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# A review on ANDA submission requirements for Generic drugs: "Paragraph IV certification" as per FDA CDER guidelines

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## ABSTRACT

USFDA is one the most regulated agencies wherein the submission process is most critical. The study depends on how to submit ANDA application as per FDA, CDER guidelines in paragraph IV submission in Federal Food, Drug, and Cosmetic Act (FD&C Act). No drug would be available in the market until and unless it get approved by Regulatory Authorities. "Paragraph IV Certification" is useful for exclusive right to market the generic drug for 180 days. Submission is for the company which is seeking to copy branded drug before expiration of patents to get benefit over it, a generic applicant must provide in its application a "certification" that a patent submitted to FDA by the brand-name drug's sponsor and listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book). A Generic Product must meet the standards established by FDA in RLD (Reference listed drug). This study covers the introduction of ANDA submission to FDA and ACT related to the submission in to paragraph IV and the details of ANDA filling in the eCTD format and overview of review process the checklist to the applicant.

**Keywords:** Orange Book, Paragraph IV, Certification, Submission, Generics, CDER, ANDA, USFDA, NDA.

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## 1. Introduction

The Food and Drug Administration (FDA or US FDA) is an agency of the United States department of Health and Human Services one of the United States federal executive departments (1). The USFDA is considered as the most stringent standards in approving the drug products into the market. "ANDA" is the abbreviation for "Abbreviated New Drug Application". It contains data which when submitted to FDA's Center for Drug Evaluation & Research, Office of Generic Drug, provides for the review & ultimate approval of a generic drug product (2). The mission of FDA's Center for Drug Evaluation and Research (CDER) is to ensure that drugs marketed in this country are safe and effective. In the ANDA submission to FDA CDER does not test drugs, although the Center's Office of Testing and Research does conduct limited research in the areas of drug quality, safety, and effectiveness (3).

Many companies submit is ANDA Application It Is the responsibility of the company seeking to market a drug to test it and submit evidence that it is safe and effective A team of CDER physicians, statisticians, chemists, pharmacologists, and other scientists reviews the sponsor's ANDA containing the data and proposed labeling. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the public. All approved products, both innovator and generic, are listed in FDAs Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) (4).

"A drug product that is comparable to a brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use". It termed "abbreviated" because they generally not required including preclinical (animal) and clinical (human) data to establish safety and effectiveness. Basic Generic Drug Requirements are: Same active ingredient(s) Same route of administration Same dosage form Same strength Same conditions of use Inactive ingredients already approved in a similar ANDA (i.e., performs in the same manner as the innovator).

An important section of Hatch-Waxman Act actually encourages generic companies to challenge patents (5). If a generic company is the first to file its Abbreviated New Drug Application (ANDA) with a Paragraph IV certification (5) and prevails in the subsequent lawsuit, that generic company is granted a period of market exclusivity of 180 days**.**

***History of Generic Drug Approval***

- As recently as 40 years ago, drug companies could release new products with far less testing than is required today the real test of a drug's safety and effectiveness came after it went to market. If too many patients had bad reactions, the drug could be pulled off the shelves. The danger of this approach became tragically clear when the sedative thalidomide caused thousands of devastating birth defects in Europe, Canada, Latin America, Africa, and Asia (6).
- In 1970 FDA established the ANDA as a mechanism for the review and approval of generic versions.
- Before 1978, generic product applicants were required to submit complete safety and efficacy through clinical trials Post 1978,
- Applicants were required to submit published reports of such trials documenting safety and efficacy.
- Neither of these approaches was considered satisfactory and so originated Hatch Waxman Act on 1984 (7).

***Indispensability grounds for Generics*** (8)

- Contain the same active ingredients as the innovator drug (inactive ingredients may vary).
- Must be identical in strength, dosage form, and route of administration.
- Must have same use/indications
- Must be bioequivalent.
- Must have same batch requirements for Identity, Safety & Purity.
- Must follow strict standards of FDAs GMPs**.**

**2. Related act's to the ANDA Submission**

***Hatch-Waxman Act***

The Drug Price Competition and Patent Term Restoration Act (known as the "Hatch-Waxman Act" enacted in 1984. In 1984, Congress enacted the Hatch-Waxman Act as an amendment to the Federal Food, Drug, and Cosmetic Act (the "FFDCA") and the Patent Act. The two main goals are to encourage innovation in pharmaceutical research and development and to help generic drugs reach the market more quickly (9). "The Hatch-Waxman Act is an act dealing with the approval of generic drugs and associated conditions for getting their approval from FDA, market exclusivity, rights of exclusivity, patent term extension and Orange Book Listing**."**

***General provisions of the act***

Creation of section 505(j), Section 505(j) established the ANDA approval process. The timing of an ANDA approval depends in part on patent protections for the innovator drug NDA must include any patent that claims the "drug" or a "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") (10).

***Objective of the act***

- FDA publishes patent information on approved drug products in the Orange Book
- Maintaining list of patents which would be infringed.
- Only Bioavailability studies and not clinical trials needed for approval.
- Para I, II, III and IV certifications
- Data exclusivity period for New Molecular Entities.
- Extension of the original patent term.
- The "Bolar" Provision (10)

***Recent additions to the Hatch-Waxman Act Under the "Medicare Prescription Drug and Modernization Act", 2003***

- Non-extension of the 30-month period
- Time limit for informing patent owner.
- Provision for allowing declaratory judgment.
- Benefit of exclusivity for several ANDAs filed on same day allowed (10)

**3. ANDA certification clauses**

ANDA has four types of the Submissions. ANDA applicants must certify to each patent for the Reference Listed Drug

- Paragraph I – patent not submitted
- Paragraph II – patent has expired
- Paragraph III – date patent will expire
- Paragraph IV – patent is invalid or will not be infringed (11)

***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 (11)

***Patent Certifications***

FDA aspires to continually improve its pre-ANDA (abbreviated new drug application) interactions with applicants. To facilitate these interactions and keep stakeholders as informed as possible, the agency regularly

publishes information on suitability petitions and Paragraph IV patent certifications (12).

### *Paragraph IV- Patent Certifications*

FDA approval to market a generic drug before the expiration of patents related to the brand-name drug that the generic seeks to copy. To seek this approval, a generic applicant must provide in its application a "certification" that a patent submitted to FDA by the brand-name drug's sponsor and listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book) is, in the generic applicant's opinion and to the best of its knowledge, invalid, unenforceable, or will not be infringed by the generic product. This certification is called a "paragraph IV certification." The first company or companies to submit an application that is determined by the agency to be "substantially complete" upon submission and contains a paragraph IV certification to at least one of the patents listed in the Orange Book is generally eligible for the exclusive right to market the generic drug for 180 day (12).

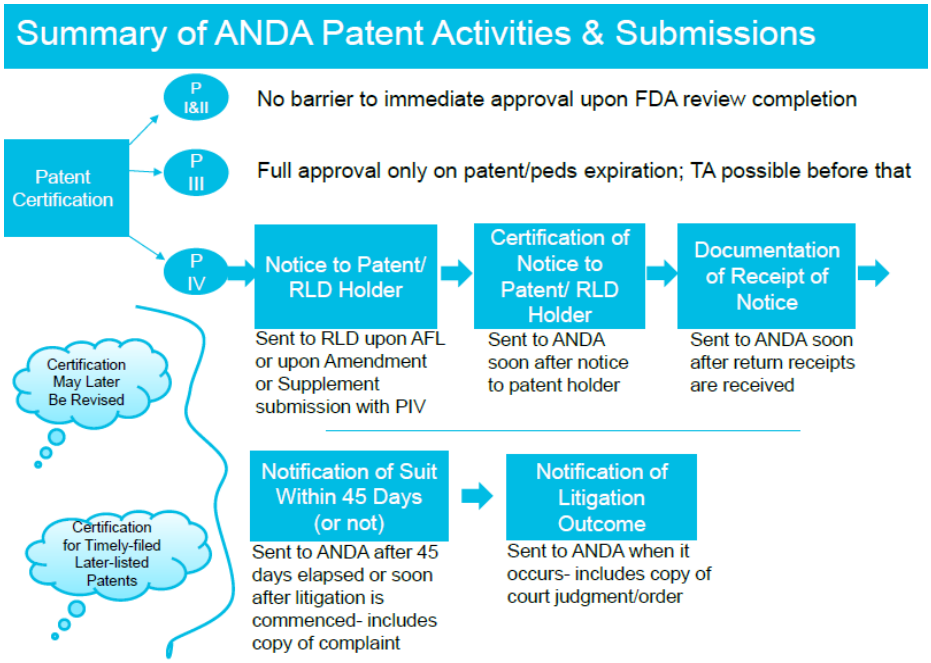


**Figure 1.**Over view of paragraphs I to IV (11)

### *Paragraph IV Certifications List*

**Table 1** FDA listed drugs with Paragraph IV Certifications (12)

| Drug name | Dosage form | Strength | RLD/NDA | Date of submission |
|---|---|---|---|---|
| Abacavir Sulfate, Dolutegravir and Lamivudine | Tablets | 600 mg/50 mg/300 mg | Triumeq/ 205551 | 8/14/2017 |
| Amphetamine | Extended-release OrallyDisintegrating Tablets | 3.1 mg, 6.3 mg, 9.4 mg, 12.5 mg, 15.7 mg, 18.8 mg | Adzenys XR- ODT 204326 | 5/10/2016 |
| Arsenic Trioxide | Injection | 1 mg/mL | Trisenox /21248 | 8/11/2015 |
| Azelastine Hydrochloride and Fluticasone Propionate | Nasal Spray | 137 mcg/50 mcg per spray | Dymista/ 202236 | 6/13/2014 |
| Balsalazide Disodium | Tablets | 1.1 g | Giazo /22205 | 11/5/2013 |
| Azelaic Acid | Gel | 15% | Finacea /21470 | 7/27/2012 |
| Argatroban in Sodium Chloride* | Injection | 1 mg/mL, 50 mL vials | Argatroban /22434 | 12/16/2011 |

**Table 2** New Paragraph IV Certifications as of June 14, 2018 (12)

| Drug name | Dosage form | Strength | RLD/NDA | Date of submission |
|---|---|---|---|---|
| Levocetirizine Dihydrochloride | Oral Solution | 0.5 mg/mL | Xyzal Allergy 24 HR (OTC) 209090 | 1/4/2018 |

***Paragraph IV certification Section***

*According to section 505(j)(2)(B)(i), 2157 CFR*

The ANDA applicant must provide appropriate notice of a paragraph IV certification to each owner of the patent that is the subject of the certification and to the holder of the approved NDA to which the ANDA refers (13).

*Section 505(j)(5)(B)(iv)*

An incentive for generic manufacturers to file paragraph IV certifications and to challenge listed patents as invalid, or not infringed, by providing for a 180-day period of marketing exclusivity (13).

***Patent Challenge Successful***

- Award of 180-Day Exclusivity Period
- Awarded to first ANDA holder to file a complete application with patent challenge
- Protection from other generic competition – blocks approval of subsequent ANDAs
- Protection triggered by: First commercial marketing Forfeiture provisions (13).

***Para IV procedure***

1. Applicant files the application to USFDA for ANDA paragraph- IV certification.

2. Patent holder has to be notified of application by the Applicant within 20 days.

3. Litigation starts in court, if patentee files infringement suit against ANDA applicant within 45 days from receiving of notification in the court.

4. When court gets the infringement suit, it gives 30 months stay for the FDA to approve the application, otherwise FDA can approve or disapprove the application; no stay would be given to the FDA.

5. If Court decision is in respect to applicant, he gets the 180 days market exclusivity (in this exclusivity period, no one other than applicant can market the product for 180 days) if the decision is against the applicant, then the available option will be Para-II/III.

6. If 30 months stay is directed by the court then FDA is not allowed from approving the application for 30 months. Or until court holds that the patent is invalid or would not be infringed. Alternatively if court gives decision in favor of patentee, FDA will not approve ANDA.

7. Once 30 months have passed, FDA will approve the application, even though litigation is ongoing and after approval both parties can market their product until the decision would be given by the court within the patent expiration period (14).

**4. FDA Review Procedure**

1. As a part of the review process FDA will send the application of the applicant to OGD/CDER review team for the approval.

2. If the submitted application is not complete or any deficiencies are identified, then "refuse to file letter" is issued by the OGD/CDER to the applicant.

3. In case the application has found complete without any deficiencies then it's accepted & application is then sent to the internal review team for the identification of Bio-Equivalence, Chemistry/Microbiology, Plant inspection & Labeling review issues.

4. If any pending results are found in the application, Bio-Equivalence deficiency letter, & pending satisfactory results are issued accordingly to the applicant.

5. Once the ANDA submission is complete and acceptable without any further queries, the applicant finally receives FDA approval letter (14).

Detailed information on Paragraph IV challenges for drugs launched since 1994, to understand their impact on the industry over time given in figure 2.

**Table 3** Innovator vs Generics

| Parameters | Innovator drug | Generic drug |
|---|---|---|
| Active ingredients | same | same |
| Safety & efficacy | same | same |
| Quality & strength | same | same |
| Performance and standards | same | same |
| Costs/prescription | Highly expensive | Less expensive |
| FDA inspection of manufacturing facilities | yes | yes |
| FDA reviews reports of adverse reactions | yes | yes |
| FDA reviews drug labeling | yes | yes |
| Extensive research and development investments | yes | yes |
| Expensive marketing & advertising | yes | yes |
| Patent protection | | |
| FDA review to show active ingredient is equivalent to original NA | NA | NA |
| Product Development | 12 years | 2-4 year |

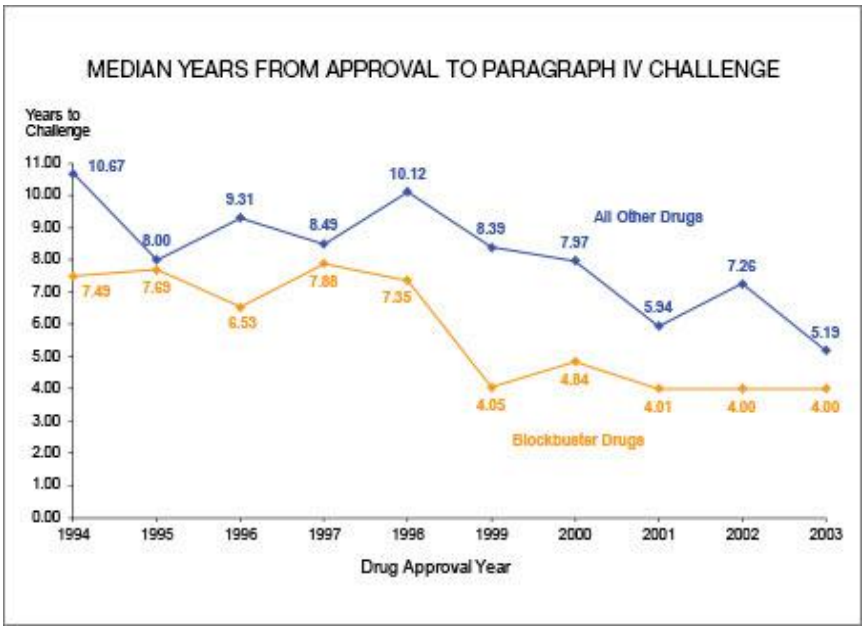


**Figure 2.** Over view of paragraphs IV challenges graph (15)

## 5. ANDA submission requirement under Para IV

### *ANDA Filling Requirement (16)*

*ANDA Forms*

In order to submit a complete ANDA, applicants should review the following forms and prepare all that are required for your specific application.

- Filing Review of ANDAs MAPP including filing checklist
- Form FDA-356h: Application to Market a New Drug, Biologic, or Antibiotic Drug for Human Use
- Instructions for using Form FDA-356h Form FDA-3794: GDUFA Cover Sheet
- Instructions for creating a GDUFA Cover Sheet
- Form FDA-3674: Certification of Compliance
- Instructions for completion of Form FDA-3674
- Generic Drug User Fee Payment Information
- Drug Master Files (DMFs)

### *Requesting a Pre-Assigned ANDA Number (16)*

Applicants may request a pre-assigned ANDA number ONLY when submitting a new ANDA. If you are converting an established ANDA to eCTD, you MUST use the original ANDA application number. For further guidance, please view Requesting a Pre-Assigned ANDA Number

***Electronic Submissions:*** This is CTD structure which is submitted in the eCTD in the ANDA submission for FDA This is prepared as following the ICH guideline.

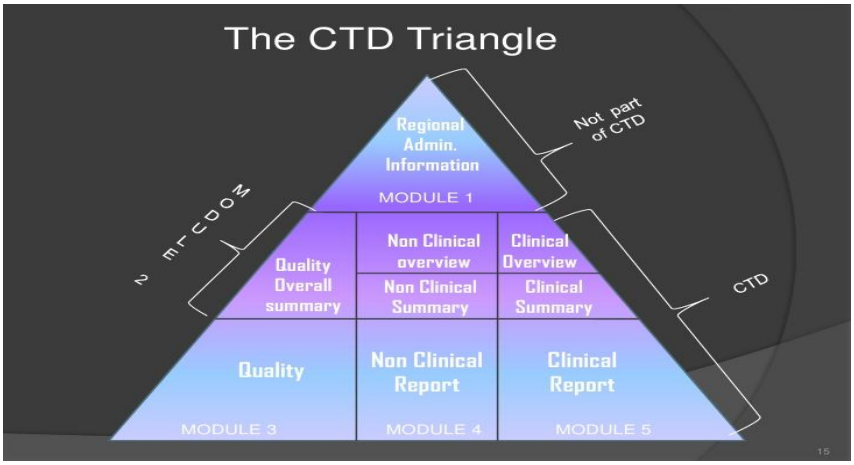


**Figure 3.** Modules described in the CTD format (18)

### *Modules in CTD*

*Module I: Administrative and Prescribing Information (19)*

1. Table of Contents.

2. Includes data of Administrative Documents entailing: Patent Information on patented product, Patent Certifications, Debarment certification.

3. Prescribing information like Package and container labels, packaging inserts, patient leaflets, etc.

4. Labelling Comparison between Innovator and Generic drug.

*Module II: Summaries and Overviews (11)*

1. Table of Contents.
2. Introduction to Summary Documents.
3. Overviews and Summaries: Module II should contain documents like:
   - M4Q: The CTD- quality
   - M4S: The CTD- safety

*Module III: information on product quality (20)*

1. Table of Content.
2. Body of Data.

Literature Reference

*Module IV: non clinical study reports (21)*

Not required in ANDA Filing.

*Module V: clinical study reports (22)*

1. Table of Contents.
2. Study Reports including Case Report Forms and Case Report Tabulations.

The FDA will no longer accept paper ANDA submissions. All ANDA submissions MUST be in eCTD format. eCTD submission sizes 10 GB**.** eCTD technical files submission was described in the ICH M2 technical specification.

***eCTD composed of two types of specification***

Content specification – As defined by ICH

Technical specification – Electronic softwares

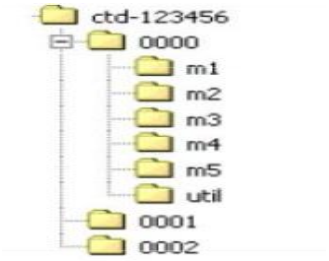


**Figure 4.** Example of eCTD template (23)

***Test Submission***

- Submit a Pilot/Test Submission to theAgency
- Request for an Pre-Assigned eCTD number
- File by electronic submission gateway orMail
- 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
- Send Test/Pilot Submission
- FDA ESG Validates
- Submit eCTD (24)

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**.**

***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.
- refuse-to-receive decision indicates that FDA determined that an ANDA is not sufficiently complete to permit a substantive review.
- FDA evaluates each submitted ANDA individually to determine whether the ANDA can be received.
- 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.
- 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.
- 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 (25).

***ANDA filing checklist***

Check list in FDA mentioned http://fdaguidance.net /anda-filing-checklist/, which is most useful for the applicant to submission of technical part without any error. 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 (26).

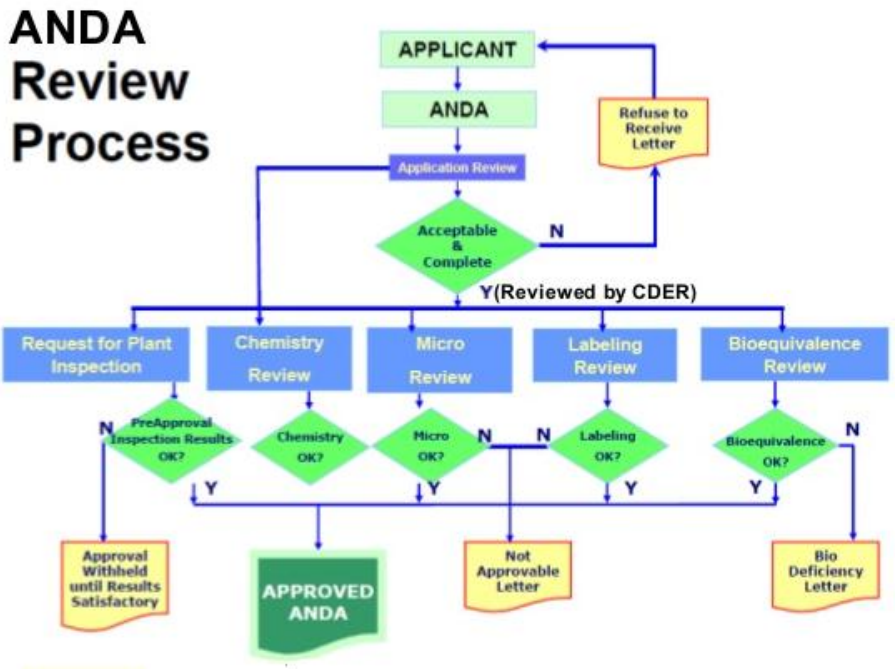


**Figure 5:** Flowchart image of ANDA review process (27)

## 6. Conclusion

From the study it was found that (ANDA) submission under the paragraph iv certification is very challenging, we had provided this review based on researching so many blogs and websites in depth as conclusion that Para - IV certification applicant has to face a lot of problem to get the benefits, since 2000, many companies have entered the P-IV Market and there has been a steady uptick in P-IV cases (per ParagraphFour.com research). For example, in 2005, 77 P-IV cases were filed, 2010 -- 234 cases were filed and in 2015 -- 402 cases were filed. Hence the ANDA submission is most important for the generic drugs companies for the marketing with low-cost compare to branded drugs there for the Para IV certifications submission play major role in submission process.

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## Conflict of interest

The authors declare that there are no conflicts of interest.

## Abbreviations

- USFDA (Food and Drug Administration)
- ANDA (Abbreviated New Drug Application)
- GDUFA II (Generic Drug User Fee Act),
- RLD (Reference listed drug), FD&C Act (Federal Food, Drug, and Cosmetic Act)
- CDER (The Center for Drug Evaluation and Research)

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