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RESEARCH ARTICLE

# Risk Assessment of Failures in Generic Drug Development and Approval Procedure under Competitive Generic Drug Therapy and Patent Challenge Exclusivities Provided by the United States Food and Drug Administration

M Vivek Reddy[1], GNK Ganesh[1*], B Babu[2], Ramesh Jagadeesan[3], Praharsh Kumar MR[4]

1. Department of Regulatory Affairs, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, Nilgiris, Tamil Nadu-643001, India.
2. Department of Pharmaceutical Analysis, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, Nilgiris, Tamil Nadu-643001, India.
3. Department of Analytical and Product development. Recipharm Pharmaservices, Bangalore, Karnataka-560002, India.
4. Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, Nilgiris, Tamil Nadu-643001, India.

**Objective**: The United States Food and Drug Administration implemented two exclusivity programs Competitive generic therapy and Patent Challenge exclusivity to develop generic drugs, which provide a 180-day monopoly market for first generic applicants in the United States of America. The aim of the present study is to find the root cause of failures in developing and filing the first generic drugs under these exclusivities and to compare both the exclusivities to find the merits and demerits. **Methods**: We used descriptive statistics for data analysis of both the exclusivities and Risk assessment was conducted on 14 industries to find the root cause of failures in every stage of the approval procedure by FMECA (Failure mode, Effects and Criticality Analysis). **Results**: We found 44% of rejections in competitive generic therapy drugs and 30% of rejections in patent challenge exclusivity drugs. The risk analysis conducted on failures found that, in drug selection, 6% of failures are occurred due to rare diseases. In drug development, 9% of failures are occurred due to formulation failures. In pre-approval, 10% of failures are occurred due to secondary patents. In post-approval, 6% of failures are occurred due to product changes after approval. **Conclusion**: We hope this study can give an idea for small and medium companies in developing countries for the early development of generic drugs for life-threatening diseases.

**Keywords**: generic drug exclusivity, competitive generic therapy, patent challenge exclusivity

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## Introduction

Generic drugs are essential for patients who are suffering from rare diseases and some life-threatening diseases. There is a need to develop generic drugs immediately after patent expiry. There are many categories in generic drugs they are small molecules, complex molecules and biologicals. Developing complex generics is more critical when compared to normal generics [1]. In support of generic companies to develop high-quality, affordable medicines, the United States Food and Drug Administration (US FDA) introduced two exclusivities that provide 180-day monopoly marketing rights. These are Competitive Generic Therapy (CGT) exclusivity and Patent Challenge (PC) exclusivity.

CGT exclusivity was introduced on 18th August 2017, under section 506H, this established a new procedure for certain drugs, where there is an inadequate generic competition even after the patent expired. For the early development of those drugs, FDA introduced incentives by reducing review cycles and focused on the expedited review and expedited development assistance [2-3]. For claiming this 180-day exclusivity period, the FDA kept a time-bound of 75 days to initiate the first commercial marketing. If the applicant fails to initiate the marketing within the prescribed time, it leads to CGT forfeiture; then, the exclusivity claim will not apply [4].

The Patent Challenge 180-day exclusivity (PC) has to be filed through Paragraph IV certification. To seek this approval, the generic company must provide a certification that a patent submitted by the innovator company to FDA, which is listed in FDA's orange book, is invalid, unenforceable, or will not be infringed by the generic product. The 180-day exclusivity is the first company or companies which submit the complete dossier determined by the agency and should contain Paragraph IV certification to one of the patents listed in the orange book. If the generic applicant challenges a patent in court through paragraph IV certification, it must give prior intimation to the patent holder regarding Abbreviated New Drug Application (ANDA). If a patent holder filed a patent infringement suit within 45 days of the ANDA notification, the FDA would postpone the ANDA for 30 months, commonly referred to as 30 months stay [5].

The branded companies will prevent the generic entry through strategic secondary patents and new clinical indications to extend the patent life through life cycle management [6-9]. If there are no valid secondary patents for branded drugs, they will go for settlement with the first

* Correspondence to: GNK Ganesh
E-mail: gnk@jssuni.edu.in

generic applicant, it will again increase the branded market share and lead to inadequate generic competition [10]. The timing of generic drug entry is crucial in the drug price; if there is no generic competition, the price will increase if more generic competition is there, the price will decrease [11-13]. So, there will always be price dispersion [14].

## Materials and Methods

### Data sources

The data required for this study was publicly available from the web source. The number of ANDA's approved, first generic approved drugs, Patent challenge, Competitive generic therapy drugs are available from the FDA website [15-18]. The data regarding the patent litigations are available from the District Court of Delaware website [19]. The data relating to patents and exclusivities was available from the orange book of FDA, it includes patents and exclusivities, small molecules, new indications, active molecules, approval dates, brand names and manufacturers [20]. To understand the subject's background clearly, we performed a detailed literature review, the sample collection, selection, and analysis of CGT and PC exclusivity drugs. A high-level comparison was conducted to identify areas of compliance and non-compliance between CGT and PC drugs. Risk analysis was performed to identify the areas of concern and overcome the failures by FMECA (Failure mode, Effects and Criticality Analysis).

### Questionnaire

In this research, we used the data from the FDA website and correlated the data with the questionnaire. The questionnaire was developed by literature review and opinion from subject experts of various organizations where it is used as a part of research and not as a primary tool. The main domain of the questionnaire was to find the failures, advantages, challenges and future perspectives. It contained failures from four stages of drug approval divided into 16 sections, each stage having four sections. By thoroughly analyzing issues and literature survey, we framed the ten questions, including internal industrial challenges. Eight experts were involved in framing the questions and they were asked to validate by correlating FDA data and industrial issues. We collected 448 responses; it took seven months to collect responses. These were collected from 14 industries by using the google forms platforms. We evaluated these responses with the help of external experts. Only fully completed answers were considered and personal data was not collected on google forms. The google forms generated a spreadsheet with the answers to questionnaires. The data collected were used without any manipulation to perform statistical analysis.

## Results

The study was divided into two categories Comparative studies and Risk analysis by Industrial case studies. In comparative studies, we are comparing the CGT with Patent Challenge exclusivity in Number of Approvals, Therapeutic evaluation, Initiating First commercial marketing and Forfeiture.

### Competitive Generic Therapy

In CGT exclusivity, 96 drugs were claimed from 2018 to August 2021, among these 54 products are eligible for CGT and 42 are not eligible. This indicates that 44% of the claimed drugs are rejected. In therapeutic classification, we found multiple areas, including cardiovascular, antibiotics, eye disorders, blood disorders, anti-psychotics, and gastric drugs. There is no particular disease having high priority. The date of first commercial marketing is very important in CGT drugs because a delay in marketing for 75 days leads to forfeiture. By analysis of date of first commercial marketing from approval, we found that the highest number of days required for commercial marketing is 70 days taken by Alkem laboratories followed by sun pharma 69 days. The Novitium Pharma took a single day for commercial marketing. By analyzing the company-wise approved products, we found Amneal got approval for (10) products, Novitium (9), Glenmark (8), Dr. Reddys (7), and the rest of the companies filed single product. The average number of days for commercial marketing for CGT drugs is 13 days. We found 9 companies under the forfeiture list; these companies claimed exclusivity but forfeiture it (Table I).

### Patent challenge exclusivity

For Patent challenge exclusivity we analyzed 1330 drugs that are claimed for the Patent challenge from 2005 to August 2021among these drugs 272 (20%) got eligible, 305 products were Extinguished, 99 were deferred, 404 (30%) of products are not eligible (Extinguished and deferred), 654 (49%) products are waiting for approval from FDA.

### Therapeutic evaluation

For therapeutic classification, we analyzed the 1330 drugs and categorized them into disease wise and formulation wise. We found three formulations and 16 therapeutic areas (customized to 7 categories). The formulation types are three categories they are oral 1040 (Tablets, extended-release, delayed-release, oral suspensions, sublingual and Capsules), parenteral 178 (injections) and others 112 (Nasal, ophthalmic, inhalation, transdermal and topical gel). In therapeutic class, the number of drugs and its percentage is Diabetes 252 (19%), Pain 213 (16%), Cardiovascular 186 (14%), Respiratory 159 (12%), Antibiotics 121 (9%), Antipsychotics 81 (6%), and Others 318 (24%) (eye, skin, nasal, gastric, immune, blood, cancer, nervous, and kidney). The highest number of drugs are claimed for diabetes (Table II).

### Patent assessment

For 1330 drugs, we conducted a study on 950 patent infringement cases. These cases were thoroughly analyzed

Table I. Overview of Competitive Generic Therapy drugs

| Company | Number of products approved | CGT eligible | CGT Not eligible | CGT forfeiture | Days for first commercial marketing |
|---|---|---|---|---|---|
| Novitium | 9 | 6 | 3 | -- | 1 |
| Dr. Reddy's | 7 | 3 | 4 | -- | 2 |
| Glenmark | 8 | 5 | 3 | -- | 14 |
| Amneal | 10 | 8 | 2 | Yes | 5 |
| Caplin Steriles | 1 | Yes | -- | Yes | -- |
| Tenshi Kaizen | 1 | Yes | -- | Yes | -- |
| Gland Pharma | 1 | Yes | -- | Yes | -- |
| Lupin | 1 | Yes | -- | Yes | -- |
| Teva | 1 | Yes | -- | Yes | -- |
| Beloteca | 1 | Yes | -- | Yes | -- |
| Apotex (CN) | 1 | Yes | -- | Yes | -- |
| Par (US) | 1 | Yes | -- | Yes | -- |
| Others | 54 | 24 | 30 | -- | 16 |
| Total | 96 | 54 | 42 | 9 | 13 |

Table II. Therapeutic and Formulation wise Patent challenge exclusivity drugs

| Therapeutic **Formulation** | Diabetes | Pain | Cardio – vascular | Respiratory | Anti – biotics | Anti – psychotics | Others | Total |
|---|---|---|---|---|---|---|---|---|
| Oral | 231 | 178 | 139 | 85 | 103 | 62 | 242 | 1040 |
| | 17% | 13% | 11% | 6% | 8% | 5% | 18% | 78% |
| Parenteral | 21 | 35 | 47 | 10 | 18 | 19 | 28 | 178 |
| | 2% | 3% | 3% | 1% | 1% | 1% | 2% | 13% |
| Others | 0 | 0 | 0 | 64 | 0 | 0 | 48 | 112 |
| | 0% | 0% | 0% | 5% | 0% | 0% | 4% | 9% |
| Total | 252 | 213 | 186 | 159 | 121 | 81 | 318 | 1330 |
| | 19% | 16% | 14% | 12% | 9% | 6% | 24% | 100% |

and categorized into patent holder company, defendant company, nature of action and type of patent. We found that the six types of patents often challenged by patent challenge exclusivity are Process, Formulation, Esters and Isomers, New clinical indication exclusivity, pediatric exclusivity, and orphan drug exclusivity. By analyzing the data, we categorized the number of products per patent type. We found the patents belong to the process are 335 (35%), formulation 303 (32%), Isomers 86 (9%), the new clinical indication 142 (15%), pediatric exclusivity 46 (5%) and orphan drug exclusivity 38 (4%). For these patent litigations based on the court decision, there is a probability for a 30-Months stay order, and this was analyzed for each kind of patent and probability chances were categorized into High, Moderate and Poor. We found that the 30-Months stay order probability for process and formulation is high, Esters and orphan drug exclusivity is moderate, and pediatric exclusivity is poor for a new clinical indication.

## Comparison table

The comparative table was drawn for CGT and Patent challenge exclusivity, the critical similarities and differences were reported. The observations are 30-Months stay, Patent challenging, forfeiture, review cycles and expedited development of drug products. The similarities are the exclusivity period and waiver. The risk factor for both the exclusivities in every point was noted (Table III). The percentage of success and failures are calculated in CGT drugs and PC drugs (Figure1). These are reported by a thorough analysis of guidelines and suggestions from subject matter experts from industries.

## Risk analysis

Risk analysis was conducted to find the root cause of rejections for this study 14 industries were selected with CGT and PC exclusivity drugs (Figure 2). The manager level cadre was interviewed from Research, Intellectual property rights, Legal and Regulatory Affairs departments. Based upon their suggestions, we classified into four critical stages of drug approval procedure: Drug selection, Drug development, Pre-approval and Post-approval issues; these are further classified into four sections in each stage. The industries are selected based on their number of generic approvals, patent infringement cases, claiming for both the exclusivities. In drug selection, no active patents represent that the selected drug is free from patents, and those drugs should be thoroughly verified and selected. Rare diseases represent diseases that occur to a limited population. Drug discontinued represents the generic drugs are discontinued and there is no drug. The inadequate generic competition represents there is less or no generic competition. Development issues related to active ingredients are there may be quality issues in those active ingredients, formulation failures occur due to qualitative/quantitative imbalance of ingredients, the FDA recommendations should be taken before product development, analytical method development issues occurred due to lack of proper methods, then the applicant has to develop the new inhouse method and should be sent for approval, impurity issues are product

Table III. Comparing the similarities and differences between CGT and PC exclusivity

| Components | Competitive Generic Therapy | Patent Challenge | Risk factor |
|---|---|---|---|
| Act & Year | Food and Drug Administration Reauthorization Act, August 18, 2017. | Medicare Prescription Drug, Improvement, and Modernization Act (42) of 2003. | Nil |
| Section | 505(j)(5)(B)(v) | 505(j)(5)(B)(iv) | Nil |
| Prior intimation to Patent holder | Not required | Required | For patent challenge |
| Patent suit | Not required | Yes, have to challenge the patent | For patent challenge |
| Approvals for single Product | Applicable to different dosages and different strengths | Applicable to different dosages and different strengths | Nil |
| 30- Months stay | Not applicable | Applicable | For patent challenge |
| Exclusivity period | 180-days | 180-days | |
| First commercial market | Within 75 days | Within 75 days | Nil |
| Forfeiture | failure to market, should not claim 180 PIV exclusivity, Withdrawal, amendment of certification, agreement with another applicant | failure to market, withdrawal, amendment of certification, agreement with another applicant | Both |
| Market entry | After patent expires | Before patent expires | Nil |
| Relinquishment and Selective Waiver | Provided | Provided | Nil |
| Expedited Development and Review | Provided | Not Provided | For patent challenge |
| Facility approval | Required | Required | Both |
| ANDA approval | Normal procedure | Complicated (objection from a branded company) | For patent challenge |
| Formulation development | Normal | Complicated (Raw material, Reference drug) | For patent challenge |
| Total Claims | Claims-96 | Claims-1330 | Nil |
| 2019 | 24 | 33 | Nil |
| 2020 | 37 | 25 | Nil |
| 2021 (Aug) | 27 | 18 | Nil |

degradation or physical change in colour or texture. In the Pre-approval stage, the secondary patents or exclusivities will prevent the approval of the ANDA. FDA audit issues are related to data integrity where the original data is breached and wrong data entered, which leads to audit failure. Approval delays occur due to mistakes found during the inspections are suggested to rectify for this process time will be consumed so that the approval will be delayed. In conducting bioequivalence studies, the data should be similar to the reference product. The post-approval issues are wrong clinical indication in the label, a typographical error in the label, reporting adverse events of the drug, stability issues of the product, and post-approval manufacturing changes. Among these sections the failures were calculated, we found there is a correlation between the failures at every stage of the approval process. The mean and percentage share of failures in each section were determined (Table IV).

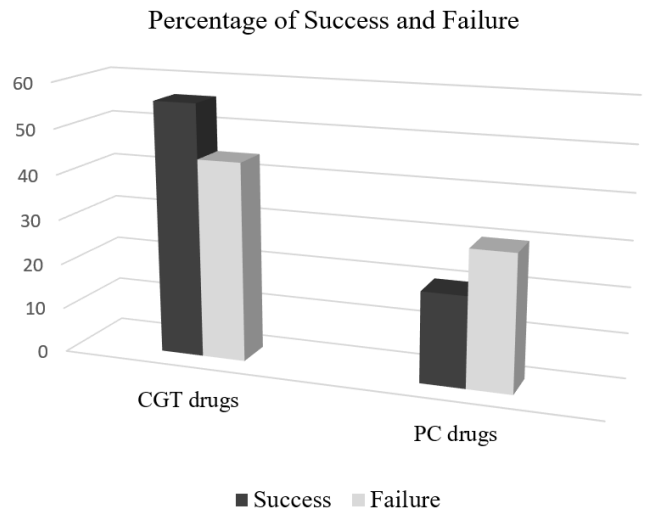


Fig. 1. Percentage of Failures in CGT and PC drugs

## Discussion

We found major differences in the areas of Number of Approvals, Therapeutic evaluation, Initiating First commercial marketing and Forfeiture between the CGT exclusivity and PC exclusivity. Most of the areas in both the exclusivities are associated with patent related issues. The patent assessment revealed that secondary patents protect the primary patents; they include formulation, process and esters, which will delay the generic entry [21]. These secondary patents are developed with the help of external collaboration [22]. Most of the secondary patents are invalid. Due to this reason, the generic companies can challenge the secondary patent in court. By the court victories and settlements with the patent owner, there is an increase in the patent challenges by generic drugs for exclusivity [23]. The chiral switches of active ingredients also act as secondary patents [24]. In patent types, process patents and formulation patents are more in number. The process patents are patents on the synthesis process. The innovator takes the patents on different synthesis routes, and the formulation patents include extended-release, delayed-release, film coating. We analyzed why the process patents and formulations patents have many patent issues and found that most of these patents are invalid so the generic companies can succeed in infringement suits. The 30-months stay probability is high for orphan drug exclusivity because the orphan drug status will be given after thorough evaluation.

Table IV. Risk analysis from 14 industrial case studies representing failures from each section from four stages of the approval procedure.

| List of firms | Drug Selection | | | | Drug Development | | | | Pre-approval | | | | Post-approval | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Limited Competition | Discontinued drugs | No Active patents | Rare diseases | Active Ingredients | Analytical Methods | Impurities | Formulation Failures | Patents, Exclusivity | Approval delay | BE studies | Facility Approvals | Product Changes | Stability | Adverse drug events | Labelling |
| Firm 1 | 12 | 9 | 18 | 14 | 14 | 11 | 16 | 25 | 18 | 12 | 21 | 6 | 13 | 15 | 8 | 13 |
| Firm 2 | 9 | 13 | 15 | 9 | 26 | 13 | 9 | 7 | 14 | 15 | 13 | 17 | 18 | 22 | 12 | 9 |
| Firm 3 | 17 | 16 | 21 | 15 | 12 | 24 | 21 | 12 | 12 | 17 | 18 | 25 | 15 | 16 | 7 | 12 |
| Firm 4 | 6 | 7 | 8 | 23 | 12 | 14 | 11 | 28 | 21 | 13 | 17 | 19 | 24 | 9 | 9 | 15 |
| Firm 5 | 10 | 6 | 16 | 11 | 16 | 12 | 22 | 11 | 24 | 19 | 23 | 16 | 12 | 17 | 14 | 11 |
| Firm 6 | 16 | 12 | 13 | 16 | 24 | 15 | 23 | 29 | 19 | 25 | 11 | 28 | 13 | 11 | 22 | 9 |
| Firm 7 | 13 | 8 | 9 | 18 | 11 | 18 | 14 | 19 | 25 | 31 | 26 | 5 | 9 | 10 | 19 | 17 |
| Firm 8 | 9 | 14 | 22 | 7 | 15 | 15 | 19 | 17 | 20 | 27 | 12 | 12 | 14 | 19 | 20 | 6 |
| Firm 9 | 6 | 14 | 15 | 12 | 11 | 9 | 27 | 16 | 29 | 21 | 9 | 7 | 9 | 8 | 8 | 18 |
| Firm 10 | 14 | 17 | 12 | 8 | 9 | 25 | 18 | 21 | 34 | 19 | 14 | 15 | 8 | 7 | 13 | 5 |
| Firm 11 | 11 | 11 | 13 | 9 | 11 | 13 | 29 | 42 | 26 | 14 | 10 | 18 | 7 | 9 | 7 | 21 |
| Firm 12 | 7 | 14 | 9 | 33 | 11 | 18 | 16 | 33 | 37 | 23 | 18 | 9 | 17 | 16 | 9 | 5 |
| Firm 13 | 18 | 21 | 18 | 16 | 19 | 27 | 25 | 14 | 30 | 16 | 9 | 14 | 11 | 8 | 16 | 3 |
| Firm 14 | 16 | 17 | 14 | 19 | 22 | 26 | 19 | 26 | 28 | 26 | 16 | 11 | 24 | 18 | 7 | 19 |
| Total | 164 | 179 | 203 | 210 | 213 | 240 | 269 | 300 | 337 | 278 | 217 | 202 | 194 | 185 | 171 | 163 |
| Mean | 12 | 13 | 15 | 15 | 15 | 17 | 19 | 21 | 24 | 20 | 16 | 14 | 14 | 13 | 12 | 12 |
| Percent (%) | 5 | 5 | 6 | 6 | 6 | 7 | 8 | 9 | 10 | 8 | 6 | 6 | 6 | 5 | 5 | 5 |

So, the stay order chances are more compared to other patents. The orphan drug development is based on the patient population, when the population increase more than the limit during the product development, there will be a risk chance for approval and there is an effective exclusivity for small molecules in orphan drugs [25, 26]. After the patent expires, the companies will apply for exclusivities. These exclusivities can extend the patent period; for example, if there is a change in the formulation, it can add exclusivity [27] and can extend the patent period.

## Risk assessment

By risk analysis, we found the major failures which arise from each section and these failures are correlated with

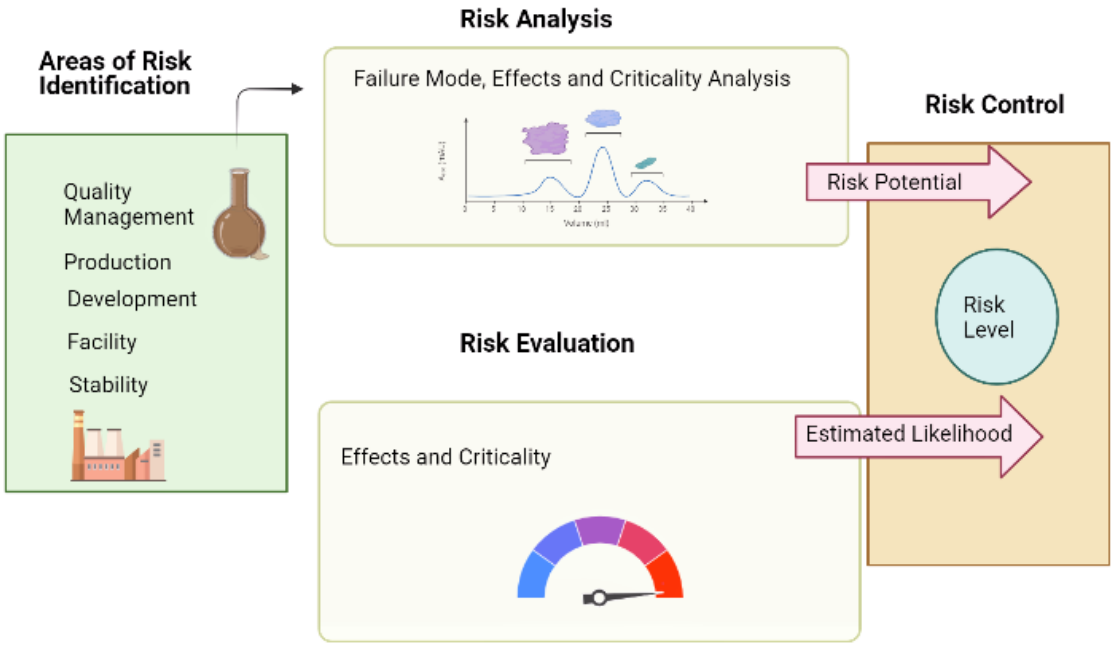


Fig. 2. Risk Assessment in Industrial case study

every stage from drug selection to the post-approval process. In drug selection, the major failures are observed by selecting the drug for rare diseases; after selecting the drug due to limited market, many companies are withdrawn. Selecting the drug under limited competition has less or no market, which leads to failure. In the drug development stage, the major risk concern areas are clinical development, Formulation development and Impurities [28-30]. The formula developed by generic companies must be verified by FDA both qualitatively and quantitatively. The analytical methods should be continuously verified through lifecycle management strategies [31]. The issues related to active ingredients are their unavailability because the branded companies have their active materials in some products. In the pre-approval stage, the secondary patents/ exclusivities will cause many failures by infringement suits. In bio-equivalence studies, many issues are related to reference products and their availability [32]. In assessing these results, there should be a novel assessment [33]. The failures related to facility audits are data integrity and Common filing deficiencies [34, 35]. The post-marketing issues should be analyzed for both the quality and safety of the product. The pharmacovigilance reports should be updated under current practices and should be reported through US FDA Adverse Event Reporting System [36-37]. The reasons for failures are reported through risk analysis. After analyzing the data and risk assessment, we found some drawbacks and opportunities related to both the exclusivities. In Patent challenge exclusivity, the first applicant has more risk factors; there is no assurance for product approval within the expected time. The applicant has to face numerous challenges and has to bear a lot of investment [38]. In CGT exclusivity, there is no threat of patent challenges; for these products, there is encouragement from FDA in product development and for quick approval.

## Conclusion

The above research concludes that CGT exclusivity can give the scope of business for start-up or small-scale industries. The review process in CGT is quick and the FDA will assist in expediting drug development. In our study, we observed many start-up companies filed their first generic under CGT exclusivity. Patent challenge exclusivity has the risk of patent infringement suit and it will take months and years to launch the product, this exclusivity is beneficial for well-established companies that can balance the investment and patent infringement cases. The risk assessment revealed the number of failures from each section, and this can help the small companies keep more efforts on particular areas of risk and avoid the forfeiture of CGT.

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## Conflict of interest

No conflict of interest is associated with this work.

## Contribution of authors

Vivek designed, performed, analysed the data, and wrote the manuscript and revised it. Ganesh supervised the data collected and reviewed. Babu helped in research related works. Ramesh helped in reviewing and industrial related issues. Praharsh performed data analysis.

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