

Review Article



Comparative Study of Generic Drug Approval process in EU, USA and China

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ABSTRACT

Generic drug registration is a very strenuous and complicated process in many countries. It varies from country to country based on their regulations. Due to various regulations, the ICH came into picture introducing 'CTD' (common technical document) for countries which come under it. Common Technical Document provides a standardized structure for regulatory submissions that is acceptable in all ICH countries. Although the CTD makes multinational filings easier, there are significant differences in the dossier submission requirements in these countries. This study deals with the differences in registration requirements for generics in European Union, United States and China. Generic drugs in EU are approved under the Marketing Authorization Application and in US they are approved under the Abbreviated New Drug Application, whereas in China it is under the filing of provincial FDA. Bioavailability and Bioequivalence study data is critical in the generic drug approval process as clinical trials can be omitted. This study also deals with the few comparisons of generic drug registration requirements in these three countries. Understanding the differences in registration process will have a substantial impact on the success of its multicountry submissions strategy. Therefore, the appropriate submission strategy in advance could make a smooth review process without any significant delays or failures.

Keywords: ICH, CTD, Dossier, Registration.

INTRODUCTION

A generic drug (shortly: generics) is a drug defined as "a drug product that is comparable to brand/reference listed drug product in dosage form, strength, route of administration, 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. Generic drugs are therapeutically equivalent to a branded drug.¹

Although they may not be associated with a particular company, generic drugs are subject to the regulations of the governments of countries where they are dispensed. Generic drugs are labeled with the name of the manufacturer and the adopted name (non-proprietary name) of the drug. A generic drug must contain the same active ingredients as the original formulation. In addition, a generic drug must be bioequivalent to the brand drug, that is there must be no significant difference between the generic and brand product in the rate or the extent to which the active ingredient is delivered to the patient.

The US Food and Drug Administration (FDA) considers a generic drug to be "identical, or bioequivalent, to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use".

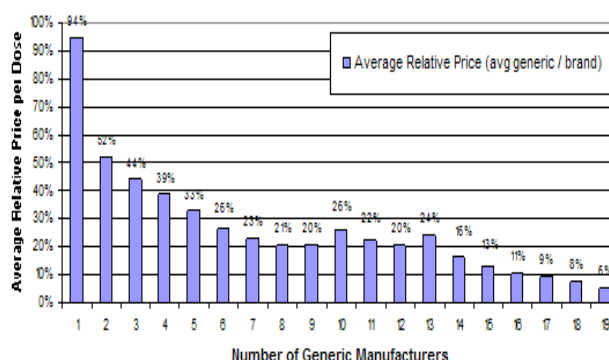
In most cases, generic products are available once the patent protections afforded to the original developer have expired. When generic products become available,

the market competition often leads to substantially lower prices for both the original brand name product and the generic forms. Generic drugs are usually sold for significantly lower prices than their branded equivalents.

Generic drugs do not require the submission of clinical data regarding safety and efficacy since this information was already provided for the pioneer product.

Since the original active ingredient was already proven safe and effective, the manufacturer must now prove bioequivalence for the pharmaceutically equivalent generic drug product.²

Generic Competition and Drug Prices



Source: FDA analysis of retail sales data from IMS Health, IMS National Sales

Figure 1: Average relative price of generic to brand by number of generic competitors.

US Food and Drug Administration

The United States food and drug administration is



government agency of the united states department of health and human services and is responsible for the safety regulation of most types of food, tobacco products, dietary supplements, drugs, vaccines, biological medicinal products, blood products, medicinal devices, radiation-emitting devices, veterinary products and cosmetics. The USFDA is a scientific, regulatory and public health agency that jurisdiction encompasses on most food products (other than meat and poultry), human and animal drugs,

therapeutic agents of biological origin, medicinal devices, radiation-emitting products for consumer, medical and occupational use, cosmetics and animal feed.³

The FDA is also responsible for advancing the public health by helping to spend innovations that make medicines and food more effective, safer, more affordable and helping the public to get the accurate, science based information they need to use food and medicines to improve their health.

Organization

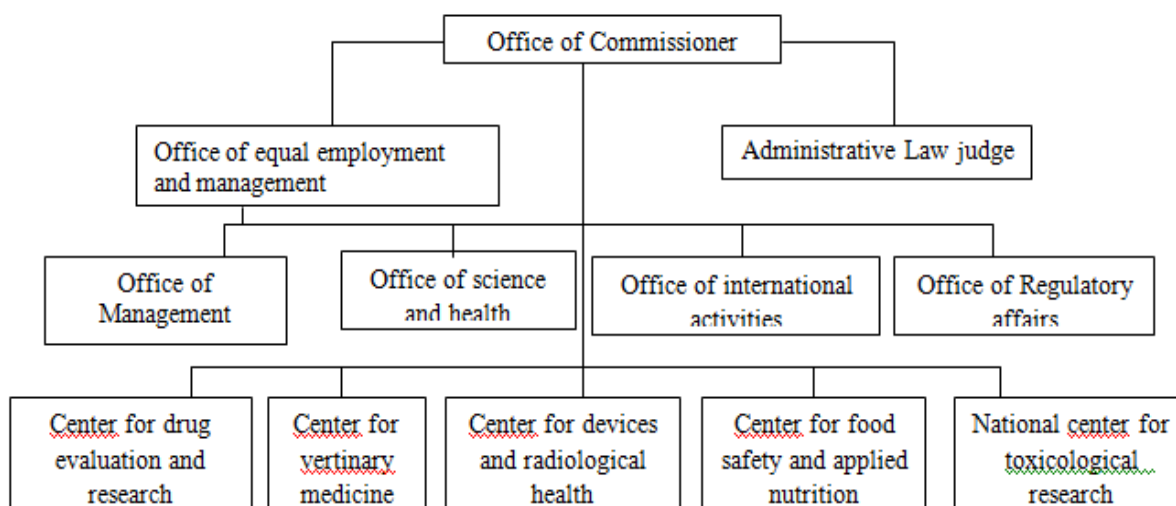


Figure 2: Organization chart of the US food and drug administration

Generic Drug Approval Process (ANDAs) in United States

Generic-drug products have been around since as early as the 1800s, when the pharmacy and medical communities in the U.S. were first established. The National Formulary published by the American Pharmaceutical Association (APhA) in the late 1800s was one of the first literary publications aimed at the prevention of brand-name counterfeits. The passage of the Federal Food and Drugs Act of 1906 and the Federal Food, Drug, and Cosmetic Act (FDCA) of 1938 helped to further ensure that the integrity and safety of medications were at the forefront.^{7,8} Subsequent legislation, including the Kefauver-Harris Drug Amendments of 1962, the Medicaid and Medicare amendments to the Social Security Act passed during the 1960s, and the Drug Price Competition and Patent Term Restoration Act of 1984 (frequently referred to as the *Hatch-Waxman Act*), was pivotal in further defining manufacturing procedures and ensuring healthy competition for prescription products with the availability of generics.⁴

Hatch-Waxman Act^{5, 6}

In 1984 Hatch- Waxman Amendments to Federal Food, Drug and Cosmetic Act (FD&C Act) came and it was considered one of the most successful pieces of legislation ever passed and created the generic drug industry (Drug Price Competition and Patent Term

Restoration Act of 1984). This act required FDA to publish received patent information and began printing the patent listings in a volume entitled “Approved Drug Products with Therapeutic Equivalence – Orange Book.” All approved products, both innovator and generic, are listed in this book.

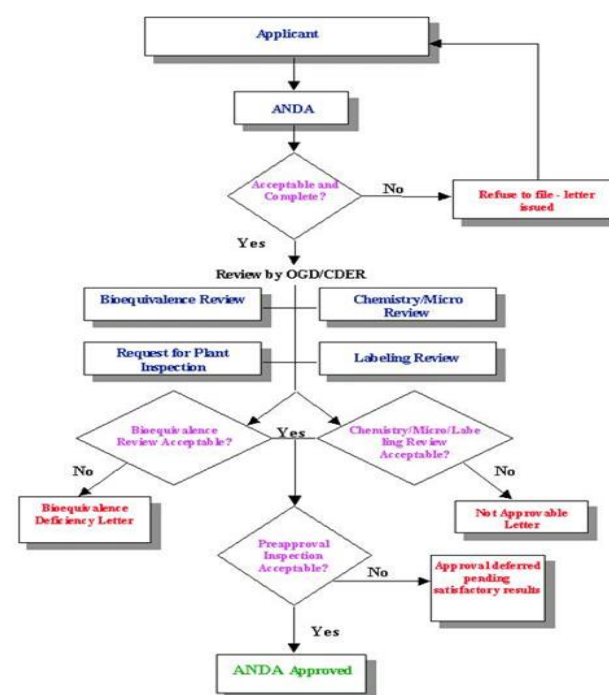


Figure 3: Flow chart on ANDA review process

Bio Equivalence Review Process

After an ANDA is accepted for filing by the RSB, the bioequivalence section is assigned to the Division of Bioequivalence (DBE) to review. For the generic drug to be therapeutically equivalent, two clinical characteristics must apply: It must be pharmaceutically equivalent as well as bioequivalent. Pharmaceutical equivalence means that the active ingredient(s), dose form, route of administration, and strength are the same for both the branded product and the generic product. Bioequivalence is when both products have comparable bioavailability when studied under similar conditions.

Bioequivalence is determined by evaluation of the AUC and the maximum concentration of drug (C_{max}). 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 C_{max} is 80% to 125%. This criterion is the same standard used for testing the bioequivalence of branded products with reformulation or manufacturing changes.⁷

Chemistry Review Process

After an ANDA has been accepted for filing by the 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

After an ANDA has been accepted for filing by the RSB, the Labeling section of the application is assigned to the appropriate labeling reviewer based on the therapeutic category of the drug product. The basis for the labeling review is to ensure that the generic drug labeling is the same as the branded (pioneer) drug 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 RLD⁸.

European Medicines Agency – EMA

The European Medicines Agency (EMA) is a European Union agency for the evaluation of medicinal products. From 1995 to 2004, the European Medicines Agency was known as European Agency for the evaluation of medicinal products.

Roughly parallel to US Food and Drug Administration (FDA), but without FDA-style centralization, the European Medicines Agency was setup in 1995 with funding from the European Union and the pharmaceutical industry, as well as indirect subsidy from member states, in an attempt to harmonize (but not replace) the work of existing national medicine regulatory bodies.

Marketing Authorization

To place a medicinal on the market in the European Economic Area (EEA) a “**Marketing Authorization**” has been issued by the competent authority of a Member State (or EEA country) for its own territory (national authorization) or when an authorization has been granted in accordance with Regulation (EC) No 726/2004 for the entire Community (a Community authorization). The marketing authorization holder must be established within the EEA.

Marketing authorization procedures in EU

- I. Centralized Procedure (CP)
- II. National Procedure (NP)
- III. Mutual Recognition Procedure (MRP)
- IV. Decentralized Procedure (DCP)

Procedure for submission of marketing authorization application to EMA

When preparing the submission of a MAA, applicants have the opportunity to meet the EMA to discuss any procedural or regulatory issues on the proposed submission. Requests for Pre-Submission Meetings should be sent to the EMA using the “Pre-Submission Meeting Request Form” which is included in the “EMEA Pre-Submission guidance document”.⁹

Pre-submission meetings

At least seven months before submission, applicants should notify the EMA of their intention to submit an application. In that notification applicants should include:

- A draft summary of product characteristics
- A justification of the product's eligibility for evaluation under CP.
- An indication on the number of strengths / pharmaceutical forms / pack sizes (if already known).



Admissibility to the centralized procedure

The applicant's request for eligibility for evaluation via the centralized procedure justification and summary of product characteristics/product profile from the applicant will be presented to all CHMP members at the subsequent CHMP meeting. Following discussion at CHMP, the EMA will then inform the applicant of the CHMP position as to whether the product is eligible for evaluation via the centralized procedure.

Selection of Rapporteur/Co-Rapporteur

For any scientific evaluation in respects of a procedure a Rapporteur, and if relevant a Co-Rapporteur shall be appointed. The role of the Rapporteur is to perform the scientific evaluation and to prepare an assessment report to the CHMP. Requests for Rapporteur/Co-Rapporteur appointment should optimally be provided seven months before the intended submission date, and should arrive at the EMA at least 2 weeks in advance of the CHMP meeting.¹⁰

Submission of the application

The date and time of delivery of the dossier to the EMA should be arranged between the applicant and the EMA. The EMA will inform future applicants well in advance of the program of scheduled CHMP meetings in order to be able to identify preferred optimal submission dates. As soon as the applicant is aware that the original indicated submission date cannot be met he should inform the EMA, Rapporteur and

Co-Rapporteur immediately, since a delayed submission can have consequences for already planned activities of the assessment teams of the Rapporteurs and Co-Rapporteurs. It may even be the case that assessment capacity is not immediately available at the moment a delayed submission is received and that therefore Rapporteur and/or Co-Rapporteur may in exceptional cases request the appointment of a new Rapporteur and/or Co-Rapporteur.

Dossier to be submitted

The EMA requires from the applicant:

- One full copy of the dossier (modules 1-5 according to the EU-CTD format), including the applicant's part of the Active Substance Master File, if any;
- Two additional copies of Modules 1 and 2 including the draft summary of product characteristics, labelling and package leaflet in English;
- One electronic copy of module 1 and 2 (at least 2.1-2.5) in WORD.

In addition, applicants must submit the dossier to both the Rapporteur and the Co-Rapporteur in parallel to the EMA. Otherwise there may be a delay in the start of the procedure because of the time lapse between the validation by the EMA and the confirmation from the

Rapporteur and the Co-Rapporteur that they have received the dossiers.^{11, 12}

Validation by the EMA

During validation the EMA Product Team Lead (PTL) consults the Rapporteur and Co-Rapporteur, on the need for action relating to matters such as GMP inspection, ad-hoc expert groups, Scientific Advisory Groups, GCP inspections, and completeness of data. In the event that the EMA requires additional data, information in order to complete its validation of the dossier, it will contact the applicant requesting supply of this data, information or clarification within a specific time limit.

Positive outcome of the validation

In case of a positive outcome, the EMA shall notify the applicant in writing that the validation has been successfully completed, together with the names of CHMP members to whom full or partial copies of the dossier should be sent.

Negative outcome of the validation

Failure to provide the data, information or clarification requested, failure to adhere to the EU CTD format will result in a negative validation, of which the applicant shall be informed in writing. The applicant will be invited to either collect the dossier or have it destroyed by the EMA.

Inspection Reports

The inspector provides a report with comments on major factual errors within 15 days. The final report is sent to EMA inspection sector by day 180 at the latest, and circulated to the rapporteur and co-rapporteur and CHMP.

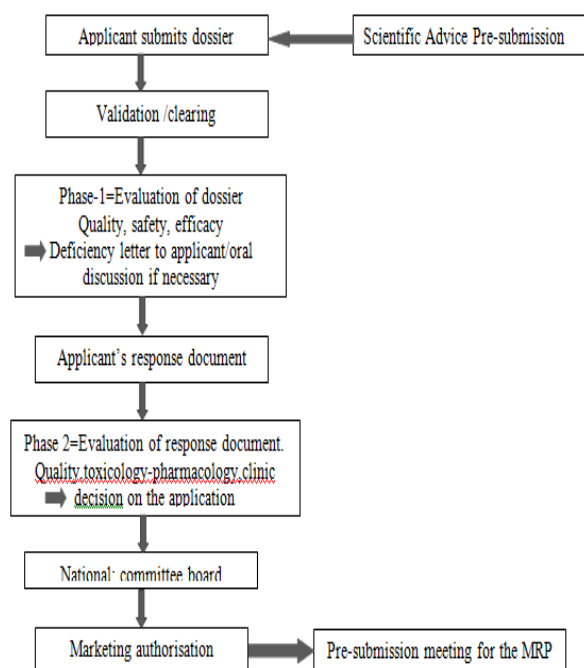


Figure 4: National marketing authorization procedure

Mutual recognition procedure and decentralized procedure

The legal provisions covering the mutual recognition procedure and the decentralized procedure for human medicinal products are contained in Directive 2001/83/EC. Both the mutual recognition procedure and the decentralized procedure aim at facilitating access to a single market by relying upon the principle of mutual recognition. Thus with the exception of those medicinal products which are subject to the centralized procedure, a marketing authorization or the assessment in one Member State (the so-called reference Member State) ought in principle to be recognized by the competent authorities of the other Member States (the so-called concerned Member States), unless there are grounds for supposing that the authorization of the medicinal product concerned may present a potential serious risk to public health.¹³

Table 1: Flow chart for the mutual recognition procedure

Approx. 90 days before submission to CMS	Applicant requests RMS to update Assessment Report (AR) and allocate procedure number.
Day -14	Applicant submits the dossier to CMS. RMS circulates the AR including SPC, PL and labelling to CMSs. Validation of the application in the CMSs.
Day 0	RMS starts the procedure
Day 50	CMSs send their comments to the RMS and applicant
Day 60	Applicant sends the response document to CMSs and RMS
Until Day 68	RMS circulates their assessment of the response document to CMSs.
Day 75	CMSs send their remaining comments to RMS and applicant. A break-out session can be organised between day 73 – 80).
Day 85	CMSs send any remaining comments to RMS and applicant.
Day 90	CMSs notify RMS and applicant of final position (and in case of negative position also the CMD secretariat of the EMEA). If consensus is reached, the RMS closes the procedure. If consensus is not reached, the points for disagreement submitted by CMS(s) are referred to CMD(h) by the RMS within 7 days after Day 90.
Day 150	For procedures referred to CMD(h): If consensus is reached at the level of CMD(h), the RMS closes the procedure. If consensus is not reached at the level of CMD(h), the RMS refers the matter to CHMP for arbitration
5 days after close of procedure	Applicant sends high quality national translations of SPC, PL and labelling to CMSs and RMS.
30 days after close of procedure	Granting of national marketing authorisations in the CMSs subject to submission of acceptable translations.

State Food and Drug Administration (SFDA), China

The State Food and Drug Administration (SFDA) is founded on the basis of the State Drug Administration. The State Food and Drug Administration is directly under the State Council of the People's Republic of China, which is in charge of comprehensive supervision on the safety management of food, health food and cosmetics and is the competent authority of drug regulation in mainland, China.¹⁴

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.

Clinical Trials

A generic drug application, or so-called “abbreviated application,” may omit preclinical and clinical test data on the basis that the drug is already on the market and its effectiveness and safety understood. The key aspects of the examination and approval process focus on the quality of the manufacturing process and conformity with the existing national drug standard. In certain circumstances, clinical trials are required for safety reasons. According to the Annex to the Amended Regulation, for generic drugs based on traditional Chinese medicine (TCM), or natural drug injections, clinical trials on no less than 100 pairs of cases are required. For generic chemical drugs where the quality is controlled by defined processes and standards, clinical trials on 18-24 cases are typically required.¹⁴

Drug Approval Process in China¹⁵

Generic drug applications must be filed by the drug manufacturer in the provincial FDA (PFDA), where the applicant is located. The PFDA serves as the receiving office for the generic application and determines whether the application dossier is in proper order. If the requirements are met, the PFDA provides notification of acceptance of the drug registration application. If the requirements are not met, the applicant is provided with an explanation of the reasons for rejection, and the opportunity to reapply. Within five days of acceptance of the application, the PFDA will conduct an on-site inspection of the production site, as well as the original drug research data, and take samples of three consecutive batches to send to the Drug Control Institute for inspection. The sample products are required to be manufactured in a facility with Good Manufacturing Practice (GMP) certification. After completing examination of the application dossier, the PFDA will submit the dossier along with its examination recommendation, verification report and results of its inspection of the production site to the SFDA Center for Drug Evaluation (CDE) within 30 days. CDE will organize pharmaceutical, medical and other technical staff to examine the verification recommendation and the application dossier, and may request that the applicant provide supplemental information if necessary. At the same time, the Drug Control Institute tests the sample products and provides its sample test report to CDE, the PFDA and the applicant. CDE prepares a general examination recommendation based on the technical examination recommendation, production site



inspection information and sample test report, and then submits to SFDA along with related data. SFDA then makes its approval decision based on the general recommendation and issues a Drug Approval Number (if no clinical trials are needed), or a Clinical Trial Approval (if clinical trials are needed). Upon completion of clinical

trials, the applicant must then submit the clinical trials data to SFDA for issuance of a Drug Approval Number. For drugs that do not meet safety requirements, the Amended Regulation grants SFDA authority to suspend acceptance or approval of the generic drug application.

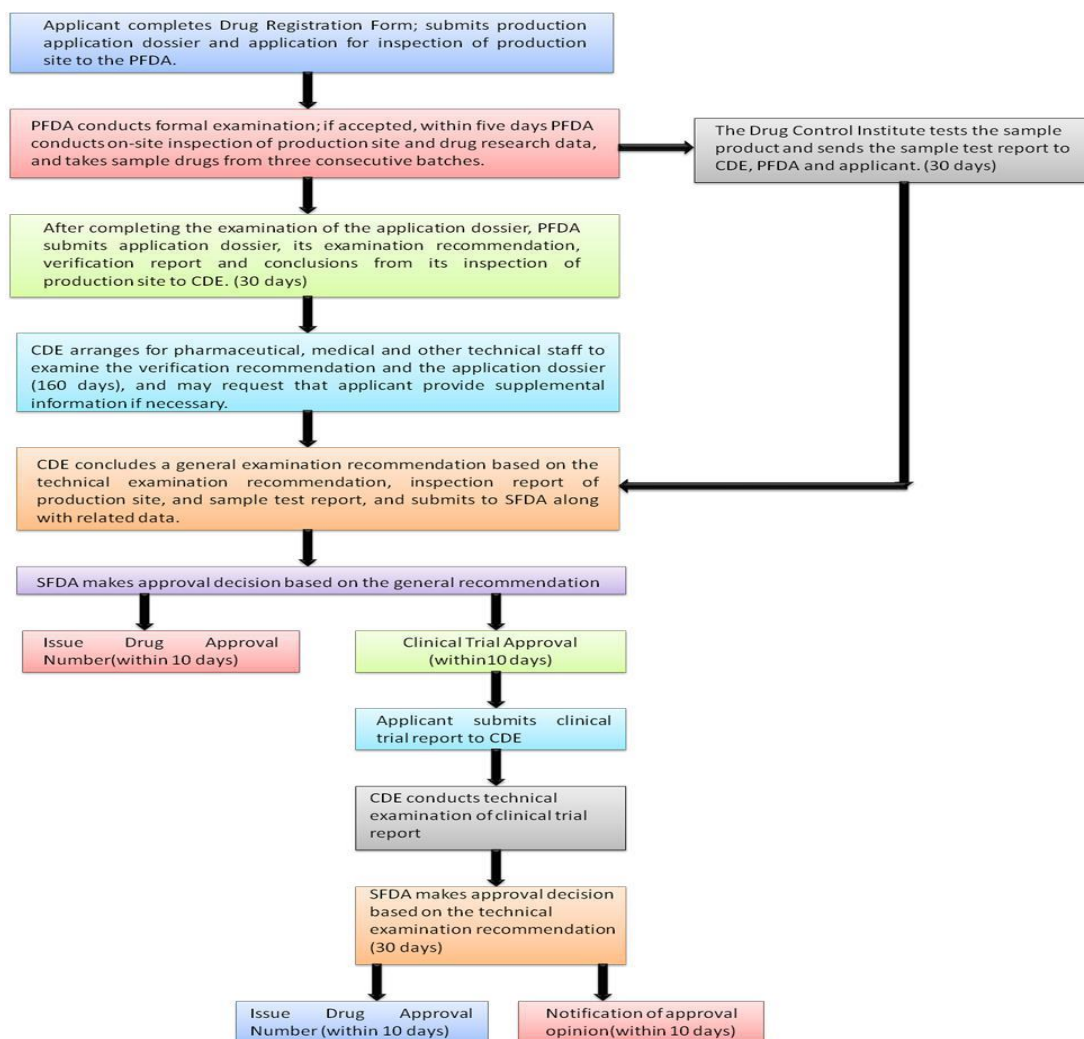


Figure 5: Flow chart & timeline of generic application approval in China

Table 2: Comparative study of various countries.

Generic Drugs	EU	USA	China
Dossier submission	MAA	ANDA	PFDA
Application submitted to	EMA	USFDA	SFDA
Type of drug filling	Centralized procedure, National procedure, MRP, Decentralized procedure.	No such requirement	No such requirement.
Approval timeline	12 months	18 months	12 to 18 months
Stability data required at the time of submission	Two batches	One batch	Three batches
Bioequivalence study followed	E.U. Guidelines It also accepts other country guidelines	USA Guideline It also accepts other country guidelines	World Health Organization guidance "Multisource (generic Pharmaceutical products: guidelines on registration requirements to establish interchangeability" It also accepts other country guidelines. Accepts Bioequivalence Studies done on its own country population only.

SUMMARY

The regulatory submissions in the EU, USA and China and elsewhere in the world continue to have significant differences. When compared to USA and China the EU approval process is typical and contain more data to be summarized for the dossier submission.

It also compares the registration procedure, regulatory pathways for the registration of drugs in EU, USA and China. The EU requires to select from any one of the marketing authorization procedures and USA requires ANDA and whereas China requires provincial FDA approval. It also compares the registration procedures for the dossier submissions in EU, USA and China.

CONCLUSION

To succeed with multinational registrations, a sponsor must:

- Identify key target markets for submissions.
- Understand important regional differences.
- Find the right local resources to avoid regulatory pitfalls.
- Create a robust CTD (Common Technical Document).
- Develop a submissions strategy that leverages the CTD (Common Technical Document) to secure regulatory approvals in the shortest possible time.

Hence by comparing the generic drug approval, the submission procedures becomes easy for registration of drugs and it also allows companies to use streamlined processes for developing and managing submissions globally, both within a company and between companies.

REFERENCES

1. "Generic Drugs", Centre for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration. [Internet]. [Cited 2012 May 23]. Available from: http://en.wikipedia.org/wiki/U.S._Food_and_Drug_Administration
2. Generic drug. [Internet]. [Cited 2012 May 28]. Available from: http://en.wikipedia.org/wiki/Generic_drug#cite_note-0
3. Abbreviated New Drug Application (ANDA): Generics. [Internet]. [Cited 2012 July 6]. Available from: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics>.
4. Steven J, Max L. Generic Drug Approval Process in China, Food and drug law institute-USA; July 2011. [Internet]. [Cited 2012 June 27]. Available from: <http://www.foley.com/files/Publication/e29262fa-55dc-4d12-9c90>.
5. ICH Guideline index. [Internet]. [Cited 2012 June 15]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Guidelines_Index.pdf.
6. Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): preparation of product dossiers (PDS) in common technical document (CTD) format. [Internet]. [Cited 2012 June 23]. Available from: http://apps.who.int/prequal/info_general/documents/generic_guide/GenericGuideline_PDS_CTD-Format.pdf
7. Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): preparation of product dossiers (PDS) in common technical document (CTD) format. [Internet]. [Cited 2012 June 23]. Available from: http://apps.who.int/prequal/info_general/documents/generic_guide/GenericGuideline_PDS_CTD-Format.pdf
8. Devesh S, Vandana S, Comparative study of dossier files submission process of drug product in USA and Europe. Int J. Pharm Res Dev., 3(7), 2011, 60-78.
9. Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product: Preparation of product dossiers in common technical document (ctd) format. Unedited version adopted by the 45th WHO expert committee on specifications for pharmaceutical preparations. World Health Organization 2010.
10. Santosh KN. Marketing authorization of human medicinal products to European union/European economic area. Int. J. Pharm Sci Rev and Res. 10(1), 2011.
11. Abbreviated New Drug Application (ANDA) approval process. [Internet]. [Cited 2012 July 10]. Available from: <http://fdadrugcompliance.com/resources/anda/>.
12. ANDA regulatory approval process. [Internet]. [Cited 2012 July 10]. Available from: <http://www.authorstream.com/Presentation/poojamb-1261138-3-anda-regulatory-approval-process>.
13. Daniel R. The food and drug administration's generic drug review process: Levinson inspector general, Department of Health and Human Services, 2008.
14. US Food and Drug Administration [Internet]. [Cited 2012 July 27]. Available from: http://en.wikipedia.org/wiki/State_Food_and_Drug_Administration.
15. State Food and Drug Administration, CHINA. [Internet]. [Cited 2012 July 27]. Available from: <http://eng.sfda.gov.cn/WS03/CL0755/>.
16. Gupta NV, Mohan CR. Process of approval of new drug in india with emphasis on clinical trials. Int J Pharm Sci Rev Res. 13(2), 2012, 17-23.
17. Gupta NV, Aswani. N Documentation in the process of obtaining USFDA approval for a tablet manufacturing industry J Pharm Res, Vol. 4 Issue 11, Nov2011, page-3989

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