The Effect of the RMAT Designation on Biotechnology Stock Prices, Drug Development Timelines and Outcomes: An Empirical Analysis

ABSTRACT

This research examines the impact of the U.S. FDA's Regenerative Medicine Advanced Therapy (RMAT) designation on biotechnology and small pharmaceutical companies, focusing on both stock price reactions and drug development timelines. The research employs an event-study methodology to analyze share price movements following RMAT announcements and evaluates the long-term product development outcomes for these companies. Findings reveal that while RMAT designation leads to an initial short-term stock price increase of approximately 8.11% within five days, this optimism diminishes over time, with long-term trends showing a decline in stock value. Furthermore, products under RMAT designation exhibited longer development timelines compared to non-RMAT therapies, raising questions about the designation's effectiveness in accelerating product availability. The study underscores the complex implications of RMAT for stakeholders, emphasizing the need for strategic planning and further regulatory refinement to better align short-term investor expectations with long-term product development realities.

Keywords: Regenerative Medicine Advanced Therapy Designation; Regulatory Designations; Economic Impact; Development Timelines; Biotechnology; Small Pharmaceutical Companies

1. INTRODUCTION

Pharmaceutical development is a complex, time-consuming, and costly process; it is highly influenced by regulatory landscapes and affected significantly by expedited programs such as the Regenerative Medicine Advanced Therapy (RMAT) designation. Established under the 21st Century Cures Act, the RMAT is granted by the U.S. Food and Drug Administration (FDA), and it is intended to expedite the development and review of regenerative medicine therapies that target severe conditions with unmet medical needs (FDA, 2020).

Regenerative therapies are a relatively new 21st century field of medicine that focuses on replenishing and repairing tissues or organs that are not operating fully because of diseases, trauma, or congenital issues (Petrosyan et al., 2022). These therapies often utilize cellular treatments, extracellular vesicles, or genetic vectors, all of which offer promising benefits to tackle a variety of inflammatory conditions and diseases within ophthalmology, cancer, surgical complications, and beyond. They offer hope for patients, especially those suffering from serious, rare diseases.

This paper investigates two intertwined facets of the RMAT designation: its effect on the share prices of biotechnology and small pharmaceutical companies and the impact on these

companies' drug development outcomes. The implications of the RMAT designation on share prices have not been extensively investigated, likely because it was only recently implemented, in December 2016. However, existing literature shows that similar FDA-accelerated approvals and breakthrough designations can significantly affect a company's stock performance (Shea et al., 2016; Carpenter et al., 2003). Therefore, the authors hypothesize that due to its promise of expedited review and potential market exclusivity, the RMAT designation may act as a positive signal to investors, thus boosting the share prices of biotechnology and small pharmaceutical firms that rely on innovative technologies for economic growth (Hoberg & Phillips, 2010). Similarly, the influence of the RMAT designation on product development timelines requires more empirical scrutiny. Previous studies have suggested that FDA-expedited programs can shorten development timelines (Kesselheim et al., 2015; Williamson et al., 2024). However, the specific impact of the RMAT designation, particularly for regenerative medicines, remains unknown.

1.1 PURPOSE & OBJECTIVES

The primary purpose of this research is to investigate the dual impact of the RMAT designation on the share prices and drug development timelines of biotechnology and small pharmaceutical companies. The study is driven by the following key objectives:

a) To analyse the immediate and long-term effects of RMAT designation announcements on the stock prices of companies within the biotechnology and small pharmaceutical sectors.
b) To evaluate whether the RMAT designation influences the development timelines of products, particularly those in the cell and gene therapy spaces, compared to non-RMAT-designated therapies.
c) To explore the broader implications of RMAT designation for regulatory practices, investment strategies, and the pharmaceutical industry's landscape.

The definition of what constitutes a biotechnology or small pharmaceutical company varies greatly across the literature. For instance, some researchers may define it based on the number of employees, while others might consider revenue, R&D expenditure, or product pipeline. To establish a uniform and practical scope for our study, we have set specific criteria for defining "biotechnology or small pharmaceutical companies". We consider such a firm to:

- Be a for-profit, pharmaceutical company (e.g., excluding university hospitals)
- Have a market capitalization of less than $1 billion (the day before the RMAT designation)
- Not operate as a subsidiary of a larger pharmaceutical entity.

We believe these parameters provide a reasonable representation of independent, emerging firms in the sector.

Through the analysis, this paper aims to extend the current understanding of the economic and developmental ramifications of RMAT. By isolating the effects of this designation on the stock prices and drug development timelines of smaller pharmaceutical companies, we aim to deliver a more intricate perspective on how such regulatory measures shape the pharmaceutical industry's landscape. Consequently, this research aims to contribute significantly to the discourse surrounding regulatory interventions, particularly the RMAT designation, within the pharmaceutical sector.

2. LITERATURE REVIEW

2.1 RMAT IMPACT ON DEVELOPMENT

The FDA's expedited programs are designed to speed up the development and review process (FDA, 2020). Several studies have shown that other designations have a positive impact on

the ease and speed of drug development. However, few studies have examined the impact of the RMAT. Given the relatively recent history of RMAT, most products that have been approved are cell or gene therapy; as such, the majority of the review will be based on these.

A study by Kesselheim et al. found that expedited approval programs led to a median time savings of approximately 3 years compared to products that went through standard review [6]. Similarly, Shea et al. found that the breakthrough therapy designation – a program similar to the RMAT – also resulted in significantly shorter development times (Shea et al., 2016). However, these studies did not isolate the specific effect of the RMAT designation.
Chhina, Drago, and Ndu (2022) studied whether the RMAT designation was delivering its intended benefits. After reviewing all the RMAT designations granted in the first 5 years of the award, they found that only 3 products had been approved, out of 72 RMAT awarded products (5%). In contrast, the FDA's similar Breakthrough Therapy Designation (BTD) saw 94 drug approvals in its first 5 years, out of 208 BTD awards (45%) (Silverman, 2021). This shows a significant difference that could be attributed to many causes such as bottlenecks around manufacturing acceptable material, and the divide in development between the US and Europe, among others.

In addition, the authors of this study found that the number of requests for the RMAT dropped by 51% between 2018 and 2021 (Chhina, Drago & Ndu, 2022). This study concludes that due to the challenges that influence the gene therapy industry, many factors could influence the development of these products. We suggest that the FDA should provide more guidance and workshops to better communicate the program's requirements and benefits. Although this study exclusively focused on gene therapies, many of the regenerative medicines, including cell therapies, suffer from the same complexity issues. Thus, it is likely similar results would have been found if this study had instead focused on cell therapy or other regenerative medicine classes.

Lapteva et al. examined the clinical development of gene therapies and their respective development timelines (Lapteva, 2020). From their limited sample size (n=6), they found a development range from Investigational New Drug (IND) filing to approval of 6-12 years, with a mean of 9.17 years. It is important to note that these products also received other FDA designations; for example, all received Orphan Drug Designation (ODD) and 83% received BTD. Although the sample size is limited, this reflected the overall limited number of gene therapy products marketed at the time the article was authored.

Creasey et al. reviewed the Chemistry, Manufacture, and Control (CMC) challenges in the cell and gene therapy industry. They determined that in the case of an effective CMC development process with a large amount of investment, the receipt of an RMAT or a BTD typically resulted in a development timeline of 3–5-years from first-in-human to BLA filing (Creasey et al., 2019). This short development timeline is significant; the industry-wide accepted average timeline is 12 years (Biostock, 2023). However, it is important to reflect that many organisations that receive an RMAT may not have the capital for large-scale investment early in the drug development process to facilitate this. Previous information shows that regulatory awards need to be received early in development to maximize impact. The significance and earliness of the RMAT designation is too premature to determine.

The RMAT designation's potential to expedite development timelines is particularly salient given the typically long and costly development process for regenerative medicine therapies (Silverman, 2021). While reflecting on the CMC requirements for regenerative medicines, one should not overlook the disparity in manufacturing cost between cell and gene therapies compared with the rest of the industry. Some estimate the average cost of manufacturing cell and gene therapies to be $1 million per dose (Salcedo & Rosellini, 2022). In contrast, a study

of non-regenerative COVID-19 medicines in the US found a range of manufacturing costs between $1-$875 per dose (Wang et al., 2021). This shows that most of the investment must be used to support CMC rather than being focused on the development. This also shows the vast risk associated both with the capital needed as well as the potential of failure. This could be a factor in why small pharma and biotech aim to gather early FDA designations, such as RMAT, to lower the risk of their drug development plans and increase value to shareholders.

This risk is multiplied by the already stretched manufacturing capacity for such therapies, which had a predicted 500% shortage in 2020 (Rader, 2020), even before the recent raw material shortages, which was further depleted by the vast numbers of regenerative medicines being developed for the COVID-19 pandemic. In addition, the smaller biotechnology and pharmaceutical companies that do not have their own dedicated manufacturing facilities struggle further to begin development as they fight for CMC slots that do not exist.

The FDA has tried to react to the needs of RMAT developers across the spectrum of the industry by making changes to the latest guidelines to try to support innovative clinical designs by introducing basket trials. However, this introduction only exacerbates the problems surrounding the shortages of manufacturing spaces.

This study aims to provide some empirical data to establish a direct link between the RMAT designation and development times across all RMAT-designated drugs. In addition, the study aims to determine whether regulatory designations also have the potential to enhance the market prospects of small pharmaceutical companies by increasing their chances of drug approval and commercialization, as this will ultimately lead to a positive impact on their share prices (Golec & Vernon, 2010).

2.2 RMAT IMPACT ON SHARE PRICE

Several studies have shown that the regulatory decisions made by the FDA can have a significant impact on the share prices of pharmaceutical companies (Hoberg & Phillips, 2010; Berndt et al., 2015). The prospect of gaining an expedited review and potential market exclusivity is frequently perceived as positive signals by investors, and this translates into increased share prices (Danzon & Nicholson, 2012). However, the authors of this review could not find any peer-reviewed publications that examined the specific effect of the RMAT designation on stock prices.

Bubela et al. (2015) suggested that investors value the acceleration of the lengthy regulatory process, such as the accelerated approval pathways because they believe that they reduce the time to market and the overall development costs; as well, they feel that a “nod” from the agency shows approval of the science behind the drug (Bubela et al., 2015). In a similar vein, an article by Zucconi (2019) suggested that designations such as the BTD had become valuable to investors; this can be seen by the positive correlation between a granted BTD and the increase in capital from VCs, due to the promise of shorter development times and higher approval rates. Similarly, Gorry and Useche (2019) explored the role of regulatory designations in attracting venture capital (VC) investments; they found that biotechnology and small pharmaceutical companies with an FTD or a BTD were more likely to receive VC funding.

However, few articles explicitly mentioned the RMAT, instead focusing on other FDA designations. Norviel et al. were the first to examine the impact of the RMAT designation announcement on company share prices. This study looked at public companies that had announced they had been granted an RMAT, as of Q4 2019 (Norviel at al., 2019). The study found that RMAT had a minimal general impact on company share price, except for two small pharmaceutical companies, which achieved 67.3% and 87.7% gains overnight (Norviel et al.,

2019). However, outside of this, there were very few significant changes once the RMAT announcement was made. It is important to note that this study was not peer-reviewed and does not utilise a benchmark such as the S&P 500, which compares any changes to the overall financial market; therefore, the impact may not have been accurately assessed.

Although it does not contribute to the literature, one investment analyst assigned little value to the granting of the RMAT designation (Peciulis, 2020). Although this analyst appreciated the potential impact the RMAT could have on the drug development process, they valued clinical data, regulator discussions, and partnerships to a greater extent.

3. MATERIALS AND METHODS

In this investigation, event-study methodology is utilised to scrutinize investor reactions to the FDA's RMAT designations. Event-study methodology, a staple in the fields of Economics and Finance, evaluates the fluctuations in security prices in relation to events, predicated on the premise that markets rapidly assimilate the impact of such events (Woon, 2004; Fama et al., 1969). The analytical process adhered to the following principles:

a) Event and period specification: The public dissemination of the RMAT designations from its inception until July 1, 2023.
b) Definition of event windows: -5 to +5 days, 30 days, 6 months, 1 year, 2 years, and 3 years.
c) Event's reach: Initial RMAT designations awarded to publicly-listed small pharmaceutical entities, which are identified as those with a market capitalization below $1 billion and who were not acting as a subsidiary of a larger pharmaceutical corporation at the time of their RMAT proclamation. Multiple RMAT awards for identical products were excluded from consideration.
d) Data procurement: Stock prices of recipient firms within the event windows were examined and supplemented with data from the SPDR S&P Biotech ETF (XBI) and the S&P 500 index (SPX) for comparison.
e) Measures employed: Average Abnormal Return (AAR) and Cumulative Average Abnormal Return (CAAR) are set against the selected benchmark indices.
f) This methodology facilitates a comprehensive assessment of the influence of the FDA's RMAT designation on the stock performance of small pharmaceutical firms. The total number of RMAT recipients that met these criteria amounted to 26.

Once the above parameters were applied to all RMAT awards, 26 events were considered in this analysis. The majority of RMAT events excluded were due to the company market cap being above $1. However, due to the analysis period over which they were collected, only 25 of the events had reached the one-year event day at the time of writing this paper. In addition, only 20 events had reached the two-year and three-year event days to be considered in the data analysis. When reflecting on the companies receiving the sampled 26 RMATs, it becomes increasingly difficult to accurate assess certain factors such as portfolio size or preclinical outcomes. Not all companies have curated public information when reflecting to a period of almost 7 years prior to this investigation, therefore it is very difficult to assess what was public information at the time of each announcement. As such, this research aimed to keep the criteria as simple as possible, focusing on the short- and long-term share price data.

Additional data gathering is undertaken to assess the product developmental out-comes of the products and companies involved in the 26 events, as of July 2023. This is performed utilising press releases, and any public information regarding clinical trial results, company partnerships or development updates. However, like that of the share price data, assessing

the availability of public information is difficult, and some information may be difficult to obtain. Therefore, the categorisation of development outcome is at a high-level, without examining individual events contributing to the outcome.

Selecting suitable benchmarks is essential in financial and event studies, as it allows for the assessment of "normal" returns (Eckbo, 2007). The XBI was chosen for its broad encapsulation of the biotechnology sector, while the SPX was chosen for its representation of wider market trends. These selections support a comprehensive market performance analysis, taking into account both industry-specific and broader market dynamics.

4. RESULTS

Utilising the XBI as a benchmark, the data from Table 1 and Figures 1 and 2, we found that on day 0 of the RMAT announcement, the CAAR was 5.12%, while on day +5, it was 8.11%; on day +30, it was 6.32%; it reached a peak of 30.44% at 6-months, before gradually reducing to 5.15% at 3-years. Utilising the SPX as a benchmark, the same data found that the CAAR on day 0 post-announcement was 4.98%; on day +5, it was 7.88%; on day +30, it was 4.66%; it peaked at 31.09% at 6-months before declining to -2.17% at 3-years. The short-term share price data shows significant short-term share price increases for public, biotech, and small pharma companies after announcing the first RMAT for their products. However, the long-term benefit is questionable.

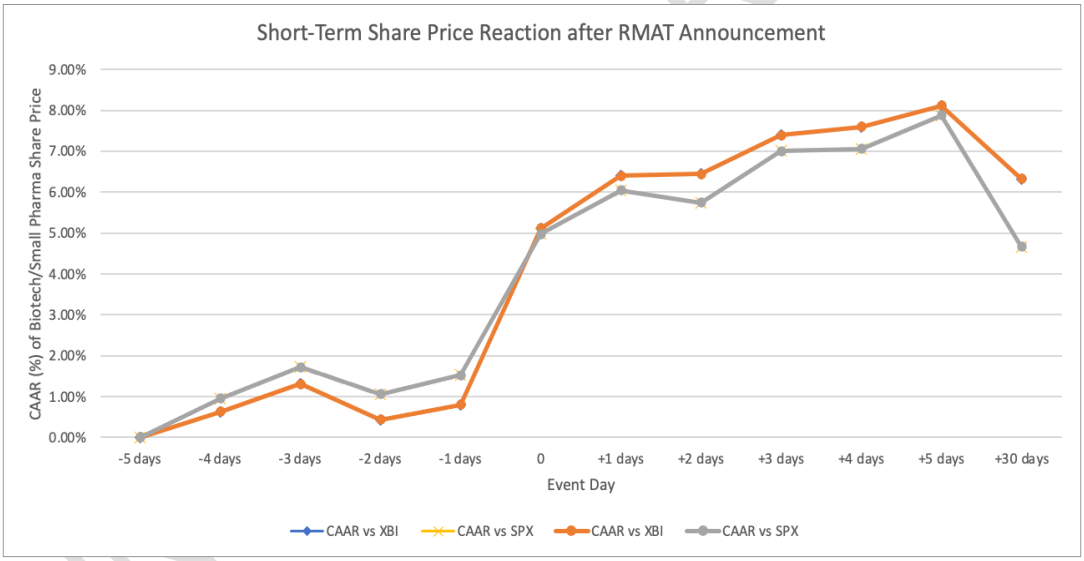
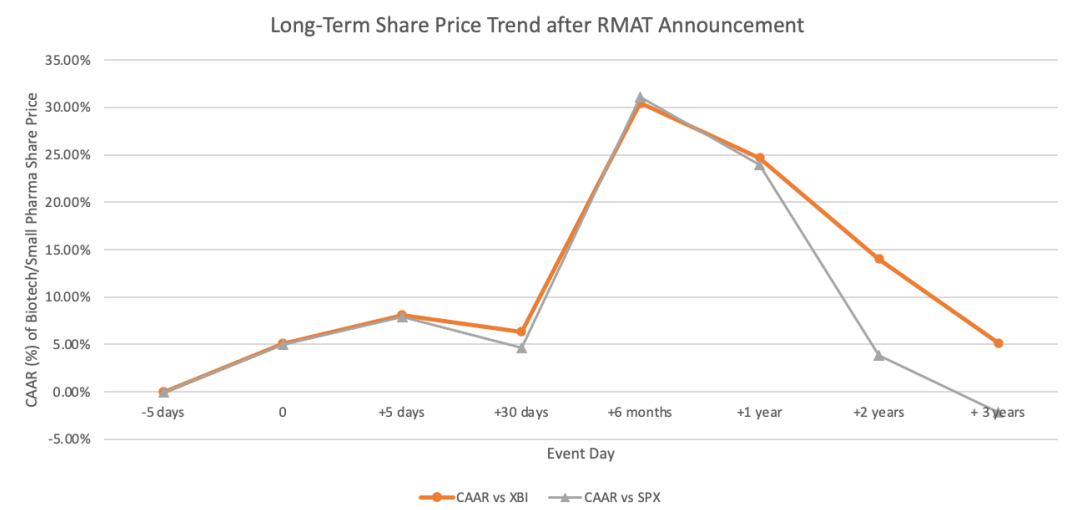


Fig. (1). CAAR surrounding the announcement of an RMAT over a short-term event window at biotech and small pharma.

Fig. (2). CAAR surrounding the announcement of an RMAT over a long-term event window at biotech and small pharma**.**



Event Day	AAR vs XBI	CAAR vs XBI	AAR vs SPX	CAAR vs SPX
-5 days	0.00%	0.00%	0.00%	0.00%
-4 days	0.63%	0.63%	0.95%	0.95%
-3 days	0.68%	1.31%	0.77%	1.72%
-2 days	-0.87%	0.44%	-0.66%	1.06%
-1 days	0.36%	0.80%	0.46%	1.52%
0	4.32%	5.12%	3.46%	4.98%
+1 days	1.28%	6.40%	1.06%	6.04%
+2 days	0.04%	6.44%	-0.30%	5.74%
+3 days	0.95%	7.39%	1.26%	7.00%
+4 days	0.21%	7.60%	0.06%	7.06%
+5 days	0.51%	8.11%	0.82%	7.88%
+30 days	-1.79%	6.32%	-3.22%	4.66%

+6 months	24.12%	30.44%	26.43%	31.09%
+1 year	-5.75%	24.69%	-7.17%	23.92%
+2 years	-10.70%	13.99%	-20.09%	3.83%
+ 3 years	-8.84%	5.15%	-6.00%	-2.17%

Table 1. Summary of results showing the AAR and CAAR after RMAT announcement.

Table 2 and Figure 3 summarise the outcomes of the studied products that received an RMAT in the event scope, as of July 2023. This study found that only one of the studied products (3.85%) was approved to market. Meanwhile, 12 of the products (46.15%) showed some level of negative trial results, with 7 of those (26.92%) being formally discontinued by the owning company. In addition, 5 of the products and/or companies (19.23%) had undergone a merger, acquisition, or significant licencing as of July 2023. Table 2 and Figure 3 examine the CAAR with segregation based upon the development outcomes discussed above. This data found that the CAAR for the products that had received positive results to date but had not been marketed had significantly higher gains, with a CAAR of 68.21% over 3 years. As expected, the only company that marketed a product experienced some significant share price increases, with a CAAR of 36.78% over 3 years. However, surprisingly, products and companies that ultimately ended up having a merger, acquisition, or significant licencing, but whose product was still under development, had had decreased in value significantly over the 3-year sample data, with a CAAR of -155.09%.

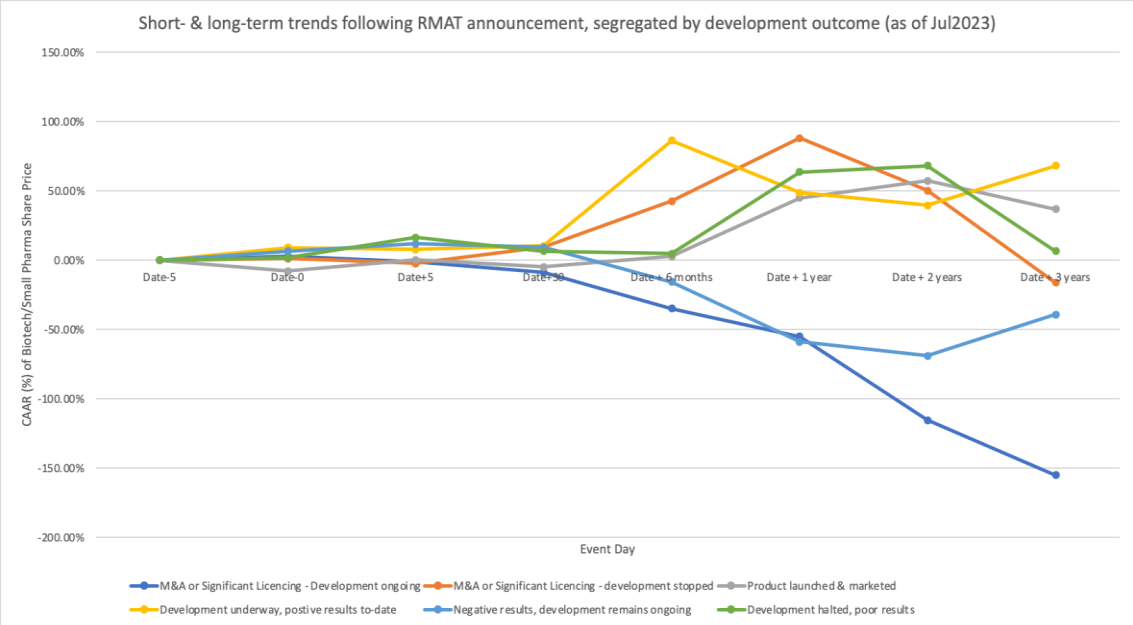


Fig. (3). CAAR of products and companies, dependent on the development outcomes (as of July 2023) of the studied products that received an RMAT**.**

Outcome	%	Date-5	Date-0	Date+5	Date+30	Date + 6 months	Date + 1 year	Date + 2 years	Date + 3 years

M&A or Significant Licencing - Development ongoing	11.54%	0.00%	2.79%	-1.14%	-8.86%	-34.98%	-55.04%	-115.59%	-155.09%
M&A or Significant Licencing - development stopped	7.69%	0.00%	1.11%	-2.44%	9.57%	42.57%	88.13%	50.26%	-16.31%
Product launched & marketed	3.85%	0.00%	-7.78%	0.29%	-4.82%	2.62%	44.89%	57.36%	36.78%
Development underway, positive results to-date	38.46%	0.00%	8.96%	7.74%	10.27%	86.20%	48.72%	39.69%	68.21%
Negative results, development remains ongoing	19.23%	0.00%	6.43%	11.89%	9.38%	-15.80%	-59.02%	-69.00%	-39.29%
Development halted, poor results	19.23%	0.00%	1.69%	16.38%	6.42%	4.63%	63.49%	68.14%	6.42%

Table 2. Summary of CAAR, utilising the XBI as a benchmark, across selected event windows, categorised by development outcomes.

Figure 4 looks has looked at all the cell and gene therapy products that have been approved in the US, not simply the biotech and small pharma. This aims to compare the development time of cell and gene therapy products that received an RMAT with those that did not. As can be seen in Figure 4, the development time from IND filing to marketing averaged 10.22 years; this was 1.05 years longer than cell and gene therapies that did not receive an RMAT (Lapteva et al., 2020).

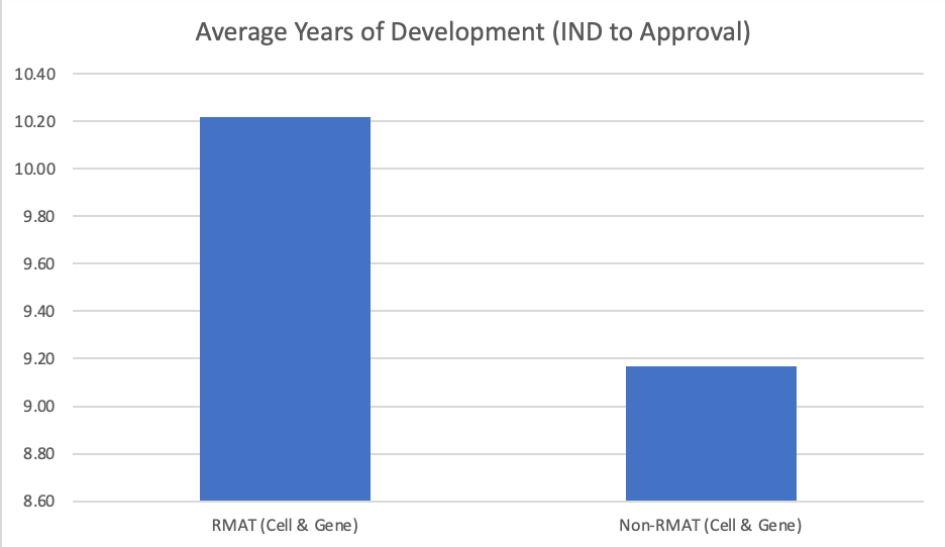


Fig. (4). Average development timelines of RMAT-awarded cell and gene therapies compared to non-RMAT products (Lapteva et al., 2020).

5. DISCUSSION

For data analyses and discussion, the results have been categorised into four headings: short-term economic impact, long-term economic impact, economic impact aligned with development outcomes, and RMAT association to drug development timelines.

5.1 Short-Term Economic Impact

Based on the findings of this study and corroborated by the very limited existing literature, the short-term economic ramifications of the RMAT designation, particularly for small biotech and pharmaceutical companies, appear substantial (Danzon & Nicholson, 2012; Zucconi, 2019).

Immediately following an RMAT announcement, an upswing is observed in the CAAR of the awarded companies. On the announcement day (day 0), an approximately 5% boost in CAAR is recorded against both the XBI and SPX benchmarks. This positive trend sustains over the subsequent 5 days and remains significantly elevated even 30 days after the announcement.

These observations align with previous research that has indicated that regulatory milestones such as RMAT designations can trigger strong, positive stock market reactions (Norviel et al., 2019). The market response can be attributed to heightened investor optimism concerning the future trajectory of the designated products because of the expectation that the expedited development and review processes will be facilitated by the RMAT designation. This interpretation finds further support in the six-month CAAR data, which peaked at 30.44% and 31.09% against the XBI and SPX benchmarks, respectively.

Nevertheless, these findings should be interpreted cautiously considering certain inherent limitations. The sample size under investigation was relatively small, with only 26 companies receiving RMAT awards for their products. This smaller sample might not provide a comprehensive representation of the diverse small biotech and pharmaceutical industry, and it could lead to potential bias in the findings.

Furthermore, the study timeframe coincides with the COVID-19 pandemic, a period of exceptional volatility for the global pharmaceutical industry. This global crisis has shaped investor behaviours and market trends in unparalleled ways (Baker et al., 2020). This could have added confounding elements to the analysis of the impact that RMAT designations had on stock performance. The global urgency for the expedited development of vaccines and therapeutics during this period could have amplified the perceived value of regulatory designations like the RMAT, which may have introduced additional complexity to the study.
Moreover, the general upsurge in the biotechnology sector during the study period, largely driven by the response to the COVID-19 pandemic, could have inflated the positive economic impacts of the RMAT designation.

These factors highlight the need for undertaking more robust research to validate these initial findings, taking into consideration a larger sample size and varying market conditions. Despite the outlined challenges, the current study provides crucial insights into the short-term economic impact of the RMAT designation and presents a starting point for future studies.

5.2 Long-Term Economic Impact

Unraveling the long-term economic effects of RMAT designations is complex; it is characterized by an initial boost in the CAAR followed by a gradual decline. This pattern emerges against the both XBI and the SPX benchmarks, thus suggesting a broader trend that extends beyond industry-specific dynamics.

Compared with the XBI benchmark, the data reveals a peak in the CAAR of 30.44% at the six-month mark. By the one-year stage, considering the data available from 25 companies, the CAAR regressed to 24.69%. At the two and three-year stages, the data from 20 companies revealed a further decline in CAAR to 13.99% and 5.15%, respectively. A similar pattern emerges when applying the SPX benchmark. The six-month CAAR reached a high of 31.09%. At the one-year stage, the CAAR dropped to 23.92% based on the data from 25 companies. The pattern of deceleration continued at the two and three-year stages, with the CAAR falling to 3.83% and 2.17%, respectively, based on data from 20 companies.

These findings, with an initial surge followed by a long-term deceleration in the CAAR, suggest a readjustment in the market perceptions and investor sentiment over time. The contrast between initial optimism and longer-term caution may reflect the intricate landscape of drug development, which is underscored by inherent risks, evolving market dynamics, and complex regulatory landscapes.

The interpretation of these findings is subject to several limitations, notably, the sample size, which was reduced from 26 at the outset to 25 and then 20 at the one-, two-, and three-year stages, respectively. The reduced sample sizes at later stages may constrain the generalizability of these findings. Moreover, the unprecedented influence of the COVID-19 pandemic during the study period may also have influenced investor behaviors and market trends, perhaps even significantly.

This complexity is further compounded by the multifaceted nature of pharmaceutical development, wherein a myriad of factors such as trial outcomes, regulatory challenges, and the competitive landscape can affect long-term stock performance.

Notwithstanding these limitations and challenges, the current study provides valuable preliminary insights into the long-term economic effects of the RMAT designation. Nevertheless, it also underscores the need for further research to validate these findings, to explore the influencing factors in more depth, and to gain a more nuanced understanding of the long-term economic impact of this important regulatory pathway.

5.3 Economic Impact Aligned with Development Outcomes

Analysing the economic impact that aligns with the development outcomes presents an intriguing dimension to understanding the implications of the RMAT designation. As shown, there were six distinct outcomes: Mergers and Acquisitions (M&A) or significant licencing with ongoing development, M&A or significant licencing with development halted, product launch and marketing, development underway with positive results to date, negative results with ongoing development, and development halted due to poor results.

For the firms engaged in M&A or significant licencing with ongoing development (11.54%), the study suggests a sharp decrease in the CAAR across the timeline; they registered a negative value of -155.09% by the end of the three-year period. This counterintuitive result may reflect various market factors including investor scepticism regarding their long-term prospects or strategic considerations associated with M&A activities.

Conversely, for the companies in which M&A or significant licencing occurred but development had ceased (7.69%), there was a peak CAAR of 88.13% at one year before regressing to -16.31% at three years. This might reflect initial investor optimism, followed by a revaluation because of the cessation of development.

It is noteworthy that only one product (out of 26) had been launched and marketed during this period. The CAAR trajectory for this category, peaking at 57.36% at two years and reducing

to 36.78% at three years, reflects the potential for considerable economic gains following a successful product launch.

The category with the highest representation (10 out of 26) was ongoing development with positive results reported to date. This group experienced a substantial CAAR growth over the period, with a peak of 86.20% at six months and a sustained elevation of 68.21% by the three-year stage. This underscores the potential long-term economic benefits that result from positive clinical trial results.

For the products with negative results but for which development was still ongoing (5 out of 26), the CAAR trajectory was negative, reaching -39.29% by the three-year stage. This may reflect a market recalibration due to adverse trial results. Interestingly, for organizations in which development was halted due to poor results (5 out of 26), their CAAR showed an initial increase, peaking at 68.14% at two years, before seeing a sharp decline to 6.42% at three years. This reflects the negative impact of halted development.

There was a low number of RMAT products in this study that received approval; the reasons for this could be multi-fold. A plausible hypothesis is that the increased interaction and scrutiny from the FDA associated with the RMAT designation could have resulted in more stringent criteria before they received accelerated approval. The RMAT designation is intended to streamline and expedite the approval process; however, paradoxically, the close oversight and higher regulatory standards could have intensified the challenge of getting these products to market.

Moreover, it is conceivable that the accelerated development pathway could lead to a higher likelihood of failures in later stages due to the complex nature of cell and gene therapies and the technical hurdles that must be overcome. This raises the possibility that the RMAT designation, while ostensibly beneficial, may unintentionally introduce additional obstacles to product development and approval. These speculative explanations require further investigation and could be the focus of future research endeavours. For instance, a comparative study examining clinical trial patient numbers, a trial design, and endpoints between RMAT products and non-RMAT products could shed light on whether the RMAT designation affects the design or execution of clinical trials. Furthermore, an in-depth analysis of the regulatory interactions for RMAT products versus non-RMAT products could illuminate whether the RMAT pathway imposes more stringent standards and whether this is a contributing factor to the low approval rate observed in this study.

In analysing these findings, the limited number of approved products underscores the inherent risks in pharmaceutical development. Furthermore, the relatively small sample size in each category may limit the robustness of these findings. These considerations coupled with the unique circumstances of the COVID-19 pandemic during the study period suggest a need for cautious interpretation and further research. Nevertheless, the results offer intriguing insights into the economic impact of RMAT designations, which are shaped by the complex interplay of development outcomes, investor sentiment, and market dynamics.

5.4 RMAT Association with Development Timelines

Analysing the RMAT associations with the development timelines offers an opportunity to understand the practical implications of this designation. Based on this study, the seven products that received RMAT designations and subsequently reached approval exhibited an average development timeline of 10.22 years. Whereas Lapteva et al. (2020) assessed a small sample of six gene therapy products, regardless of RMAT status and identified an average development duration of 9.17 years.

This apparent paradox – the RMAT designation is intended to accelerate development and yet leads to a longer average development timeline – invites further exploration. It could be attributed to multiple factors. For instance, the RMAT-designated products might be more complex or require more elaborate clinical trials, thereby extending their development period. Another possibility could be that the RMAT designation incites companies to invest in more thorough development processes to maximise the chances of gaining approval, which gives the potential for considerable economic gains.

It is also important to note the considerable variation in the number of products in each dataset; specifically, the organizations analysed in this study encompass a larger number of RMAT-designated products than the dataset used by Lapteva et al. (2020). This discrepancy might affect the average development timelines observed. Further, the difference in the timelines may reflect the natural variance inherent in developing gene therapy products, given the wide array of potential targets, mechanisms of action, and associated complexities.
Evaluating the RMAT's association with development timelines requires a nuanced perspective. The seeming extension in the development duration does not necessarily reflect negatively on the RMAT designation's efficacy. Rather, it may be indicative of a more rigorous and comprehensive development process undertaken by the companies receiving the designation. Thus, in this context, the ultimate measure of RMAT's utility may not solely be its ability to shorten development timelines, but perhaps more importantly its potential to facilitate the successful navigation of the complex developmental pathways toward the launch of effective gene therapy products.

In light of these results, further research is required to fully understand the interplay between the RMAT designation and development timelines, considering the substantial impact this has on companies' strategies, investor behaviour, and, ultimately, the advancement of novel cell and gene therapies.

6. CONCLUSION

The regulatory paradigm, symbolised by initiatives like the RMAT designation, plays a pivotal role in shaping the evolution of the biopharmaceutical sector, particularly within the realm of cell and gene therapies. This study sought to elucidate the economic and developmental impacts of the RMAT designation by undertaking a comprehensive analysis of the share price fluctuations and product development timelines associated with the RMAT recipient companies.

Evidently, the RMAT designation has a substantial short-term impact on the share prices of small pharmaceutical companies, as it leads to significant increases immediately after the RMAT announcement. This indicates that investors have a positive perception of the RMAT designation. In turn, this reflects the perceived potential for accelerated development and increased chances of approval. However, the long-term economic effects of this designation are less consistent and more nuanced, as the benefits gradually diminish. This finding underscores the importance of managing investor expectations; it also emphasizes the necessity of companies devising robust post-approval strategies to sustain long-term economic growth.

In addition, the study reveals intriguing insights related to the economic impact correlated with product development outcomes. There are only a limited number of products reaching the market, and there are significant share price declines associated with companies that underwent mergers, acquisitions, or significant licensing events. This highlights the complex

nature of cell and gene therapy development and the challenges associated with translating clinical progress into market success.

Interestingly, the study also determined that the products that received an RMAT designation took longer on average to develop than gene therapies that did not receive the designation. This finding seems initially counterintuitive; thus, it prompts further exploration into the intrinsic complexities of the RMAT pathway and its impact on development strategies.

Overall, the implications of this study are multi-fold. For investors and small pharmaceutical companies, these findings may guide strategic decisions, risk assessments, and financial forecasting. Subsequently, for policymakers, gaining a better understanding of the RMAT designation's impact can help them refine regulatory frameworks to further foster innovation and expedite the availability of ground-breaking treatments.

However, it is important to remember that these findings are part of an evolving narrative. As the cell and gene therapy field continues to advance and more data becomes available, the understanding of the RMAT designation's influence will become more refined. This underscores the importance of further research in this area to ensure that regulatory designations like the RMAT are optimised; ultimately, this will contribute to the shared goal of advancing patient care.

LIST OF ABBREVIATIONS

Average Abnormal Returns **(AAR).** The average abnormal returns for multiple organisations on a set event day (MacKinlay, 1997).

Biotechnology and Small Pharmaceutical Companies (**Biotech**) & (**Small Pharma**). Typically, they spin out from academic institutes and look to take academic science to a business model. These companies frequently have a small number of assets within their portfolio. The life cycle of these companies typically ends by establishing a partnership with a strategic partner, entrance to the market, or a failure to overcome the clinical and/or regulatory hurdles.

Breakthrough Therapy Designation (**BTD**). An FDA designation aimed to support the approval process as efficiently as possible (FDA, 2019).

Cumulative Average Abnormal Returns **(CAAR).** The cumulative abnormal returns for multiple organisations on a set event day (MacKinlay, 1997).

Chemistry, Manufacturing & Controls (**CMC**). The various procedures utilised to assess the physical and chemical characteristics of drugs to ensure their consistency and quality during manufacturing (FDA, 2023).

Food and Drug Administration (**FDA**). The agency in charge of supervising medicinal products in the United States.

Investigational New Drug (**IND)**. The application and mechanism to seek approval of the clinical research of an unapproved drug, or approved drug for a new indication.

Mergers and Acquisitions **(M&A).** Transactions where the ownership of a company or its units are transferred to another entity.

Orphan Drug Designation **(ODD).** An FDA designation to support and incentivise the development of new treatments for rare diseases (FDA, 2022).
Regenerative Medicine Advanced Therapy designation (**RMAT**). An FDA designation aimed to accelerate and facilitate the approval process of regenerative medicine therapy (FDA, 2020).

Standard and Poor 500 **(SPX)**. A stock market index that tracks the stock performances of 500 of the largest companies listed on stock exchanges in the United States.

SPDR S&P Biotech ETF (**XBI**). A stock market index that is designed to represent a cross-section of US-listed biotechnology companies and the return performance of the S&P® Biotechnology Select Index (SSGA Funds Management, 2023).

Venture Capitalist (**VC**). An investor that provides companies with capital in exchange for equity.

Disclaimer (Artificial intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

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