Review Article

A review on challenges in ANDA filing with an emphasis on refuse to receive standards

J. Yoshasri*, B. Kranthi Kumar and AE. Prabahar

Chalapathi Institute of Pharmaceutical Sciences, Lam, Guntur, India.

ABSTRACT

The pharmaceutical industry is one of the most regulated industries. No drug would be available in the market until and unless it get approved by Regulatory Authorities. Regulatory Affairs is a specialized profession in the pharmaceutical sector. A generic drug is a pharmaceutical product, usually intended to be interchangeable with a new drug (an innovator product) that is marketed after the expiry date of the patent or other exclusivity rights. A Generic Product must meet the standards established by FDA to be approved for marketing in U.S . This study covers the introduction of US FDA and challenges faced during ANDA filing and the reasons why USFDA refuse to receive the ANDA's (refuse to receive standards).U.S is considered as the most stringent regulated market and it is one of the largest pharmaceutical market but unfortunately , in recent years the rejection of ANDA's was increased by FDA. So, am enthusiastic to know the reasons behind the rejection of ANDA's and issuance of warning letters.

Keywords: ANDA, RTR, FDA.

1. INTRODUCTION

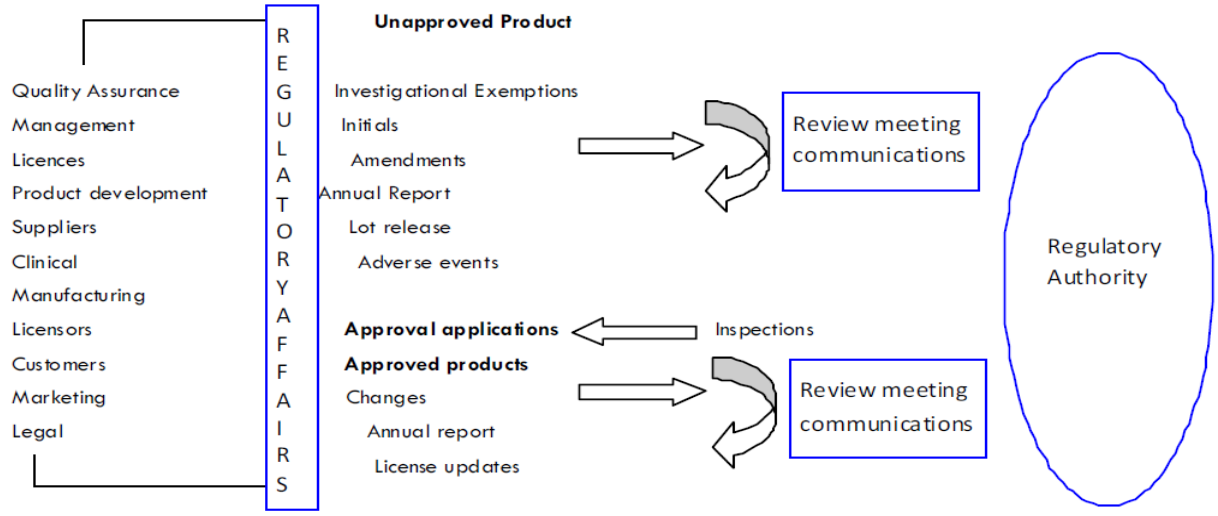
The health care system counts on drug regulatory affairs for good and safe effective medicines are available to the patients. The drug Regulatory Affairs is responsible for ensuring the efficacy, safety and quality of medicines in the product lifecycle, and is expected to carry out it tasks by applying the best available scientific knowledge and skills without bias[1].

Regulatory authorities are continually challenged by the rapid development and sophistication of medicinal product, new technologies and health care technologies. Any strategy to improve anything in pharmaceutical or any problem encountered in the area of pharmaceuticals need support from drug regulatory authorities. Such development poses a heavy demand on proper regulatory control system[2].

In drug Regulatory the government set legal requirements relating to drugs and specifies activities must be undertaken before and after a drug is placed on the market.Regulatory Affairs serve as a roadmap for prescription drugs, biologics and medical device development. Regulatory affairs focus on harmonization with international regulations, new drug applications, good manufacturing practice, quality system compliance, documentation requirements and facilitates an understanding of compliance and product approval, including clinical trial exemptions, fast track status and advisory committee procedures.

Regulatory Affairs in the pharma industry may be defined as "The interface between the pharmaceutical company and the regulatory agencies across the world."

1.1 SPECTRUM OF REGULATORY AFFAIR



1.2 RESPONSIBILITIES OF REGULATORY AFFAIR PROFESSIONAL[3]

Regulatory affair (medical affairs) professionals (aka regulatory professionals) usually have responsibility for the following general areas:

- Ensuring that their companies comply with all of the regulations and laws pertaining to their business.
- working with federal, state and local regulatory agencies and personnel on specific issues effecting their business .i.e. working with such agencies as the Food And Drug Administration or European Medicines Agency (pharmaceuticals and medical devices): The department of energy and : or the securities and exchange commission (banking)
- Advising their companies on the regulatory aspects and climate that would affect proposed activities. Describing the regulatory climate around issues such as promotion of prescription drugs.

1.3 MAJOR REGULATORY AGENCIES WORLD WIDE

- Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue of guideline for drug development, licensing, registration, manufacturing, marketing and labeling of pharmaceutical products.

Table 1: MAJOR REGULATORY AGENCIES WORLD WIDE

Country	Name of Regulatory Authority
USA	Food and Drug Administration (FDA)
UK	Medicines and Healthcare Products Regulatory Agency (MHRA)
Australia	Therapeutic Goods Administration (TGA)
India	Central Drug Standard Control Organization (CDSCO)
Canada	Health Canada
Europe	European Medicines Agency (EMEA)
Sweden	Medical Products Agency (MPA)
Italy	Italian Pharmaceutical Agency
Nigeria	National Agency for Food and Drug Administration and Control (NAFDAC)
Singapore	Centre for Pharmaceutical Administration Health Sciences Authority
Japan	Ministry of Health, Labor & Welfare(MHLW)
Brazil	Agencia National de Vigiloncia Sanitaria (ANVISA)
Sweden	Medical Products Agency (MPA)
Thailand	Ministry of Public Health
China	State Food and Drug Administration
Germany	Federal Institute for Drugs and Medical Devices
Malaysia	National Pharmaceutical Control Bureau, Ministry of Health
South Africa	Medicines Control Council
Sri Lanka	SPC, Ministry of Health

In the field pharmaceutical industry the process of drug development is mainly two ways, which are

1) New drug (innovation) development
2) Generic drugs development

New drug development process takes about 10 to 15 years and investment for development process also very huge amount.

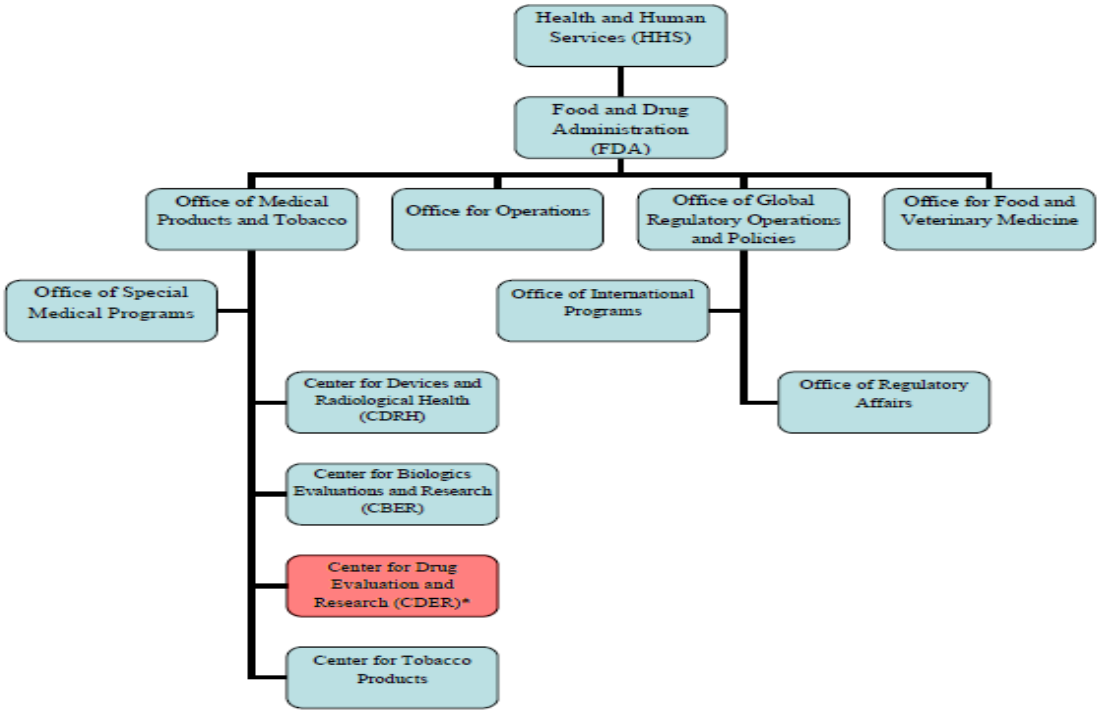
But generic drug development takes around 2 to 3 years as compared to new drug development.

1.4 DRUG DEVELOPMENT[4]

1.5 INTRODUCTION TO USFDA

The Food and Drug Administration (FDA or USFDA) is an agency of the United States department of Health and Human Services one of the United States federal executive departments. The USFDA is considered as the most stringent standards in approving the drug products into the market.

Regulatory frame work at the Food & Drug Administration, United States



2.ANDA

What is ANDA?

An Abbreviated New Drug Application (ANDA) contains data which when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the application that contains information to show that the proposed product is identical in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics and intended use, among other things to a previously approved application (the reference listed drug (RLD)

2.1 Scenario of Pharmaceutical Industry in U.S before & after 1984

Before 1984 a new brand name drug generally enters the market with many years of patent protection at that time manufacturer enjoys monopoly status. There is no generic available that can be substituted for the brand name drug.

In 1984 the pharmaceutical field for generics drugs altered substantially. this was the year when the bill, now known as the HATCH WAXMAN ACT which is also known as" The Drug Price Competition and Patent Term Restoration Act " proposed by senators Orrin Hatch and Henry A. waxman was approved, making it easier for generic drugs to enter the market.

The Hatch Waxman act (The Drug Price Competition Act and Patent Term Restoration Act) brought the following changes.

Reducing the cost associated with approval of generic drug. allowing early experimental use. compensating the branded drug manufacturers for the time lost from the patent term because of the regulatory approval formality. motivating the generic drug manufacturers "HWA strives to strikes a balance between the interests of branded drug manufacturers, generic drug manufacturers and the consumers.

- ✓ generic drugs no longer need to prone their safety and efficacy. under the act, generic drug manufacturers need only submit an Abbreviated New Drug Application (ANDA) to prove their products bioequivalence to the original branded drug.
- ✓ generic drugs are granted a 180 - day period of exclusivity. Either the first drug to file an ANDA, or the first group of drugs, is granted this period.
- ✓ manufacturers filing ANDAs can only do so for drugs that have not been patented.
- ✓ ANDAs can only be filed when a branded drug patent has expired
- ✓ generic drugs cannot go on to the market until the branded patent has expired
- ✓ branded drug patents must not have been infringed or proven invalid. (if a patent is shown to be invalid, the FDA must wait 30 months until it approves a generic.)
- ✓ Because branded drugs loose so much of their revenue when generic drugs are introduced, the act provided them with patent extensions options, which now average about three years.

creation of section 505(j) established the ANDA approval process. the timing of an ANDA approval depends on patent protections for the innovator drug. NDA must include any patent that claims the "drug" or " method" of using the drug for which a claim of patent infringement could reasonably be asserted. on approval of NDA, FDA publishes patent information for drug in ORANGE BOOK ("Approved Drug Products with Therapeutic Equivalence Evaluations")

When a generic manufacturer files an ANDA to the FDA , it must make one of four possible certifications (under section 505(j)(2)(A)(vii)) for each patent listed in the orange book for the brand name version of the drug . those four certifications are as follows:

Paragraph I certification : for the launch of generic drug is made when the innovator has not made the required information in the orange book .

Paragraph II certification : is made when the relevant patent has expired.

paragraph III certification : where there is patent but the applicant certifies that the generic version will come to market only after expiry of patent term .

Paragraph IV certification : There is a patent on the brand name drug, but it is invalid or will not be infringed by the generic.

Paragraph I & II Litigations:

An ANDA certified under paragraph I or II is approved immediately after meeting all applicable regulatory & scientific (efficacy, safety & bioequivalence requirements)

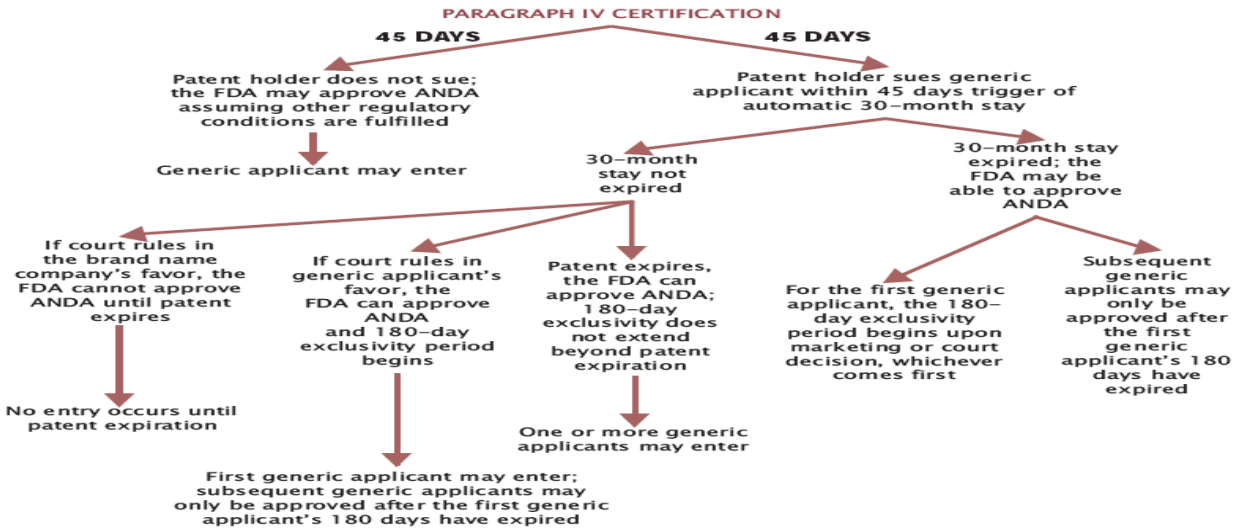
Paragraph III:

- At the time of filing, the product is still under patent protection but about to come off patent.
- The company wants to get ANDA approved in advance and keep the product ready for market on the day of patent term expires.
- The risk is that the innovator may get patent addition or exclusivity in the intervening time.
- For example, in one case, the brand name manufacturer claimed a patent on a method of use of metabolite produced by the administration of the drug
- The patent was for the combination of the chemical compound in the drug and stomach acid, when the drug was ingested.
- This patent was listed on the day the existing patents on the drug were due to expire.

As a result, the FDA could not approve the marketing of a generic that the manufacturer had already loaded on trucks for shipment.

Paragraph- IV Litigation[9]*:*

- The real gambling in generic market is ANDA with paragraph IV certification
- Para IV filing means the generic company is challenging the patent claim of innovator
- Here the ANDA is filed with the intension to market the product while the product is still under one or more patent protection
- Since the ANDA applicant feels that his product is not infringing the patent or the patent is invalid
- Once the ANDA with para IV certification is filed the real legal battle starts.
- Legal battle may result in huge profit or huge loss to the ANDA applicant
- Once the ANDA with para IV certification is filed the same has to be notified to the patent holder by the applicant
- The notice should include a detailed statement of the factual and legal basis for the ANDA applicant's opinion that the patent is not valid or will not be infringed
- If patent owner desires to files patent infringement suit against the ANDA applicant it has to do so within 45 days of the receipt of notice.
- FDA cannot give final approval to the ANDA for 30 months unless the court reaches a decision earlier in the patent infringement case.
- After 30 months the FDA may review the ANDA and give approval
- The first ANDA containing a paragraph IV certification is eligible for a 180-day period of exclusively .
- This 180 days begins either from the date it starts commercial marketing, or from the date of a court decision finding the patent invalid, unenforceable or not infringed, whichever is first.
- During this 180 days ANDA holder and the innovator only will be in the market and no other ANDA will be approved
- If there is no court decision and the first applicant does not begin commercial marketing of the generic drug, there may be indefinite delay in the beginning of the first applicant's 180-day exclusivity period.After the 180 days period, if the court ruling is in favour of patent holder the ANDA applicant has to pay a huge compensation decided by the court.



SOME PERILS

- The companies resorting to a Para IV filing must have the financial muscle and strong technical team to face the onslaught of litigation.
- In spite of the interest in this field, Para IV filings are risky, due to high litigation expenses.
- There is also the uncertainty of legal outcome. However, on winning a litigation, the costs are covered in the six months, which makes generic companies enthusiastic of the option.
- "Litigations on a single Para IV filing can cost the company about $20 million.
- However, a successful Para IV filing gives the generic drug company exclusive marketing rights for 180 days and it can reap huge profits during the period."
- There are many first-to-file on the same day in some cases

WHY PARA IV IS POPULAR ?

- Highly lucrative if properly proceeded
- More than 50% of the case got judgment in favor of generic
- Many frivolous patents giving loopholes to challenge

REQUIREMENTS FOR SUCCESSFUL PARA - IV

- Strong technical expertise to understand the technical intricacies of the patents
- Expertise in IPR to decide how to challenge the patents
- Strong financial background to meet the litigation cost

2.2.Submission Of ANDA application in eCTD format

Another major challenge for ANDA filing is it should be formatted according to the eCTD format and it should be submitted electronically.Electronic Common Technical Document - common format for Quality, safety and efficacy information .

- Electronic submission give more accountability and ease decision making process.
- eCTD is a superior technology.
- Establish a single application format for all applications.
- Avoids expensive internal processes and systems for receiving and archiving applications
- FDA stated effective Jan 1, 2008 all electronic submissions in eCTD format.
- FDA still prefers FTF's in CD and not in electronic gateway submission – litigation issues.
- USFDA's electronic gateway constantly update their database and linkages – with constant contact with applicants .
- eCTD is an interface for industry to agency transfer of regulatory information composed of:
  - ✓ XML backbone
  - ✓ Modules
  - ✓ Granul
- folder or tree structure.
- XML backbone file is Table of Contents .
- Additional 'util' information (Document type definition rule book for tags and attributes)
- Regional information and files.

Preparing documents

Templates should be used where possible
Documents to be:

- technically correct
- have the right granularity
- conform to external regulations/guidelines
- consistent with internal standards and styles – naming conventions, etc.
- 'intelligent' PDF files

MODULES in eCTD format

- Module 1 : Administrative
- Module 2 : Summaries
- Module 3 : Quality (CMC)
- Module 4 : Non clinical study reports

GRANULARITY

- Defines how the completed document is broken down, tagged and stored for reuse
- Determines smallest piece of information that is reusable
- Changing granularity during lifecycle is difficult, therefore must be planned at the beginning.
- FDA Guidance-Each document should be provided as a separate file. A file converted to special PDF format enabling links and bookmarks to be applied, and hence is searchable.

eCTD submission checklist

- eCTD Software

- Software training and support from the supplier
- Compiling and eCTD
- eCTD hyper linking
- QC of eCTD
- Submit eCTD on CD/DVD or Use electronic gateway

TEST SUBMISSON

- ✓ Submit a Pilot/Test Submission to the Agency
- ✓ Request for an Pre-Assigned eCTD number
- ✓ File by electronic submission gateway or Mail
- ✓ Send an e.mail to esub@fda.hhs.gov
- ✓ Ask for sample eCTD submission
- ✓ Submit a sample submission
- ✓ Agency checks the sample submission
- ✓ Resolve technical issues
- ✓ Resubmit sample submission
- ✓ Get Secure e.mail
- ✓ Pre-assigned eCTD number expires in 60 days
- ✓ Read and follow information onhttp://www.fda.gov/cder/ogd/#enuber
- ✓ Create a Gateway Test Account : esgprep@fda.gov
- ✓ Send Test/Pilot Submission
- ✓ FDA ESG Validates
- ✓ Create Actual Production Account
- ✓ Submit eCTD

REGULATORS CONCERN

- Ability to process without error in review system
- Is the submission content readily available
- Security/Accountability
- Consistently good application across agencies
- Review experience

The ANDA should be formatted according to the eCTD format and it should be submitted electronically and FDA will refuse to receive an ANDA that is submitted as a single, continuous, unbookmarked PDF file. These are the major challenges in filing an ANDA application to the USFDA.

The US Food and Drug Administration (FDA) has released two new guidance documents intended to clarify for generic drug makers the criteria by which the agency determines which applications it will "refuse to receive" due to deficiencies in an Abbreviated New Drug Application (ANDA) filing**.**

2.3.ANDA Submissions - Refuse - to - Receive Standards

The Reasons Why FDA Refuses An ANDA Application

- The submission of an ANDA, as with most applications submitted to FDA, involves two stages: the submission of the application to FDA, and FDA agreeing to file the application with its review team.
- Each stage has its own set of submission criteria, which are meant to weed out deficient applications which would otherwise cause an application not to obtain approval.
- For example, if FDA notices that an application is missing an entire section, the agency might refuse to accept it. Similarly, if a section is complete but is missing key information, FDA might similarly refuse to accept an application.
- This presentation will address Refuse to Receive standards when Submitting ANDAs and Prior approval supplements (PASs) and highlights deficiencies that may cause FDA to refuse-to-receive an ANDA.
- A refuse-to-receive decision indicates that FDA determined that an ANDA is not sufficiently complete to permit a substantive review.
- Generic Drug User Fee Amendments of 2012 requires enhanced refusal to receive standards for ANDA.
- Practice of submitting an ANDA that is not sufficiently complete to permit a substantive review and then repairing it in the course of an extended review period needs several cycles of FDA response.
- FDA evaluates each submitted ANDA individually to determine whether the ANDA can be received.
- The receipt of an ANDA means that FDA made a threshold determination that the ANDA is sufficiently complete to permit a substantive review. FDA may in certain cases and will in others, refuse-to-receive an ANDA. (21 CFR 314.101)
- Generally, FDA will not receive an ANDA unless it contains the information required section 505(j) of the FDC act and as specified in more detail in
  21 CFR 314.50
  21 CFR 314.94
  21 CFR 320.21

21 CFR 320.22

- Recent data underscore the need for improvement in the quality of original ANDA submissions.
- Between 2009 and 2012 FDA refused to receive 497 ANDAs
  12% in 2009
  18% in 2010
  5.5% in 2011
  9.4% in 2012
- FDA refuse- to- receive ANDA'S were serious bioequivalence and chemistry deficiencies , format or organizational flaws ,clinical deficiencies ,Inadequate microbiology (sterility assurance) information and Incorrect reference listed drug (RLD) was cited as the basis of submission.
- FDA 's filing review

FDA will determine any major or minor deficiencies

- Major deficiency
  - ✓ One that cannot be easily remedied .
  - ✓ Certain deficiencies found in 21 CFR 314.101(d) or 21 CFR 314.101(e) .
  - ✓ Will not permit a substantive review under 21 CFR 314.101(b)(1).then FDA will refuse - to- receive the ANDA .
- Minor deficiency
  - one that can be easily remedied

FDA will allow the applicant a prescribed time period to provide a response to such deficiencies.

- If an ANDA contains ten or more minor deficiencies or one or more major deficiencies. Then FDA will consider such an application not sufficiently complete to permit a substantive review under 21 CFR 314.101(b) (1).
- FDA will notify the applicant that FDA considers the ANDA not to have been "received".
- applicant can submit additional materials to correct the deficiencies
- Amended ANDA will consider the new ANDA
- date of receipt will be the date the amendment to the ANDA is received
- applicant will require to pay the new GDUFA fee
- if an ANDA contains fewer than ten minor deficiencies
  - FDA will notify the applicant of the deficiencies usually by phone, e-mail, or fax
  - Applicant can satisfactorily amend the ANDA within 7 calendar days
  - If FDA receives the application as amended, the application will be considered received as of the date on which it was first submitted to FDA.
  - If within 7 calendar days the requested information is not received, FDA will refuse to receive the ANDA.
- There may be circumstances, however, under which an exception to or a waiver of, a regulatory requirement may be granted.
- FDA will consider the merits of such circumstances on a case- by -case basis

2.3.1.Major reasons for ANDA rejection by USFDA

- Form 356h
- Organization /Format
- Non- Payment Of GDUFA Obligations
- Lack Of Designated U.S Agent For A Foreign Applicant
- Failure To Provide Environmental Assessment (Ea) Or Claim Of Categorical Exclusion
- Citing A Pending Suitability Petition As A Basis Of Submission
- Reviews For API
- Chemistry, Manufacturing, And Control, Deficiencies

A)Inactive ingredients

a) Inactive ingredients exceeding the Inactive Ingredient Database (IID) limit

b) Changes to Non- Exception inactive ingredients in Parentral, ophthalmic and Otic products.

c) Elemental iron impurities

B) Inadequate Stability

1) Number of Batches And Length Of Studies

2) Container Closer system

C) Packaging Amount Considerations

D) Batch Records

E) Method Validation / Verification Reports

F) Special Consideration for Transdermal Patches

1) Matrix Systems

2) Reservoir systems

G) Scoring and Conditions Use

1) Functional Scoring Configurations That Are Inconsistent with the RLD

2) Fill Volumes For Parentral Drug Products That Differ From The RLD

3) Differences In Packaging And /Or Labeling That May be associated with the safe / effective use of the drug product

H) Microbiology Considerations

1) Bioequivalence and Clinical Deficiencies

2) Failed In vivo BE Studies

3) Alternate BE Studies

4) Q1/Q2 Sameness Requirement For Consideration of an in-vivo BE study wavier

5) Inadequate Dissolution Data (In vitro Studies)

6) Miscellaneous Factors Study Information BE Table

7) Missing Case Report forms

I)Dispute of a Refuse to Receive Decision

- ✓ If an applicant disagrees with or wishes to discuss a refuse-to-receive decision.
- ✓ The applicant should present its concerns first to the contact person named in the refuse-to-receive letter.
- ✓ If this does not resolve the matter, a teleconference can be scheduled with the applicant, the contact person, a supervisory consumer safety officer, and if needed, the appropriate division director.
- ✓ If the matter still remains unresolved, the applicant can use the dispute resolution procedure; (see 21 CFR 314.103 and guidance for industry Formal Dispute Resolution: Appeals above the Division Level

2.3.2.JUSTIFYING IMPURITY LIMITS IN DRUG SUBSTANCES AND PRODUCTS

All ANDAs must contain a description of the composition, manufacture and specification of the drug substance and the drug product (21 CFR 314.94(a)(9) and 314.50(d)(1)).

Applicants are required to submit a full description of the drug substance including, but not limited to: its method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and the specifications necessary to ensure the identity, strength, quality, and purity of the drug substance (§314.50(d)(1)(i)).

Applicants are also required to submit a list of all components used in the manufacture of the drug product (regardless of whether they appear in the drug product) and a statement of the specifications for each component and the specifications necessary to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product (§314.50(d)(1)(ii)(a)). To ensure purity, applicants should propose and justify appropriate limits of the impurities in their drug substances and drug products.

Refusal to receive for lack of impurities information

FDA may refuse to receive an ANDA that is not sufficiently complete because it does not on its face contain information required under §314.50, which includes a demonstration of the purity of the drug substance and drug product and information on impurities and residues (§314.101(d)(3))

FDA may refuse to receive an ANDA for:

1) failing to provide adequate justification for proposed limits in drug substances and drug products for specified identified impurities that are above qualification thresholds;
2) failing to provide adequate justification for proposed limits for specified impurities that are above identification thresholds.

Providing proper justification for impurity limits

If a generic product contains specified identified impurities that exceed the qualification thresholds or specified unidentified impurities that exceed identification thresholds, the ANDA should propose impurity limits and including supporting data to demonstrate that:

1) the observed impurity levels and proposed impurity limits do not exceed the level observed in the reference listed drug product;
2) the impurity is a significant metabolite of the drug substance;
3) the observed impurity levels and proposed impurity limits are adequately justified by the scientific literature; or the level do not exceed that has been evaluated in toxicity studies

The ANDA Checklist is good at describing what must be delivered, but there's no room for detail on what has to be in each of the documents. This guidance does a much better job of describing just what makes a generic drug filing "good enough."Lastly, you can dispute such a refusal via the contact in the refuse- to-receive letter, and then escalate it via teleconference or using CDER's dispute resolution guidance [12].

3. CONCLUSION

I hereby conclude that the regular reviews by the higher authorities potentially identifies problems in implementation of quality standards in an organization

- The refusal of ANDA's by the USFDA will only be reduced when the companies are through with the cGMP regulations and be updated with FDA regulatory or statutory requirements time – to – time.

BIBLIOGRAPHY

1. Introduction to regulatory affairs. Published in Regulatory Affairs Professional Society(RAPS). [Internet] Available from: http://www.raps.org/uploadedFiles/Site_Setup/Home_Page/About_RAPS/The_Regulatory_Profession/PDF_Framework_Whitepaper.pdf.
2. Pharmaceutical Markets. Published by Alistair Davidson Senior Director, Global Regulatory Development, PPD.[Internet] Available from: https://www.topra.org/sites/default/files/assets/reg._strategy_for_the_emerging_markets__a.davidson.pdf
3. Devendra Pratap Singh .Generic drug access in global scenario. Published in JPSR.[Cited in 2014] [Internet] Available from: http://www.jpsr.pharmainfo.in/Documents/Volumes/Vol2Issue2/jpsr02021005.pdf pharma info 2010.
4. Montu P.B, Rajendra Songara. Design and development of common Generic product development strategy. Published in Asian journal of pharmaceutical science and research[Internet][Cited online on 25th June 2014] Available from: http://www.ordonearresearchlibrary.com/data/pdfs/ajpsr2.pdf
5. Introduction to Generic Drug. Published in WHO. [Internet] Available from: http://www.who.int/trade/glossary/story034/en/
6. Stages involved in Generic Drug Development. Generic drug Development Published by Dr.v enkateswarlu Head of FR&D Dr.Reddys laboratories. [Internet] Available from: http://www.authorstream.com/Presentation/ravikumarpharma-1090595-generic-product-development-by-dr-venkateswarlu/
7. Specific Requirements for Chemical Drugs.[Internet] Available from: http://eng.sfda.gov.cn/WS03/CL0769/98162.html
8. Registration Categories of Drugs and Applications.[Internet] Available from:http://eng.fda.gov.cn/WS03/CL0769/98158.html
9. Collection of information about challenges, http://www.fda.gov
10. Online resource for latest information from the world of pharmaceuticals http://www.drugregulations.org
11. Collection of information about GDUFA guidelines http://www.fda.gov
12. Refuse to receive standards guidelines highlights the deficiencies that may cause FDA to RTR an ANDA. http://www.authorstream.com/Presentation/ravikumarpharma-1090595-refuse-to-receive- standards-by-ravikumar/