2.R.
18. Transmissible Spongiform Encephalopathy (TSE) and Bovine Spongiform Encephalopathy (BSE) certificates are not attached in this section whereas submit in DMF.
19. Certificate of suitability (CEP certificate) is not applicable.
20. Comparability protocols are not attached to both the drug substance and drug products.
21. The stability data for accelerated studies are submitted for three months at the time of original submission.
22. Node extension is not allowed in the eCTD XML in software
23. SPL and STF is mandatory by the USFDA in eCTD of a drug registration application.[4]

ANDA Regulatory Review Process

The ANDA process begins when an applicant submits an ANDA to the OGD (Office Generic Drugs) or CDER (Centre for Drug Evaluation and Research). The document room staff process the ANDA assigns it an ANDA number, and stamps a received date on the cover letter of the ANDA. The ANDA is then sent to a consumer safety technician, who reviews the preliminary sections of the ANDA checklist. The submitted ANDA is reviewed taking into consideration bioequivalence of the drug, chemistry and microbiology, and also the labeling. Within the first 60 days following the submission of an ANDA, a filing review is completed. The ANDA regulatory review process of USFDA is simplified as a flowchart below.

Bio Equivalence Review Process

The two main characteristics of a generic drug to be therapeutically equivalent to the innovator drug are to be pharmaceutically equivalent and also bioequivalent. Both the innovator and generic drug should be pharmaceutically equivalent i.e. they should have the same strength, dosage form and same route of administration. The products are said to be bioequivalent when they have similar bioavailability when they are studied under same conditions.

Bioequivalence is determined by evaluation of the AUC and the maximum concentration of drug (Cmax). A generic product is considered to be bioequivalent to the branded product if the 90% confidence interval (CI) of the mean AUC and the relative mean Cmax is 80% to 125%.[5]

Chemistry Review Process

After an ANDA has been accepted for filing by the Registration support branch (RSB) , the Chemistry, Manufacturing and Controls (CMC) section of the application is assigned to the appropriate Chemistry Division and Team, based on the therapeutic category of the drug product. The Chemistry Divisions review the CMC section of ANDAs, Drug Master Files, Supplemental ANDAs, Annual Reports, and Controlled Correspondence. The goal of the chemistry review process is to assure that the generic drug will be manufactured in a reproducible manner under controlled conditions. After designating the chemistry deficiencies as Minor or Major, the APM faxes them to the applicant. When the application is ready for final approval, the approval package is processed through the immediate office and the

applicant is contacted. Chemistry division coordinates with all disciplines prior to full approval, generates the final approval letter for office director

Labeling Review Process

The labeling review process is to ensure that both the innovator and the generic drug have the same labeling. After the final level administrative review and individual disciplines have resolved their deficiencies, the application will either receive a full approval or a tentative approval letter. A full approval letter details the conditions of approval and allows the applicant to market the generic drug product. A tentative approval letter is issued if there are unexpired patents or exclusivities accorded to the Reference Listed Drug (RLD).[6]

Withdraw of Approval of an ANDA

FDA may withdraw/suspend approval of an ANDA when the approval of the listed drug on which the ANDA relies is either withdrawn or suspended. Further, an approval of an ANDA or 505 (b)(2) application may be withdrawn on the basis of evidence showing that the drug is unsafe for use or ineffective or that the ANDA or 505 (b) (2) application contains any untrue statement of material fact. FDA must withdraw approval of an ANDA if it finds that the approval "was obtained, expedited or otherwise facilitated through bribery, payment of an illegal gratuity, or fraud or material false statement", or may withdraw approval of an ANDA if it finds that the applicant has "repeatedly demonstrated a lack of ability to produce drug, and has introduced or attempted to introduce, such adulterated or misbranded drug into commerce".

Once ANDA approved, the applicant may manufacture and market generic drug product to provide a safe, effective, low cost alternative to American public. FDA guidance provides information about applications contents and to ensure that a complete, high-quality application is submitted to FDA. FDA has previously published guidance on the filing process, including the refuse-to-receive standards, which should be reviewed thoroughly to avoid common deficiencies found in ANDA submissions.[7]

Generic Drug Product Registration Requirements in China

1. The first page of the dossiers shall be a directory for application items, which shall be arranged in order as per the "Provisions for Drug Registration" (SFDA Order No. 28). Each dossier shall indicate on its cover: the name of the drug and application item, document item number, and the name, phone number and address of contact person and the applicant.
2. All documents in the dossier shall be printed or copied in A4 size paper. The content shall be complete, standardized, clear, without alteration, and the data must be real and reliable.
3. The documents shall be put in portfolio envelope(s), on which the application classification, registration category, drug name, the envelope number of set X, the total number of envelopes in the set, original or copy, the contact person, phone number and the name of registration application agent shall be indicated.
4. Two sets of complete application dossiers (at least one set is in the original) and one set of review documents in hard copy shall be submitted for registration application. Four application forms (1 in the original and 3 in hard copy) shall be separately put into each set of dossiers (the original application form and a hard copy shall be put in the set of the dossier in the original).
5. "Import Drug Registration Application Form": the drug registration application form submission program could be downloaded from CFDA website (www.cfda.gov.cn); the application form shall be filled in as required, printed and saved, and shall be signed by the overseas applicant, and signed & sealed by its domestic agent.
6. When mailing or submitting the application dossiers, the electronic version of the application form shall be sent to the following e-mail address dedicated for drug registration: slzx@cfda.gov.cn.
7. The data checking code on the electronic and paper application form should be identical.
8. Foreign language materials shall be translated into Chinese.

Other materials required for submission:

1. The verified documents for market access to the country of origin of the drug, approved or recognized by the government of that country or region if the drug has been marketed, if not, the documents can be submitted to SFDA along with clinical study report after the clinical study has been done in China.
2. The copy of the Certificate for Foreign Firm's branch permanently located in China when the applicant's branch located in China filing the application; or the copy of authorization, notarization and the Business License of the China's agency when the China's agency is authorized to submit the application;
3. The patent information and ownership certificate of the drug submitted for registration, or of the formula and technology used in manufacture of the drug, and the guarantee of not constituting an infringement
4. Clinical and scientific documentation substantiating the safety and efficacy of the product (except for generic products the originator product of which has been registered in Hong Kong for over 5years);
5. One set of prototype sales pack (e.g. outer carton, container label, and other component(s) comprising the sales pack) for each pack size of the product, complied fully with the labelling requirements
6. The following document(s) to support the proposed indication(s), dosage, and route of administration and other contents of the package insert (if any): a)copy of reputable references (e.g. American Hospital Formulary Service Drug Information, British National Formulary (BNF), Medicines Compendium, Drug Information Handbook, Drug Facts and Comparisons, Martindale the Complete Drug

Reference or Physicians' Desk Reference); and / or b) documentary evidence showing countries in section 8 (D) (g)(i);

7. Sample of the pharmaceutical substance as it is sold to the purchaser or scanned image in PDF format (scanning based on 300 dpi or higher) or photo graph image in JPEG format (pixel not less than 320×200) of the prototype sale pack or sample sale pack, including the inner container/packaging and the unit dosage form image of the product sample showing its contents in detail.
8. Detailed and complete qualitative and quantitative composition of the finished product.
9. Specifications of the product issued by the manufacturer and document(s) showing compliance with one or more pharmacopoeia.
10. Pharmacopoeia of the People's Republic of China, British Pharmacopoeia, European Pharmacopoeia, International Pharmacopoeia, Japanese Pharmacopoeia and/or United States Pharmacopoeia
11. Detailed method of analysis of the product for all tests stated in the finished products specifications
12. Certificate of Analysis of the representative batch of the finished product, issued by the manufacturers or the company performing the analysis
13. The BE studies should be conducted in accordance with World Health Organization guidance on the "Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchange ability" or another international guideline.
14. If materials of animal origin are used in the manufacturing of the product, documentary evidence of the absence of TSE must be provided.[8]

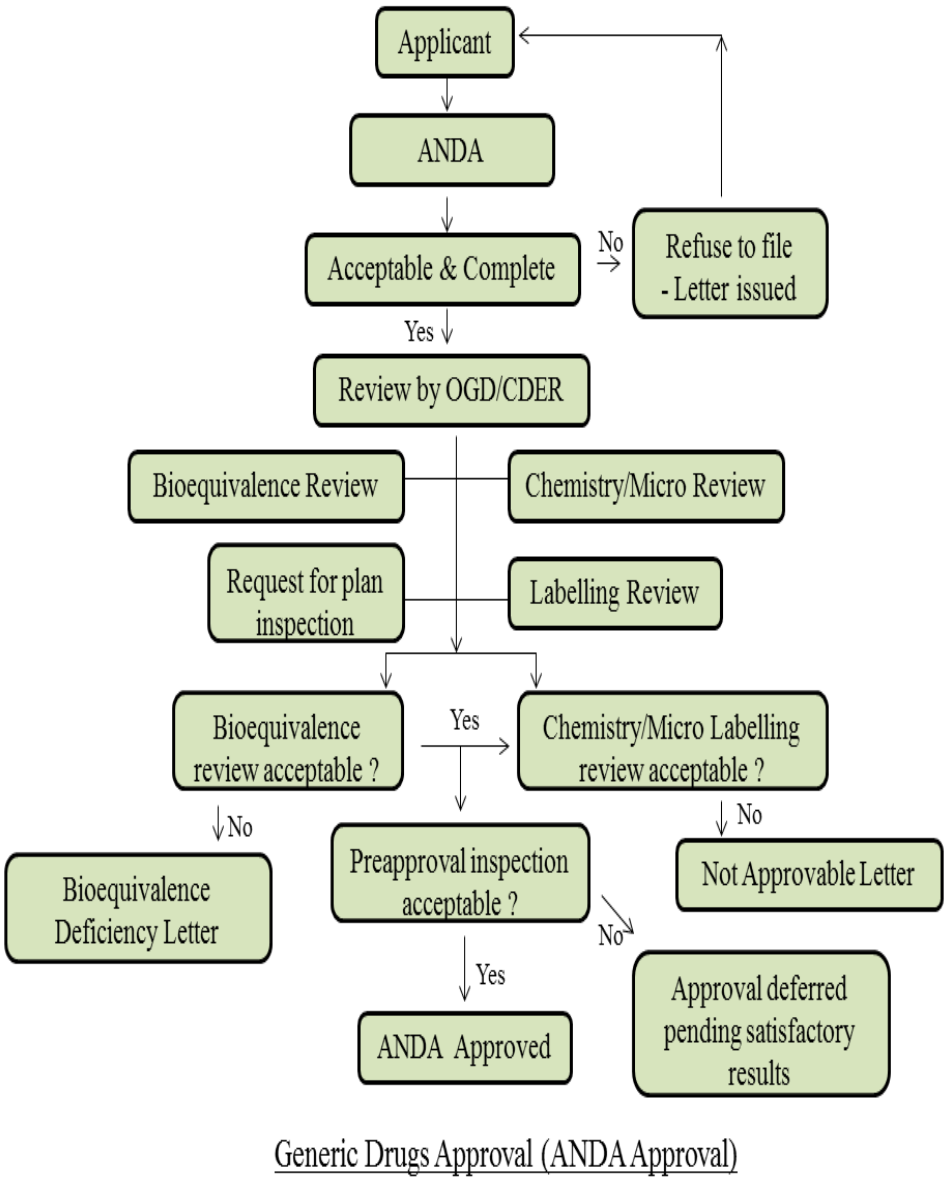
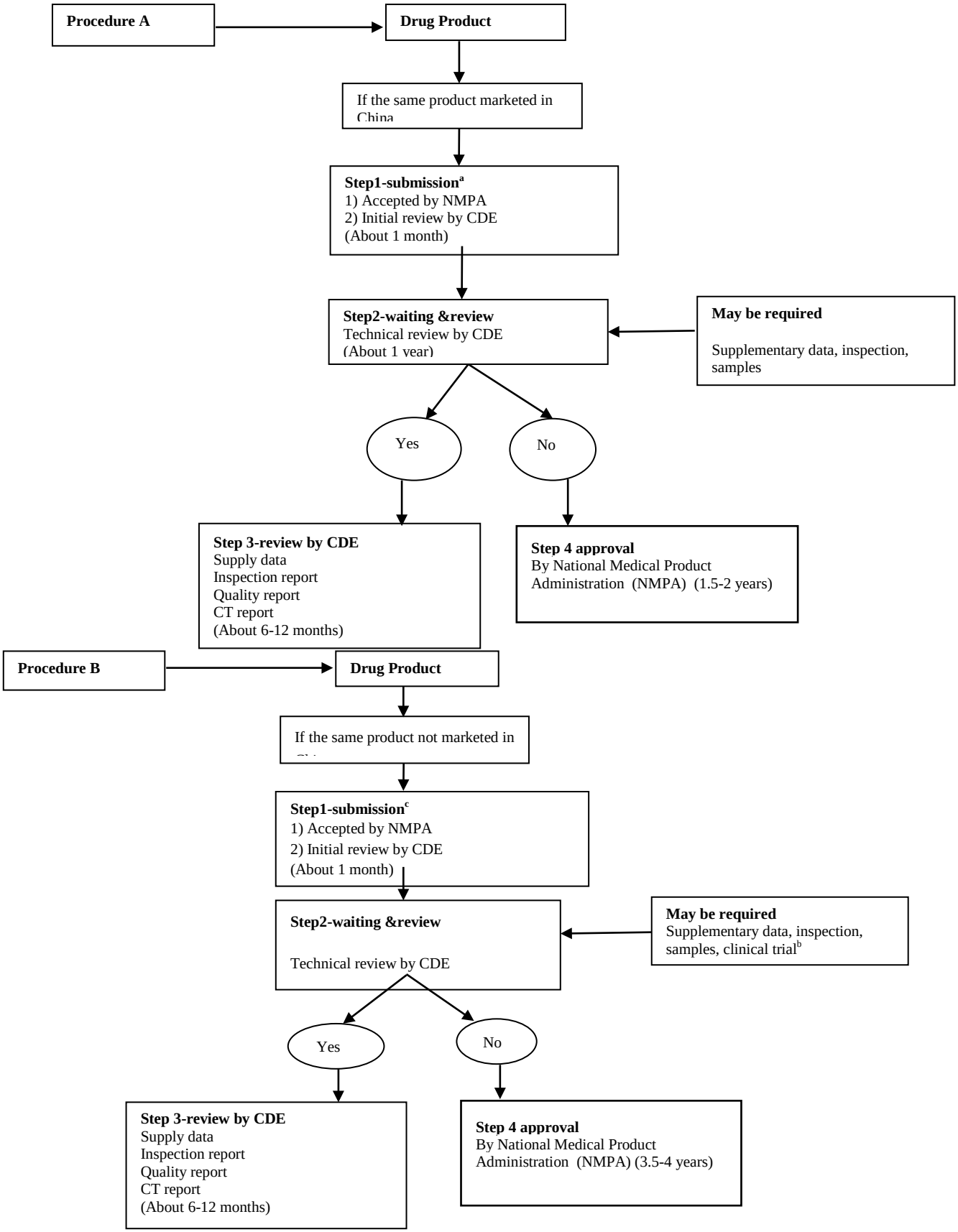


Figure 1: ANDA review process



a: Supplementary documents may be required

[b]: If clinical trial (phase 3) required, it may take 2 more years for conducting the Clinical Trial in China

c: In step 3, when CDE is waiting for the data or reports (if required), times are mainly dependent on our response (supplementary data), NIFDC (quality report), and CFDI (inspection report), 6 months or 6-12 months is estimated time, and the approval time is estimated as well.

Figure 2: Approval procedure of Generic Drugs in China

Approval procedure of Generic Drugs in China

Bioequivalence Testing

The Amended Regulation specifies that the generic drug shall have the same active component, route of administration, dosage form, strength and therapeutic effect as the existing, approved drug. To the extent possible, bioequivalence testing is an important aspect of the SFDA approval process for generic drug applications. Bioequivalence tests include human tests to determine if there is any statistical difference in absorption and absorption speed of the active component between the same or different dosage forms of the same drugs under the same test conditions, by using the methodology of a bioavailability study with pharmacokinetic parameters.

Criteria to get acceptance of overseas BE Studies

1. RLD should meet either one of following criteria's, if RLD used in bio study is procured either from US/EU or Japan.
   (a) MA holder & manufacturer of RLD used in bio study and MA holder & manufacturer of China RLD should be same.
   (b) RLD is acceptable if both the RLD's are from same manufacturer even though MA holder of RLD used in bio study is different with MA holder of China RLD, if parent company is same.
   (c) Manufactured by the same manufacturer but supplied by different MA holder and parent company also different, in this case enough proofs should be submitted showing that Composition, manufacturing process and quality of both the RLD's are same.
2. Procuring RLD from EU has got additional advantage as following
   (d) RLD gets accepted though it is manufactured by different manufacturer if MA holder is same provided enough proofs are submitted showing that Composition, manufacturing process and quality of both the RLD's are same.

**** BE study in both Fasting and Fed condition is mandatory for China filing.**

Table 1: BA/BE Criteria for Generic Drugs Approval in China

	Point 1 (RLD from US/EU /Japan					
BE study in both Fasting and Fed condition is mandatory for China filing.	**Point 1 (RLD from US/EU /Japan**		**Manufacturer**	**MA Holder**	**Remarks**	**comments**
	a	Bio Study RLD China RLD	Same (X)	Same (X)	Acceptable	------
	b	Bio Study RLD China RLD	Same (X)	Different (X or Y) Different (Z)	Parent company is same	Acceptable
	c	Bio Study RLD China RLD	Same (X)	Different (X or Y) Different (Z)	Parent Company is Different	Acceptable, when enough proofs should be submitted showing that Composition, manufacturing process and quality of both the RLD's are same
	Point 2 (RLD from EU) - Advantage					
	d	Bio Study RLD	Different (X)	Same (Z)	-------	Acceptable, when enough proofs should be submitted showing that Composition, manufacturing process and quality of both the RLD's are same

Table 2: Comparison Study:

A) Principle differences between USA &CHINA

Requirements	USA	CHINA
Dossier submission	ANDA	PFDA
Application submitted to	USFDA	SFDA
Registration Process	One Registration Process	One Registration Process 2 types: Standard review procedure Special review procedure
Web Address	https://www.fda.gov/	eng.sfda.gov.cn/
Climatic Zone	Zone I and II	Climatic Zone II
Language	All information should be provided in English	All information should be provided in Chinese and original language
Braille code	Not required on labelling	Not required on labelling
Registration Validity Term	Lifetime	Valid for 5 years
Pharmacopeia's	USP	BP/USP/Ph.Eur

B) Administrative Requirements[9]

Requirement	USA	CHINA
Application	ANDA	Generic drug application
Debarment classification	Required	Not applicable
No of Copies	3	3
Approval timeline	18 months	12-18 Months
Fees	<table><tr><th>User Fee Type</th><th></th><th>FY 2019</th><th>FY 2018</th></tr><tr><td colspan="2">ANDA</td><td>$ 178,799</td><td>$ 171,823</td></tr><tr><td colspan="2">DMF</td><td>$ 55,013</td><td>$ 47,829</td></tr><tr><td rowspan="3">Program</td><td>Large Size</td><td>$ 1,862,167</td><td>$ 1,590,792</td></tr><tr><td>Medium Size</td><td>$ 744,867</td><td>$ 636,317</td></tr><tr><td>Small Size</td><td>$ 186,217</td><td>$ 159,079</td></tr><tr><td rowspan="5">Facility</td><td>Domestic API</td><td>$ 44,226</td><td>$ 45,367</td></tr><tr><td>Foreign API</td><td>$ 59,226</td><td>$ 60,367</td></tr><tr><td>Domestic FDF</td><td>$ 211,305</td><td>$ 211,087</td></tr><tr><td>Foreign FDF</td><td>$ 226,305</td><td>$ 226,087</td></tr><tr><td>Domestic CMO</td><td>$ 70,435</td><td>$ 70,362</td></tr><tr><td></td><td>Foreign CMO</td><td>$ 85,435</td><td>$ 85,362</td></tr></table>	• Generic drugs made in China: 318,000 Renminbi(46,349.61USD) • Generic drugs made outside China: 502,000 Renminbi(73,177.85 USD)
Presentation	Electronic	Paper

C) Finished Product Control Requirements

Requirements	USA	CHINA
Justification	ICH Q6A	ICH Q6A
Assay	90-100%	95-105%
Disintegration	Not required	Required
Color Identification	Not required	Required
Water Content	Required	Required

D) Manufacturing & Control Requirement

Requirements	USA	CHINA
No of Batches	3	3
Process validation	Required at the time of submission	Required at the time of submission
Batch size	A minimum of 1,00,000 units	A scaled-up batch or a full production batch

E) Stability Requirements

Requirements	USA	CHINA
No of Batches	3	3
Condition	25/60 - 40/75	40/75-30/65
Date and Time of submission	6 Months Accelerate & 6 Months long-term	6 months accelerate and 6 months long-term
Container orientation	Inverted & Upright	…….
Clause	21 CFR part 210 & 211	SFDA Order No. 28
QP Certification	Not Required	Required

Table 3: Comparison of General Parameters for the conduct of BA/BE study[9]

Requirements	USA	CHINA
Age (Year)	18 years of age or older	18 to 40 years of age generally, the same subjects Were not different from10 years of age.
BMI (Kg/m^2)	18.5 - 24.9	Standard weight range. (within the normal range according to accepted normal values for BMI; avoid high variances in subjects' body weights)
Gender, ethnicity	Any healthy males and females. If females used in the bioequivalence studies, should not be pregnant	In general, it is recommended to recruit healthy male subjects. The study population should be determined based on the specific situation for each drug product; if female subjects are recruited they should not be pregnant
Number of subject's minimum	12	18-24
Genotyping or phenotyping	Not mentioned	Consider for safety or pharmacokinetic reasons
Dose strength used in the *in vivo* studies	The strength to be used depends upon the type of nonlinearity 1. If the non-linearity is characterized by greater than proportional increases in AUC with increasing dose, conduct the BE studies on at least the highest therapeutic dose 2. If the non-linearity is characterized by less than proportional increases in AUC with increasing dose and results from saturable absorption, conduct the *in vivo* studies on the lowest strength.	Should be performed on the highest strength, unless reasons of safety justify use of a lower strength
Diet and Fluid Requirements	➢ No food should be allowed for at least 4 hours post-dose ➢ Subjects should start the recommended meal 30 minutes prior to administration of the drug product. Study subjects should eat this meal in 30 minutes or less; however, the drug product should be administered 30 minutes after start of the meal. ➢ Standardized meals scheduled at the same time in each period of the study. Total Energy from meal :800-1000 cal (US FDA BA/BE, 2003)	It follows the guidance's and specifications proposed by guidance "Multisource (generic Pharmaceutical products: guidelines on registration requirements to establish interchangeability".
	Following an overnight fast of at least 10h, subjects should be administered the drug product with 240mL (8 fluid ounces) of water. No food should be allowed for at least 4h post-dose. Water can be allowed as desired except for one hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.	At least 8 hours prior to administration of the products. If the Summary of Product Characteristics of the reference product contains specific recommendations in relation with food intake related to food interaction effects the study should be designed accordingly.
Immediate release (IR) solid oral dosage forms	A single-dose bioequivalence study under fasting conditions A fed bioequivalence study should always be conducted for IR formulations, with the following exceptions • When reference product labeling recommends taking on an empty stomach • When test and RLD product are rapidly dissolving, have similar dissolution profiles and contain a drug substance with high solubility and high permeability	A single-dose bioequivalence study under fasting conditions; and do not request a fed bioequivalence study for IR dosage forms
Fed BE study for modified-release (MR) solid oral dosage forms	Single-dose BE studies under fasting and fed conditions	Single-dose BE studies under fasting and fed conditions
Basic study design	The standard study design is a two-period crossover, in which each subject is given the test and reference formulations; Replicated crossover designs may also be used; and Parallel designs may be used for long half-life drugs.	The standard study design is a two-period crossover, in which each subject is given the test and reference formulations; Replicated crossover designs may also be used; and Parallel designs may be used for long half-life drugs.
Add on Design	None	None
Type of designs	Total of 2 studies: 1 single dose crossover study fasted 1 single dose crossover study, fed* * If food mentioned in the product monograph if a multiple-dose study design is important, appropriate dosage	The design of BA BE studies should be based on randomized two or more-way crossover designs or Latin square designs in order to reduce the variation among the subjects. Is the crossover design is not applicable then the

	administration and sampling be carried out to document attainment of steady state.	parallel design can be used as an alternative? Parallel design for long half-life drugs and replicate designs for drugs with highly variable disposition. Single dose studies are preferred except for some special situations, where the conduct of steady state studies is acceptable.
Strength to be investigated	Linear pharmacokinetics: Reference Listed Drug (RLD) in the Orange Book* *usually the highest strength if formulations are proportionally similar	Usually the highest Marketed Strength
Parameters to be defined or measured	• AUCt, AUC∞, C_{max}, t_{max} for plasma concentration versus time profiles • AUCt, C_{max}, C_{min}, fluctuation (% PTF) and swing (% Swing) for studies conducted at steady state. • Cmax, AUC $_{0-t}$, $AUC_{0-\infty}$, residual area T_{max}, Kel, $t_{1/2}$, MRT • For multiple dose studies AUC $_{(0-)}$, $C_{max,ss}$ and $T_{max,ss}$ determined using plasma time concentration Profile of drug. • The method of estimating AUC-values should be specified	
Populations considered for study	Studies conducted outside the US population will also be accepted	Clinical data from the drug already in the regulated markets are accepted, depending on the type of drug.
Reference Product	Standard formulation which is in the market in the regulated countries.	Chinese Reference Product
Highly variable drugs	• A Reference-scaled Average Bioequivalence (RSABE) approach may be applied to AUC and C $_{max}$. A brief summary of study design and acceptance criteria is as follows: • The reference product should be administered at least twice to determine within-subject variability • Either a 3- or 4-period replicate design study is acceptable; The AUC and C_{max} max GMRs in the study should fall within 0.80 to1.25 • BE limits are scaled to the within subject variability of the reference product, but not until the within-subject standard deviation of the reference product (s WR) is ≥ 0.294; and 95% upper confidence bound for ($\mu T - \mu R)2 - \theta s WR2$ must be ≤0, where μT = test product mean μR = reference product mean • Non-Compartmental analysis to determine the PK Parameters. ANOVA, performed at the 5% level of significance, on the GMRs	No info. Given the BE guidance

A) Hold time study data

Parameters	USA	China
Lubricated Blend	**Tests Required** 1.Description 2.Water by KF 3.Assay 4.Related Substances 5.Microbial Enumeration Tests (Total Microbial Count, Total Yeast Mould, E.Coli)	1.Description 2.Water by KF 3.Assay 4.Related Substances
Core Tablets	1.Description 2.Water by KF 3.Related Substances 4.Assay 5.Microbial Enumeration 6.Dissolution 7.Hardness 8.Disintegration time	1.Description 2.Assay 3.Water by KF% 4.Dissolution 5.Hardness 6.Thickness 7. Related Substances.
Coating Dispersion	1.Description 2.Microbial Enumeration test	1.Description 2.Microbial Limits (Total Aerobic Microbial Count, Total combined yeast and mould count

Parameters	USA	China
Coated Tablets	1. Description 2. Water by KF% 3. Related substance 4. Assay 5.Microbial Enumeration 6. Dissolution 7.Hardness 8.Disintegration time	1.Description 2.Assay 3. Water by KF% 4.Related Substances 5. Dissolution 6.Microbial Enumeration 7. Thickness
Wet Mass	Not Applicable	1.Batch Number 2.Quantity tobe withdrawn from the study Sample 3.Packing style Sample packing Area 4.Sample Storage Area 5. Type of products 6.Remarks (If any)
Dried Granules	Not Applicable	1.Description 2.Water by KF% 3. Assay 4. Related substances.
In process Control Steps	1.Description 2.Identification by HPLC 3.Water content by KF 4.Blend Uniformity by HPLC 5.Assay by HPLC	1.Description 2.Identification by HPLC 3.Water content by KF 4.Blend Uniformity by HPLC 5.Assay by HPLC

B) Acceptance criteria for Bioequivalence

Country	90% confidence interval on log transformed data		
	Cmax%	**AUC0-t %**	**AUC0-∞ %**
USA	80-125	80-125	80-125
China	80-125	80-125	80-125

C) Acceptance criteria for Narrow Therapeutic Index Drugs

Country	Narrow therapeutic index drugs 90 % confidence interval Log transformed data	
	C_{max}	**AUC0-t**
USA	80-125%	80-125%
China	Acceptance level may need to be tightened.	Acceptance level may need to be tightened.

SUMMARY AND CONCLUSION

In this study the Regulatory requirements Registration and Approval process of Generic drug filing in most stringent regulated market USA and most stringent emerging market China was discussed. Even though all countries had their own set of formats, CTD provides a globally harmonized format that is accepted in many regions, avoiding the need to compile different registration dossiers for different regulatory authorities. The key factor in the generic drug filing is that the drug product must meet all the necessary criteria to be therapeutically equivalent to the innovator drug product. The generic drug filing in the United States & China are the most demanding, because these two countries are holding the first and second position in Pharmaceutical market in the world.

Generic drug filing comparison has showed various similarities and differences between specified countries that includes differences in the

- ✓ Registration process
- ✓ Procedures
- ✓ Fees structure
- ✓ Applications
- ✓ Approval timeline
- ✓ Manufacturing & Control Requirement
- ✓ Finished Product Control Requirements
- ✓ Stability Requirements
- ✓ General Parameters for the conduct of BA/BE study
- ✓ Comparison of Paper and Electronic submissions

Hence by comparing all the above, generic drug approval and the submission procedures becomes easy for registration of drugs and it also allows companies to use streamlined processes for developing and managing submissions both within a company and between companies. It also significantly reduces the time and resources need to compile application for registration, easy in the preparation of electronic submission, simplifies exchange of regulatory information between regulatory authorities and playing field good for export market.

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