GENERICS DRUG (ANDA) APPROVAL PROCEDURE IN UNITED STATES

B. Prakash*, K.Praneetha,K.Umasankar, V.LeelaPrabhakar,P.Jayachandra Reddy

Krishna Teja Pharmacy College, Chadalawada Nagar, Renigunta Road, Tirupati - 517501, Andhra Pradesh, India.

ABSTRACT

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 put forth the differences in registration requirements for generics in United States. Generic drugs in US they are approved under the Abbreviated New Drug Application. Bioavailability and Bioequivalence study data is critical in the generic drug approval process. There are several approaches to assess BA/BE, each regulatory authority has put forth its own regulations/guidance for conducting BA/BE studies required for approval of generic products. This study also emphasizes on the BA/BE concepts, study conditions, designs and methodology in conducting these studies in US. The ability to accommodate country specific requirements and understand regulatory differences will have a substantial impact on the success of its multi-country submissions strategy. Therefore, the appropriate submission strategy in advance could make a smooth review process without any significant delays or failures.

Key Words: CTD, BA/BE, ANDA, ICH, Regulatory Authority, Generics.

Introduction:

Generic pharmaceuticals and encourage competition through the Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Act"). The Act established a new process for generic drugs to enter the market, the Abbreviated New Drug Application ("ANDA"). Congress intended the Act to "make available more low-cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962." However, with the Hatch-Waxman Act, Congress also sought to balance the ability of competitors to bring cheap generics to the marketplace with the need for companies producing brand-name drugs to research and develop new pharmaceuticals. To accomplish the first objective, the Hatch-Waxman Act's ANDA provided generics with a new approval process, during which generic producers need only prove the equivalency of their generic product to the pioneer drug on which FDA testing and approval had already taken place. This was intended to allow generic manufacturers to avoid the enormous costs inherent in duplicating the NDA process, particularly the expensive data on human subjects.The Act also gave generic manufacturers the opportunity to petition for generic drugs that list different drugs as the active ingredient or have a different dosage or strength, provided that the change does not require a separate review of clinical data. Additionally, Hatch-Waxman aimed to maintain investment in research and development of new innovator pharmaceuticals. To this end, the Act established two new FDA pharmaceutical approval processes: the ANDA and the Section 505(b)(2) application. These approval processes allow manufacturers of equivalent pharmaceuticals, similar but non-equivalent pharmaceuticals, and pharmaceuticals for which significant safety and efficacy testing have been heretofore conducted by third parties to avoid duplicative innovator research and to develop products during innovator exclusivity periods. To aid concurrent development of generics, the Hatch-Waxman Amendments also allowed generic manufacturers to use the patented pioneer drug during the patent life to test and develop generics, which might otherwise be patent infringement. Thus, proprietary pioneer drugs and their testing data were made available to generic manufacturers, allowing the manufacturers to put a competitor pharmaceutical on the market sooner. However, in accordance with the first goal of maintaining the incentives for research and development, several restrictions on competition were included in the Hatch-Waxman Act. First, pioneer drugs, those with NCEs new to the market, receive a five-year exclusivity period, during which time no ANDA may be submitted. When generic manufacturers wish to market a bioequivalent, the Act requires that producers notify the corresponding pioneer pharmaceutical's patent owners of a possible exclusivity infringement so that the issue may be litigated promptly. Once a generic manufacturer files an ANDA, if a patent infringement action is brought within forty-five days after notice of final certification, approval is stayed for thirty months, or until a court decides that the patent is not infringed.If after thirty months no federal court has ruled on the validity of the patent infringement, the generic manufacturer who filed the ANDA may distribute and market the drug; however, the ANDA filer that chooses to follow this course may thereafter become liable for infringement damages if infringement is found later by a court. Once a generic pharmaceutical has filed for final

ANDA certification, the Hatch-Waxman Act gives the marketer of the generic drug 180 days of market exclusivity for that generic.In implementing this provision of the Hatch-Waxman Act, however, the FDA determined that the provision could not be read literally; it then added the requirement that the first applicant must have "successfully defended against a suit for patent infringement" before the exclusivity period can begin to run. Thus the FDA inserted an additional hurdle of litigation before the generic manufacturer can enjoy the 180-day exclusivity period.Furthermore, federal courts have limited the 180-day generic exclusivity period, allowing the producer of the innovator drug (the NDA holder) to market its own generic version of the drug during the ANDA holder's 180-day exclusivity period. Thus, during their period of supposed exclusivity, generic manufacturers may have to defend patent infringement suits and face generic competition from the innovator drug producer, a company already equipped and engaged in the manufacture of the same pharmaceutical.

The Hatch-Waxman Act also provides the section 505(b)(2) application for innovative pharmaceuticals that offer a new therapeutic benefit or alternative for consumers. In essence, section 505(b)(2) constitutes a hybrid between the NDA and ANDA processes, allowing applicants to avoid duplicative research for drugs that would not qualify as bioequivalent for the ANDA process. Section 505(b)(2) provides this alternative for two types of drugs: drugs that cannot be approved solely on the basis of studies conducted or compensated by the applicant and drugs that are similar to innovators but not sufficiently similar to constitute therapeutic equivalents. In practice, section 505(b)(2) applications are used by producers of NCEs and new molecular entities ("NMEs") that rely on FDA findings or studies to which the applicant has not been afforded a right of reference. Also, section 505(b)(2) applications are used by producers of pharmaceuticals that modify previously approved drugs, creating equivalents not similar enough to warrant the approval of an ANDA. A section 505(b)(2) applicant pharmaceutical may receive a five-year exclusivity period for an NCE or NME; if the drug is not an NCE, and one or more of the clinical studies was conducted or sponsored by the applicant, the section 505(b)(2) applicant can receive a three-year exclusivity period. The section 505(b)(2) applicant may also be eligible for orphan drug or pediatric exclusivity. Furthermore, a brand-name drug manufacturer that takes anticompetitive measures beyond the FDA-prescribed windows of market exclusivity can face antitrust liability in the American system. The Sherman Act punishes all behavior that "attempt[s] to monopolize" in restraint of trade, aiming to protect competition in a market, and thus the consumer, rather than merely the rights of the competitor. In this regard, federal courts have found that brand-name drug manufacturers attempting to block generic entry through unfounded lawsuits would be guilty of antitrust violations. Holding that filing frivolous lawsuits constitutes an antitrust violation rather than a minor violation of the Federal Rules of Civil Procedure perhaps demonstrates the federal judiciary's acknowledgement of the time required for effective marketing and for a consumer to switch to generics.

OBJECTIVES:

The present work aims to develop a robust core dossier for regulatory filing so as to reduce the risk of regulatory delays by anticipating the questions raised by the individual regulatory authorities.

The objectives of the proposed work includes

- ✓ To review the regulatory framework in ICH region.
- ✓ To review the drug registration and approval procedures in US
- ✓ To review the regulatory requirements for the preparation of CTD
- ✓ To compare the regional and technical requirements between US
- ✓ To review the BA/BE concepts, approaches, design and various basic regulatory considerations for conducting BA/BE studies.

RESEARCH METHODOLOGY:

Literature review was done mainly on collection of the legislations, concentrating on their generic drug registration procedures in EU and US. The research carried out with the collected data by analyzing the terms of the below parameters:

Methodology:

Each and every study has some patterns and follows certain pathways in order to reach the objective. Thus, the method to be followed plays an important role in determining the outputs as well as the consequences of study.

Types of study:

The study was conducted with an objective to chalk out the regulatory framework for generic drug registration, legislations and guidelines. The major emphasis has been provided to regulatory requirements of EU and US. In addition emphasis is made on the administrative documents in the emerging nations.

Source of data:

Major part of the proposed data was collected by means of following sources:

Literature Review:

Typically reviewed the dossiers, covered the books and regulatory guidelines published officially by government authorities, including the academic journals, online journals, market research reports, news paper articles and world fact and other resources.

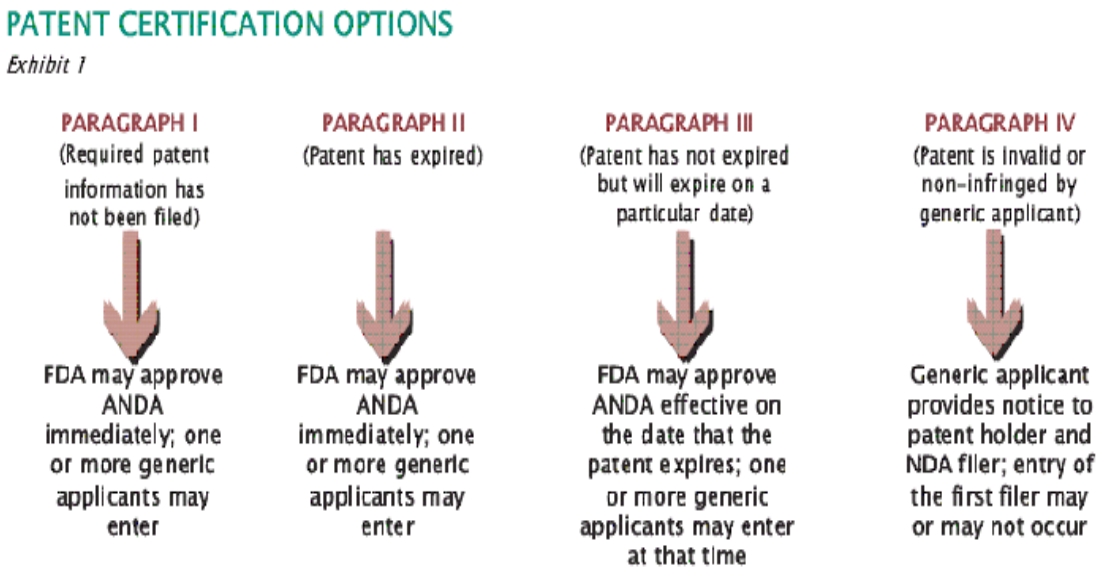
Internet using the Web Page Content:

The literature was collected using numerous search engines.E.g. Pharmabiz, RAPS, Pub med, online journals, Google Scholar and many more. Online books also served as a good source of information. Key words in the search involved generic drug registration requirements, administrative documents along with the name of various parameters associated to pharmaceutical field, name of regulatory bodies and other variations were used.

DRUG (ANDA) APPROVAL PROCEDURE IN US:

Hatch-- Waxman Act

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). The 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**. Under this act four type of certification are possible. They are



- "Paragraph I" certification states that the application does not cite patented information previously listed in the Orange Book
- "Paragraph II" certification states that the patented information cited in the application, and listed in the Orange Book, has expired
- "Paragraph III" certification states the date on which the listed Orange Book patents for the information cited in the ANDA application will expire
- "Paragraph IV" certification attests to the manufacturer's opinion that the listed Orange Book patent is invalid, or will not be infringed by the use, manufacture, or sale of the new drug for which the ANDA is submitted

Generic manufacturers filing Paragraph IV certifications were required to provide notice to the relevant pioneer drug companies and patent holders explaining why the listed patents cited in the ANDA were either invalid or not infringed by the ANDA submission. At the same time a NDA or patent holder could file a valid infringement suit within 45 days of receipt of a Paragraph IV notice. In addition the Act created an automatic thirty-month window in which the patent infringement dispute could be litigated without risk of generic entry into the market. The effective date of FDA approval was delayed until a judicial ruling on the infringement of validity of the patent, or until thirty months have elapsed, whichever occurred sooner. The Act provided additional incentives to the generic companies in the form of a marketing exclusivity provision. The first company that filed an ANDA with a Paragraph IV certification as to a particular patent or patents was granted a 180-day monopoly by the FDA. During this time, the FDA would not give any other ANDA approval for subsequent generics for 180 days. Thus this act made following three important provisions: I) it provided for the extension of the term of one existing patent for innovator drugs; II) it made provisions for the marketing of generics of patented drugs on the day after patent expiry; and III) it provided opportunities to challenge the validity of patents issued to innovator drug companies.

A generic drug product is one that is comparable to an innovator drug product (also known as the reference listed drug (RLD) product as identified in the FDA's list of ***Approved Drug Products with Therapeutic Equivalence Evaluations***) in dosage form, strength, route of administration, quality, performance characteristics and intended use. "ANDA" contains data which when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs (OGD), provides for the review and ultimate approval of a generic drug product. Once approved an applicant may manufacture and market the generic drug product provided all issues related to patent protection and exclusivity associated with the RLD have been resolved.

The OGD ensures the safety and efficacy of generic drugs by employing a review process that is similar to the NDA process. The primary difference between the Generic Drug Review process and the NDA review process is the study requirements. For example, an ANDA generally requires a bioequivalence study between the generic products and the reference listed drug (RLD) product. The safety and efficacy of the RLD product were established previously through animal studies, clinical studies and bioavailability studies. Thus, these studies need not be repeated for the ANDA.

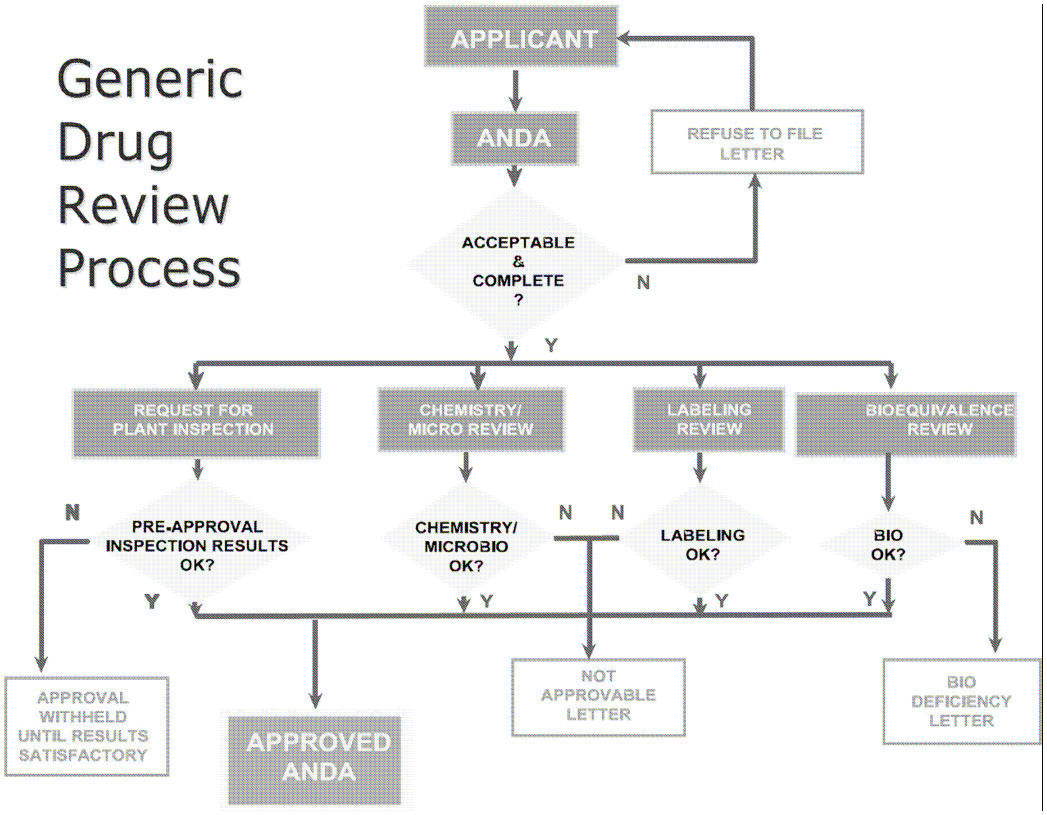


Figure : Flow chart on ANDA review process

Filling review of ANDA:

The ANDA process begins when an applicant submits an ANDA to the OGD. The document room staff processes 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. Within the first 60 days following the submission of an ANDA, a filling review is completed. The Regulatory Support Branch (RSB) is responsible for the filling review. The RSB ensures that the ANDAs contain the information necessary to merit a technical review. To determine whether an application is acceptable for filling, an RSB project manager (RPM) compares the contents of each section of application against a list of regulatory requirements. An applicant may receive a ‘‘refuse to receive’’ letter when an inactive ingredient level exceeds the level previously used in anapproved drug product via the same route of administration or may be due to incomplete bioequivalence studies, incomplete stability data, incomplete packaging, and incorrect basis for submission.The RSB verifies that all applications contain a patent certification and exclusivity statement as per 21CFR 314.94(a) (12).

Once the RSB completes the filling review of the ANDA and verifies that the application contains all the necessary regulatory requirements, an ‘‘acknowledgment’’ letter is issued to the applicant indicating its acceptance for filing and the official filing date. Upon filing an ANDA,the RPM forwards an Establishment Evaluation Request (EER) to the office of Compliance.The office of Compliance then determines if the drug product manufacturer, the drug substance manufacturer and the outside testing facilities are operating in compliance with current Good Manufacturing Practice (cGMP) regulations as outlined in 21 CFR Parts 210 and 211.

Once the ANDA is accepted for filing, the application is assigned to a bioequivalence reviewer, a chemist, and a labeling reviewer.Each chemistry team consists of a team leader, a project manager, and several reviewers. The chemistry project manager serves as the ‘‘Application’’ Project Manager (APM). TheAPMs play a key role in coordinating the various disciplines to review the applications within 180 days from the submission date.

The APMs enter key information about their applications into a project management database. The APMs use the information to provide applicants and OGD management the status of applications. The APMs are designated as the primary contacts for all issues relating to the review of the application.The APMs attempt to address all applicant inquiries within 2 working days of receiving a request.

Bioequivalence Review Process:

After anANDA is accepted for filing by the RSB, the bioequivalence section is assigned to the Division of Bioequivalence (DBE) to review.The bioequivalence review process establishes bioequivalence between a proposed generic drug and the RLD. Bioequivalence is established when the ratio of the means of the test product compared to the reference product (T=R) of the pharmacokinetic parameters for rate (Cmax) and extent of absorption (AUC) of log transformed data meet the 90% confidence intervals of 80--125%. The BPMs request and track inspections of the clinical and analytical sites through the Division of Scientific Investigations (DSI). The clinical and analytical sites are inspected for two reasons: (1) to verify the quality and integrity of the scientific data submitted in bioequivalence studies and (2) to ensure that the rights and welfare of human subjects participating in the studies are protected in accordance with theregulations (21 CFR 312, 320, 50, and 56). If any issue arises during the review process the BPM intiates a teleconference with the applicant. The applicant’s response to the teleconference is labeled as a ‘‘Bioequivalence Telephone Amendment’’. When a review contains numerous defeciencies and require more

than 10 days to resolve, a defeciency letter is issued to applicant. Once the bioequivalence review is completed and all bioequivalence requirements are addressed, and all defeciencies are fulfilled the DBE forwards an acceptable letter that states that there are no further questions at this time. The bioequivalence review is then forwarded to the APM.

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. The chemistry reviewer drafts a primary review that is forwarded to the team leader for secondary review. Once the team resolves the issues internally, the review is finalized and signed by the team leader, primary reviewer and APM. The Deputy Director, or in some cases the Division Director, completes the tertiary review. If the application is a ‘‘first generic drug product’’, the Associate Director for Chemistry performs a quality control audit. After all issues are resolved within the Chemistry Divisions, the APM communicates the status of the application to the applicant. After designating the chemistry defeciencies 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 the applicant is contacted.

Labeling Review Process:

After anANDAhas 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 RLD labeling. Exceptions are allowed for: differences due to changes in the manufacturer or distributor, unexpired patents, or exclusivities and other characteristics inherent to the generic drug product, such as tablet size, shape, or color.
Difference between the generic and the RLD labeling is the omission of information protected by patents and exclusivity. The applicant may submit four copies of draft labeling or 12 copies offinal printed labeling as proposed labeling. Draft copies may also be submitted for tentative approval. If the proposed labeling is defecient, the APM or the labeling reviewer communicates the defeciencies to the applicant. If the proposed labeling is acceptable, an approval or tentative approval summary is forwarded to the APM.

After the final level administrative review and individual disciplines have resolved their defeciencies, 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 RLD. Once the Director or his designee has signed the final approval letter, the APM calls and faxes a copy of the approval letter to the applicant.The document roomstaff then mails the final approval letter to the applicant. Thus the team, work together to accomplish the OGD’s mission of providing safe and effective generic drugs to the American People.

SUMMARY:

The CTD makes multinational filings easier, it is important to remember that regulatory submissions in the US and elsewhere in the world continue to have significant differences. An opposed to the cross references to full reports typically seen in submissions to the FDA.

Each module of the CTD has a specific function; the key areas for creative and informative content are Modules 2 and 3. These sections allow for integration of data between studies, presentation of both the strengths and limitations of the data, and giving the reviewer an opportunity to see the big picture at any of several levels of details. Clear and compelling presentations in these two modules are critical to the success of the application.

The ICH has laid the foundation for a global harmonized trade of pharmaceutical products. As of now 45 guidelines have been harmonized between three regions these are divided into 4 categories quality, safety, efficacy and multidisciplinary.

ICH Quality guidelines focus on the two areas of stability data and impurities. This led to a reduction of duplicate testing. The ICH guidelines reduced the testing that was necessary when a registration should be made in different climate regions. Before the ICH guidelines existed, it was typical to test at "room temperature", which was different from company to company and dependent on climatic zones. There was also no standardized humidity control done before ICH guidelines were implemented. The quality guidelines provided standard sets of conditions taking account to the climatic zones of the ICH region. Stability tests that were made in one ICH region are acceptable in all three ICH regions as per Q1 stability guidelines.

The impurity guidelines (Q3) provide scientific agreement on the recording and reporting of impurity levels. Threshold limits for impurity qualification and impurity identification are defined in the Q3 guidelines. These guidelines make it possible that a single specification for a drug substance or a drug product is acceptable in the ICH regions. To have only one specification for three markets makes the supply chain easier and supply errors are reduced.

The bioequivalence trials are not yet harmonized by ICH, as part of establishing equivalence between the innovator and the comparator these trails are run under the principles of GCP according the guideline E6 "Good Clinical Practice" for a marketing authorization application. The guideline E3 "Structure and Content of Clinical Study Reports" established a common format for clinical study reports. This guideline was the basic framework for the Efficacy section of the CTD.

Few highlights from this study on registration requirements for generics in US are listed below:

- The requirement to file a generic drug application in US is based on the patent certification (Paragraph I, II, III, IV) whereas in EU it's based on the data and market exclusivity. The added benefit of filling generic drug through paragraph IV filling in US is 180 day exclusivity to the applicant.
- The number of batches data required during the submission from US in number of US FDA requires single exhibit batch.
- The stability data required during submission varies with the time lines and number of batches FDA requires single batch data with three month accelerated and 3 month long term data.

- The selection of reference listed drug is relied on the listing out the patents in orange book.
- Single dose studies are preferred to multiple dose studies as single dose studies are considered more sensitive to measure the release of active pharmaceutical ingredient from the pharmaceutical product into systemic circulation.
- For immediate release formulations fasted studies are generally preferred. Both fed and fast studies are required for the modified release formulations. Food effect studies in modified release formulations are necessary to ensure the absence of "dose dumping".
- Basically two types of study designs are possible that is parallel and crossover. The major difference between these two designs is the ways they deal with inter subject and intra subject variability. Both types of variability are present in both designs. But in the cross over design inter subject variability is eliminated. This makes the crossover design more efficient in terms of sample size.

Conclusion:

Thus ICH has provided a logical framework for submission content that allows companies to use streamlined processes for developing and managing regulatory submissions globally, both within a company and between companies. 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 and to secure regulatory approvals in the shortest possible time.

REFERENCES:

1. Orange Book: Approved Drug Product with Therapeutic Equivalence Evaluations.[Online].2010 Feb

23[cited2010Feb23];Available from:URL:http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=0818343&Product_No=003&table=OB-Rx .

2. FDA came up with Hatch-Waxman Amendments to Federal Food, Drug and Cosmetic Act (FD&C Act) in 1984.

3. Congress passed the Generic Drug Enforcement Act in 1992, which allows the FDA to debar drug companies or individuals convicted of misconduct in the drug approval process prohibiting these companies from introducing productsgeneric drug approvals and fine companies up to $1 million and individuals up to $250,000 for violations of the Act.

4. www.fda.gov/cder/gudidance

5. ShaikMastan briefly reviewed the BA\BE concepts, approaches, designs, and various basic regulatory considerations2nd ed. Inform healthcare. p. 49.

6. Useful Information at www.ich.org ,and in Federal Register.

7. Abbreviated New Drug Application (ANDA) : Generics.[Online].2013 Jul 07 [cited 2014 Jan 03];Available form:

   URL:http://www.fda.gov/Drugs/DevelopmentApporvalProcess/HowDrugsareDeveloped andApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/default.htm.

8. 2005 Fundamental of US Regulatory Affairs,RAPS,2005

9. Richard A.Guarino-New Drug Approval process-The New Drug Application Content, Format; Abbreviated and Supplementary New Drug Application-Fourth edition-Marcel Dekker,inc-page no 113-183.

10. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.[Online].[cited 2014 Jan 03]; Available from:URL:http//www.ich.org/cache/compo/276-254-1.html.

11. ANDA checklist for CTD format.[Online].2008 May28[cited 2010 Jan 03];Available from:URL:http://www.fda.gov/downloads/Drugs/DevelopmentApprovalprocess/HowDrugsareDevelopedandApproved/ApprovalAppilcations/AbbreviatedNewDrugApplicationANDAGenerics/UCM154150.pdf

12. Abbreviated New Drug Application (ANDA) : Generics.[Online].2013 Jul 07 [cited 2014 Jan 03];Available form:

    URL:http://www.fda.gov/Drugs/DevelopmentApporvalProcess/HowDrugsareDeveloped andApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/default.htm.

13. The United States Pharmacopeia 29 National Formulary 25: The Official Compendia of Standards. Asian ed.Rockville (MD): The united States Pharmacopeial Convention; 2006.P.365-7.

14. Douglas J.Pisano, David S.Manlus – FDA Regulatory Affairs, A Guide for Prescription Drugs, Medical

Devices and Biologics –New drug Application –Second edition-Marcel Dekker, inc-page no 69-108.

15. Significant Dates in U.S.Food and Drug Law History,http://www.fda.gov/AboutWeDo/History/Milestones/ucm128305.htm(assessed on March 09th 2010).