UNITED STATE FOOD AND DRUG ADMINISTRATION'S ACCELERATED APPROVAL PATHWAY – PROGRESSIVE JOURNEY AND OPPORTUNITIES FOR A BALANCING ACT FOR ONCOLOGY DRUGS

by

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DISSERTATION

Presented to the Swiss School of Business and Management Geneva

In Partial Fulfillment

Of the Requirements

For the Degree

DOCTOR OF BUSINESS ADMINISTRATION

SWISS SCHOOL OF BUSINESS AND MANAGEMENT GENEVA

OCTOBER, 2024

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Dedication

I dedicate this work to my family – firstly, my wife, **Amita**, who had been my constant support throughout the journey of this work and sacrificed her time and all those moments of togetherness that had been traded off in completion of this work. She steadfastly kept motivating me throughout. I owe a lot to my children – **Aayaan and Alayna** – as I was able to shape this work up at the behest of their quality time. Aayaan kept constantly encouraging me, despite I not being there for him whenever he was needing me the most. Alayna had to play with her small toys, as I was not there to take her out and play with her.

I am indebted to my parents – my father, **Mr. Jai Prakash Sharma and my mother, Mrs. Gyaneshwari Devi**, who despite not being physically with us, kept encouraging me and blessing me to complete this work and finally joined us in Mumbai from Delhi to see it culminating.

I am also forever grateful to my Revered Teacher and Guru, **Dr. J. Venkata Rao**, whose teachings have shaped me up as a wise individual to be able to understand the nuances of professional and personal composure.

Acknowledgements

At the behest of compilation of my work, words do not justify the feelings that I hold in my heart. I honestly hope that I manage to express my gratitude to all my well-wishers.

Firstly, I would like to wholeheartedly thank my mentor **Dr. Isaac Ahinsah-Wobil, DBA**, for his faith, constant guidance, encouragement, and support at all the milestones of this study.

My friend, **Zafar Parvez Khan**, **DBA,** deserves a big thanks firstly for introducing me to this program. His invaluable suggestions, encouragement, and healthy criticism have been instrumental in completion of this project.

My deepest gratitude to **Mohammad Saad**, my friend whose statistical inputs hold key in completion of this work. Despite of my constant troubling, he carried it out with utmost zeal and enthusiasm.

It is indeed my great pleasure to thank my friend, **Vijaya Kumar**, from Tata Consultancy Services, for his constant encouragement, completely shouldering all my professional burdens and timely help in carrying out the analysis of the data without which it would have been impossible to shape up this project.

I would also like to thank my friends, **Dr. Harshad Kothawade and Dr. Rajesh Pandey**, who rendered every possible help in expediting the information and artefacts needed to complete my work.

I express my sincere thanks to my friends, **Tarun, Dr. Manthan, Ashish, Dr. Sandeep, Dr. Subhashish, Dr. Omkar, Dr. Sabyasachi, Dr. Vivek, Abhishek, Dr. Bhagat, Suraj, Dr. Raghavendra, Dr. Shreedhar, Rahul, Rajaneesh B.R., Divakar, Dr. Shazli, Dr.**

Paresh, Dr. Nilanjan Saha, Sameer and Dr. Anup who not only helped me with the responses needed for this study, but also for the encouragement to complete this study.

I was also really fortunate to have my colleagues and seniors from Industry, **Dr. T.G. Venkateshwaran, Dr. Michael Malone, Dr. G. Subrmaniam, Anna Kaltenboeck, Nitish Aggarwal, B. J. Varma, Dr. Pavan Muttil, Dr. Nitin Kaila, Vivek Kapur, Mark Steele, Ramesh Pimple, Dr. Gurvinder Singh, Neeraj Soni, Surajit Roy, Parimal Limburkar, Dr. Nitin Mehrotra, Atul Kuksal, Anirudh Vashishth, Rajdeep Majumdar, Vikas Johri, Pankaj Bhatt Jr., Pankaj Bhatt Sr., Bhaskar Tyagi, Ashish K Singh, Vikas Bhardwaj, Manish Rai, Guriqbal Singh, Dr. Nagendra Singh Chauhan, Sanjay Kumar Hardwariya and Manish Meshram** for their timely and constant support in responding to questionnaire.

I would also like to thank my friends at my home who provided me respite after the day's hard work and helped me charging up for another day with more energy and vigor. A special thanks to **Dr. Hemant Goel, Kapil Dev Tyagi, Sudhanshu Sharma, Neetu Sharma, Alok Vijayvergiya, Dr. Komal Vijay, Dr. Harshad Patil, Jitendra Wilankar, Sagar Rangrej, Mr. Karan Sitaraman, and Mr. Rajendra Dandale**.

Nothing can resist a determined will, and without an intense desire to succeed, no man or woman can ever achieve anything remarkable.
In the words of Victor Hugo – 'People do not lack Strength, they lack will.'

I thank The Lord Almighty for giving me the strength, will, and wisdom to carry out the project work successfully.

Lastly, I would like to thank all those who helped me directly or indirectly during this project work.

ABSTRACT

UNITED STATE FOOD AND DRUG ADMINISTRATION'S ACCELERATED APPROVAL PATHWAY – PROGRESSIVE JOURNEY AND OPPORTUNITIES FOR A BALANCING ACT FOR ONCOLOGY DRUGS

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2024

Dissertation Chair: <Chair's Name>
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Accelerated Approval Pathway is one of the most sought-after approval approaches of USFDA for Oncology Drugs. It has been criticized for some of its shortcomings that may leave a void to expose Cancer patients to not so better perceived safe, efficacious and quality drugs. Out of various challenges associated with it, challenges associated with timeboxing of confirmatory clinical studies; incentivization opportunities or exercising penalization of Sponsors for diligently conducting or not conducting the confirmatory clinical studies, respectively; introduction of drug product label modifications for drug products which have received accelerated approvals; and striking checks and balances on the costs of drug products approved through this approval pathway were chosen to be studied as part of this research work. This work involved quantitative & qualitative methods on the responses received to questionnaires containing close-ended and open-ended questions on topics of highlighted challenges from relevant professionals from R&D, Regulatory Affairs, Clinical Healthcare & Key Opinion Leaders (KOLs) and

pharmaceutical academics, primarily. Efforts were also made to reach out to Health Authority stakeholders and seek their viewpoints on these issues; however, no response was received from their side. A total of 57 participants responded to the questionnaires and out of them 51 were legitimate respondents. On responses to close-ended questions, analysis was done with the help of application of statistical techniques, like, mean, median, mode and standard deviation. Also, Chi-square analysis and Cramers' V analysis were performed to see the association of variables and strength of association of variables, respectively. On responses to open-ended questions, analysis was done with the help and Natural Language Processing (NLP) techniques comprising of Topic Modeling (LDA). From the analysis, it can be understood that timeboxing holds the key in good conductance of clinical trials and prove be an important torchbearer for early patient access of drugs with utmost safety, efficacy and quality profiles. Similarly, both incentives and penalties play a crucial role in ensuring that sponsors conduct their clinical trials on time. By offering prioritization in review processes, market exclusivity, and public recognition, sponsors are motivated to complete their trials efficiently. On the other hand, financial penalties, FDA involvement, and the withdrawal of approvals serve as strong deterrents for sponsors who fail to meet their obligations. For label modifications, the responses are indicative of a positive perception of modifications proposed on the labels/ prescribing informations. The suggestions provided by respondents reflect a deep concern for safety, transparency, and effectiveness when it comes to drug labeling. Costs of drug products always hold the key in better patient access. This analysis reveals that respondents identified a wide range of variables and measures that could help regulate drug prices.

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INTRODUCTION

1.1 Introduction

Cancer has always been one of the most prominent causes of mortality across the world. According to estimates of GLOBOCAN 2022 produced by the International Agency for Research on Cancer, worldwide an estimated 20 million new cases of cancer occurred in 2022. These estimates do predict that by 2050, the global burden of cancer is expected to be 35.3 million cases, which is a whopping 76.6% increase from what the figures have been in 2022 (WHO IACR GCO Report, 2022). These rising numbers certainly fuel the need for more and more research to be done in the area of Oncology. Alongside increasing R&D efforts, it is also highly imperative that the Health Agencies also do their part to bring these newer Oncology drugs available to the patient population in the swiftest manner possible.

Figure 1.1
Cancer prevalence across the globe

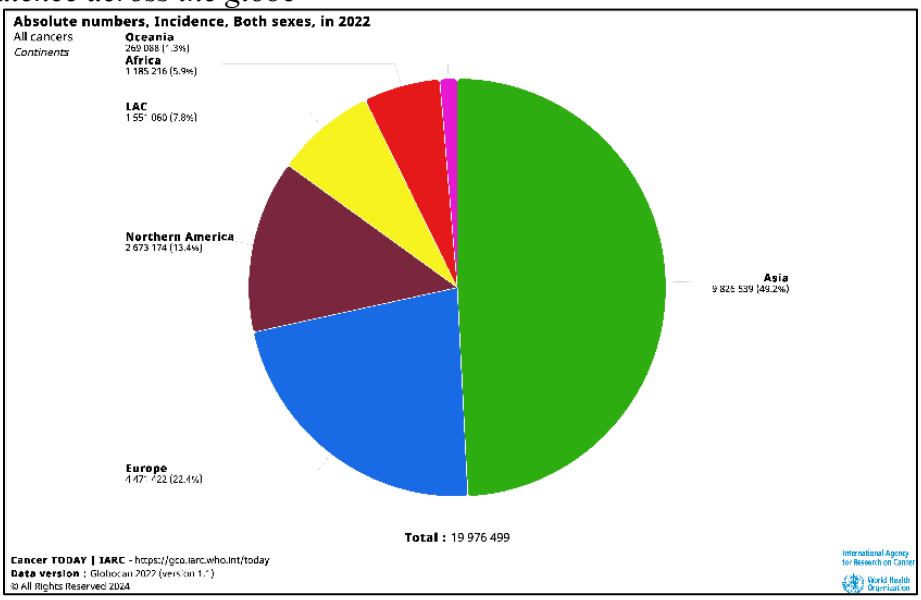
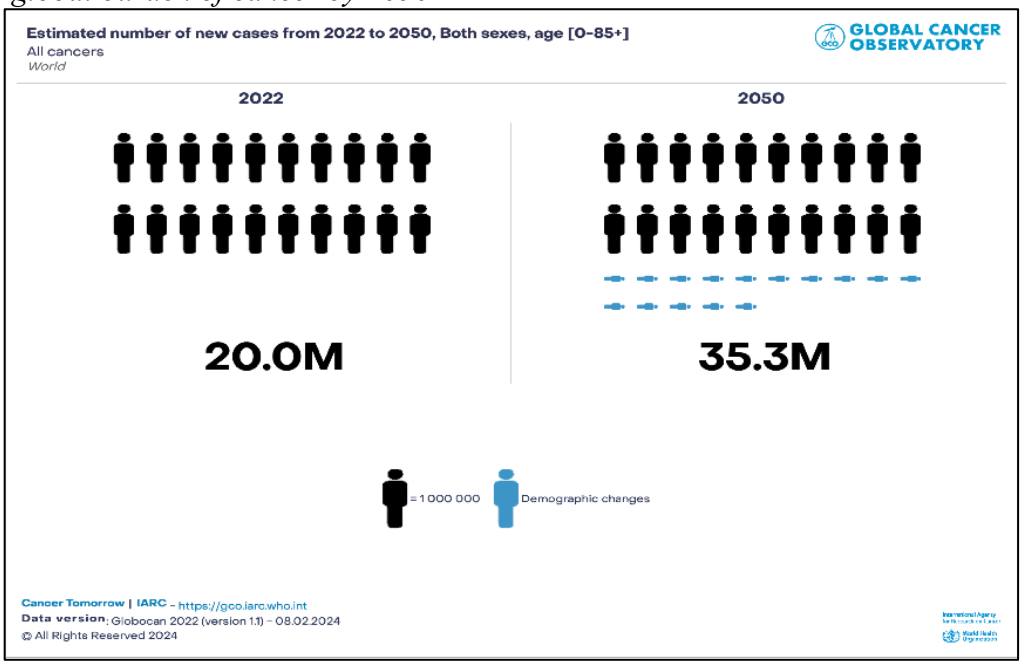


Figure 1.2
Expected global burden of cancer by 2050



Accelerated Approval Pathway is one such regulatory mechanism introduced by USFDA in 1992 that allows faster approval of drugs that are needed to treat serious and life-threatening diseases and makes those treatment modalities available to the needy patient population earlier than those would have been approved through conventional approval pathway. The conventional pathway utilizes the evidence to measure of direct clinical benefit generated by that particular drug or its benefit upon a validated surrogate endpoint. This is a time-consuming process, as these studies and their outcomes take time and hence the approvals of such drugs. While the Accelerated Approval Pathway utilizes the demonstration of the effect of a drug on its surrogate endpoint or on an intermediate clinical end-point that is reasonably likely to predict a clinical benefit to approve drugs. As per this statute, the Sponsors should conduct post-approval studies to verify and ensure the expected clinical benefits of such drugs which have been approved through Accelerated Pathway. In case, the Sponsor is not able to establish the clinical benefit

through these confirmatory trials or if there are any safety concerns, the approval so granted could be withdrawn (Beaver et al, 2020; Bilenker et al, 2020).

The United States Food and Drug Administration **(**USFDA) has accepted the usage of Accelerated Approval Pathway by the Sponsors of drugs meant to treat various cancers and promulgated it considering the unmet needs of cancer patients. The basic tenet of obtaining approval for a drug product under the aegis of this pathway is that the Sponsors, after having submitted the preliminary data around the safety, efficacy and quality aspects of drug products, should conduct and complete the confirmatory studies in a reasonable timeframe and submit that data to USFDA to obtain a final approval. In all good faith and optimism, the USFDA has been consistently reviewing, evaluating the applications and granting approvals to Oncology drugs under this pathway over the years since its inception. Quite recently, the inflow of such applications has increased considerably, and in the last decade itself, USFDA has granted approvals to more than 172 indications, but only in case of 50% out of them, i.e. 86, clinical benefit was verified by their demonstration of improvement in survival, delay of disease progression, or durability of response. Out of these granted accelerated approvals, a total of 21 indications (i.e. 12%) have been withdrawn by the Sponsors. The median timeframe to verify the clinical benefit and grant confirmatory approval has been 3.1 years (0.5 to 17.6 years), while the median timeframe for withdrawal of an indication has been 3.8 years (1.3 to 12.5 years). (Fashoyin-Aje et al 2022). It is quite evident from the efforts of the USFDA that they are positive about the Accelerated Approval pathway's tenets and have been consistently granting approvals to Oncology drugs, but it seems the Sponsors need to be more leading in conducting confirmatory studies and withdrawing the products if they are not matching the safety and efficacy expectations.

Some of such dichotomies associated with the Accelerated Approval Pathway have motivated to carry out this particular research. Since Accelerated Approval Pathway is one of the most sought after approaches to bringing therapeutic modalities quickly to the needy patient population and it has been a good 30 years since it has come into existence, it is also important to see that while it addresses the timeliness and access aspects of treatment options of the unmet medical need, it should also be able to strike a right balance with safety and efficacy of them. If it should be able to incentivize the Sponsors who are following its tenets in their kith-and-kin, it should also be adequately able to be restrained to those who are fiddling around it. The cost of such therapies at which these are being made available to the patients in need should also be another area that should be critically looked into.

Through this research work, a little more deep dive into these issues is expected to be done to bring out some course correction suggestions for the Industry as well as the Health Authorities after having sought inputs on these areas from them.

1.2 Research Problem

The core crux of the problem is that despite Accelerated Approval Pathway being most sought-after approval mechanisms for Oncology Drugs over a period of last more than three decades, it has not been able to address the challenges associated with it to the expected extent. The USFDA's stand has been very clear that they intend to bring as much therapeutic options as possible for the patients of disease conditions with unmet needs. They have been consistently approving products under the jurisdictions of this approval pathway, but this is also a fact that there are occasions when the Sponsors have either deliberately or inadvertently not been able to meet the expectations with respect to completing the confirmatory clinical studies and being transparent about the risk-benefit

profile of these treatment modalities. Also, there has also not been an apt balance struck with respect to the cost of such therapies.

Though the Accelerated Approval Pathway was originally used for HIV drugs, but over the last 10 years, 85% of accelerated approvals have been granted to Oncology drugs by USFDA (Beaver and Pazdur, 2021). Even, research and development efforts across the industry have more been concentrated in the area of Oncology. Over the years since its inception, Accelerated Approval Pathway has been utilized as a tool by Sponsors for begetting quicker approvals for their products by working around its tenets which have been quite well accepted by the scientific fraternity as well as beneficial for patients, at large. The USFDA's introduction of other assessment and approval approaches, like, Priority Review, Fast track Approval and Breakthrough Therapy Designation, Accelerated Approval Pathway has been and likely remains the most sought-after approval approaches for Oncology drugs by the Sponsors. The USFDA has not only embraced and accepted drug product applications for assessment and review but also has been approving them with complete positive intent that the Sponsors would follow the tenets of this pathway with utmost diligence. On the contrary side of it, it has been seen that in many cases, USFDA has approved the products following its similar principles, but the Sponsors have not been able to act up to the mark in conducting the confirmatory studies (Kaltenboeck et al, 2021) or the products have not been able to stand up to the study expectations and had to be voluntarily withdrawn or have become critical discussion topics in several of the USFDA Oncologic Drug Advisory Committee meetings (Beaver and Pazdur, 2021).

A literature review of studies around Accelerated Approval Pathway suggests that the implementation and obeisance of it has not been that smooth in recent years. Time and again, there have been some pertinent issues that have been highlighted by these

studies, which tend to revolve around design of clinical studies and selection of surrogate endpoints that are used for approval decisions, delays in conductance of confirmatory clinical studies by the Sponsors after accelerated approvals have been granted, usage of non-validated surrogate endpoints instead of clinical endpoints while conducting confirmatory clinical studies, inaction or delayed action by USFDA when a confirmatory clinical study has not been conducted by a Sponsor even after passage of a considerable amount of time, inaction or delayed action by USFDA when a drug product does not show an evidence of predicted clinical benefit upon conductance of a confirmatory clinical study or the treatment outcomes could be statistically good but are not clinically significant, or high cost of availability of such therapeutic options to cancer patients after obtaining accelerated approval and, more so, after obtaining traditional approval, post conductance of confirmatory clinical trials.

According to a report of the Office of Inspector General, US Department of Health and Human Services, from 1992 till December 2021, out of 278 drugs approved under Accelerated Approval Pathway, there are 104 drugs which have incomplete confirmatory trials. Out of these 278 drugs, 139 drug products took an average of 48 months for their confirmatory trials since the time they were granted Accelerated Approvals. There are 35 of 104 drugs with incomplete confirmatory trials, which have average 1.5 years past their original planned confirmatory trials. Thirty-five of 278 drugs which were granted Accelerated Approvals have been withdrawn till May 2022. There are 4 such drug products for which the confirmatory trials have been overdue by more than 5 years to nearly 12 years. As of May 2022, for 18 drugs out of 35 which are yet to complete the confirmatory clinical trials, from 2018 to 2021, Medicare Part B and Part D have spent more than USD 14 billion. Thus, it could be seen that Medicaid and Medicare have spent billions of dollars on treatment modalities which have not been able to

establish their confirmatory clinical benefit (Report of OIG, US Department of Health and Human Services, September 2022). Along with these challenges, the USFDA's process of withdrawing a drug approved through the Accelerated Approval Pathway is lengthy and contentious. Sometimes USFDA's inability to act against Sponsors who have not been able to provide confirmatory evidence of drugs' efficacy and safety despite enjoying a considerable time post being granted Accelerated Approval or having worked on duplicative or similar indications, for which, the studies did not confirm a clinical benefit yet they continued to enjoy marketing authorization, resulting in "Dangling Accelerated Approvals" (Beaver and Pazdur, 2021; Kaltenboeck et al, 2021).

Along with these questions raised and challenges, henceforth, another big question that has always been raised is the cost of the availability of these treatment modalities. Risk-benefit balance profile and their cost trade-off have not always painted a greener picture of Accelerated Approval Pathway. Sometimes voices have also taken rounds in the healthcare fraternity around the USFDA's inability to act against Sponsors not able to produce an additional affirmatory evidence of drugs' efficacy and safety despite enjoying a considerable time post being granted Accelerated Approval or having worked on duplicative or similar indications, for which, the studies did not confirm a clinical benefit yet they continued to enjoy marketing authorization, resulting in "Dangling Accelerated Approvals" (Beaver and Pazdur, 2021; Kaltenboeck et al, 2021).

These highlighted challenges with Accelerated Approval Pathway have become the focal point to carry out this research and to find out answers to some of these identified challenges.

1.3 Purpose of Research

The primary purpose of carrying out this research on the topic, "United State Food and Drug Administration's Accelerated Approval Pathway – Progressive journey

and opportunities for a balancing act for Oncology Drugs" is to find some relevant and forward-looking answers to few of the observed challenges associated with Accelerated Approval Pathway. As highlighted above, some of these are:

- Design of clinical studies and selection of surrogate endpoints that are used for approval decisions
- Delays in conductance of confirmatory clinical studies by the Sponsors after accelerated approvals have been granted
- Usage of non-validated surrogate endpoints instead of clinical endpoints while conducting confirmatory clinical studies
- Inaction or delayed action by USFDA when a confirmatory clinical study has not been conducted by a Sponsor even after passage of a considerable amount of time
- Inaction or delayed action by USFDA when a drug product does not show evidence of predicted clinical benefit upon conductance of a confirmatory clinical study or the treatment outcomes could be statistically good but are not clinically significant
- High cost of availability of such therapeutic options to cancer patients after obtaining accelerated approval and, more so, after obtaining traditional approval, post conductance of confirmatory clinical trials

This research work intends to delve more into these areas and then try to come up with some possible recipes for the industry as well as Health Authorities to address the conceivable challenges after seeking inputs from various stakeholders from Industry on below aspects. An effort would also be made to reach out to a few Health Authority stakeholders and get their views on them.

- best possible approaches for clinical trial designs

- finalizing the surrogate and clinical endpoints
- striking the apt benefit-risk profile
- strengthening the penalties and incentivization of Sponsors for not completing and completing confirmatory studies, respectively, and possible timeframes to achieve them
- fixing a duration of time for confirmatory studies for different types of disease conditions and the possibility of automatic expiration of accelerated approval if confirmatory studies are not completed in that fixed duration of time
- specialized labelling for drugs approved under an accelerated approval pathway
- Utilization of real-world evidence and data approaches
- revocation approaches of accelerated approvals
- checks and balances on the costs of these treatment modalities
- indication-based pricing of treatment modalities
- linking reimbursement to confirmatory studies and their outcomes

Basis the outcome of above study, some recommendations would be put together for the Industry and Healthcare professionals from a further refined research effort perspective and the Health Authority from a prospective feasibility policy amendment perspective which would help this approval pathway to achieve its objective of swift patient access with utmost balanced risk-benefit profile and at a better justified cost.

Thus, it is expected that this research study would be able to put forth some answers that help holding Accelerated Approval Pathway its desired forte.

1.4 Significance of the Study

Research on this topic, “United State Food and Drug Administration's Accelerated Approval Pathway – Progressive journey and opportunities for a balancing act for

Oncology Drugs" holds significance, as this could help paving way to address some of the observed challenges associated with Accelerated Approval Pathway. Below could be some of the aspects that may make contribution of this research significant for pharmaceutical and biopharmaceutical industry, regulators, USFDA and other health authorities and, above all, patients, at large.

- **Business and commercial augmentator:** Accelerated Approval Pathway is not only an important regulatory instrument but also a business and commercial augmentator in United States which helps in bringing drug products intended to treat diseases with unmet treatment needs early to the market without compromising on drug efficacy and patient safety. By adopting this pathway, there is a win-win for both the USFDA as well as for the Industry, as it helps begeting quicker approval and commercialization for the drug products. The outcomes of this study will help enabling these business outcomes better.
- **Facilitator for better patient access:** This pathway is one of those means that aid in early patient access of those unmet needs for Oncology drugs. Though; there are other approaches that the USFDA, and even the industry, undertake to pursue these drugs in interstate commerce quickly, but Accelerated Approval Pathway holds a special place, as it being the most sought after approach. The outcomes of this research will help erasing doubts applicability of this pathway and suggest for much better means and justifed timeframes for availability of drugs to the patients, with better managed risk-benefit profiles.
- **Compliance towards regulations:** The USFDA has laid down a series of mandatory requirements for begeting drug product approvals. This pathway, as other accelerated approaches and conventional approval approaches, too is bound by those requirements. Compliance to them is the only key that can enable drug

product approvals under this pathway. Yet, deliberately or inadvertently, compliance towards those regulatory requirements is not adhered to. This study is trying to stress upon all stakeholders involved adhering to those compliance requirements and put together some recommendations that would help enabling compliance.

- **Better informed healthcare providers and patients:** Label of a drug product is approved after an approval is granted to a drug product and it is expected that it should be able to provide all the desired information that is needed to educate the staekholders involved in prescription decision and consumption of that drug product. There are regulations that are desired to be followed in order to make the label compliant and adequately informing to all stakeholders involved. Products granted approval under the accelerated approval pathway may have different dynamics than that of products that have been granted approvals as conventional products. Hence, information contained on their labels should also be different. There is a need to have some additional information to be provided on the labels of products granted approval under accelerated approval pathway, so that the healthcare decision makers in clinics or clinical trial centers and patients would be informed about the product and its dyanmics in a better manner. This study emphasises on such needs and it is expected that the outcomes of it would be able to jot down those additional information that need to be included on the labels of drug products that have been granted approvals under accelerated approval pathway.
- **Better justified costs of drug products:** A great deal of cost variance has been seen with the costs of drug products that have been granted approval under the accelerated approval pathway. This may be attributed to various reasons, which

may or may not be under direct or indirect control of the Sponsors. It is also seen that costs of same product which has been granted approvals for discrete indications have quite dichotomus price tags. This ballooning of costs has a great deal of impact on the patients and/ or the payors involved. This study intends to delve around the various variables that may the direct or indirect causes of such inflated costs. It is also expected to identify and highlight what could be the cost drivers and what could be unwarranted cost inflators so that economic burden on the patients and payors could get reduced.

- **Payors and insurance companies:** Payors and insurance companies are yet another stakeholders that sometimes seem to be on a receiving end due to the costs associated with treatments of oncologic disease conditions. Though; they may keep trying various permutations and combinations in order to remain productive and profit-making, yet this always leads to a lot of backend work and deliberations with patients and healtcare set ups. Prominent reasons for engaging in such situations is nothing but these highly varied costs. With the help of this study, it is being explored what could be various variables that lead to such situations, what could be done to curb them and what could be avoided to stay profit making.
- **Possible recommendations for USFDA:** Considering the challenges highlighted above, this study has been promulgated. It is expected that outcomes of this study will help addressing these challenges to a larger extent and support this wonderful approval instrument by USFDA. It would be expected to come up with some forward-looking recommendations in discrete identified areas to USFDA so that this approval pathway holds its value and patients, at large, would continue to get benefitted for longer periods of time.

1.5 Research Purpose and Questions

Keeping in view of the identified challenges, as above, this research is purposed to dig more into these challenges to explore some relevant remediations and seek opinions from discrete Industry stakeholders and possibly from Health Authority stakeholders as well to affirm on them and put together probable solutions around those challenges. Stakeholder opinions have been sought with the help of a questionnaire circulated to them.

The questions have been designed using 'mixed method' approach. In this research, these multi-faceted aspects are being explored with the help of secondary research as well as primary research. Questions or challenges with respect to clinical trial design, selection of trial endpoints or measures to strike the apt risk-benefit balance have been explored with the help of secondary research, but the questions or challenges pertaining to time-boxing of confirmatory clinical studies, incentivization or penalization of Sponsors, drug product label modifications and checks and balances of drug product costs have either been under-answered or unanswered through secondary research - these would be explored with the help of primary research. Below are some of these probable explorations through primary research:

Time-boxing of confirmatory clinical studies: To understand what time-boxing practices could be adopted for the conductance of confirmatory clinical studies, how much time could be granted to a Sponsor to conduct such a trial after accelerated approval has been granted

Incentivization or penalization of Sponsors: To assess the conduct practices that could make the potential for either incentivization of Sponsors for conducting

confirmatory clinical trials or penalize them for not conducting them, what could be the magnitude of these incentives or penalties

Drug product label modifications: To assess what distinct and discrete type of additional information should make way for putting on labels of products that have been granted accelerated approvals, how this information should look different from labels of traditionally approved products vs products approved under accelerated approval pathway

Checks and balances of drug product costs: To understand the practices that would be able to help in decision-making of cost of drug products that have been approved using accelerated approval mechanism, what approaches could be adopted to keep the costs of such products justified and under control, what measures USFDA could take in keeping these costs balanced vis-à-vis the research efforts

The primary research questionnaire has been designed around seeking answers to the below questions and may even go beyond them to some extent:

- What should be various time-boxing criteria for confirmatory clinical trials?
- Should time-boxing of confirmatory trials be therapeutic area/ disease agnostic or should there be confinement within these boundaries?
- What should be the most appropriate time-boxing duration for confirmatory clinical trials?
- Should this duration be a blanket time duration for all confirmatory studies or should this also be dependent on therapeutic area/ disease/ patient population, etc.? If there are some dependencies, what should be the durations for these distinct dependencies?

- How much of a broader time frame or its range is reasonable to provide an allowance to conduct confirmatory clinical studies, post-grant of an accelerated approval?
- Should there be a provision of incentivization or penalization of Sponsors around the conductance of confirmatory clinical studies?
- What are the practices that should make a Sponsor a potential candidate for either incentivization or penalization respectively?
- What are the possible ways to incentivize or penalize a Sponsor – in terms of monetary provisions, specific exclusivities, review timelines for traditional approvals, etc.?
- What information should be kept on labels of drugs approved under the accelerated approval mechanism – should it be pertaining to the approval pathway (traditional or accelerated), details of the surrogate marker, possible confirmatory clinical study timeline, post-approval commitments, etc. or all of them?
- What could be a distinct way of presenting this information on labels – should these be in different colour or in boxes, etc.?
- Should there be a cost ceiling for products granted accelerated approvals?
- Should cost decisions have disease/ indications/ population -based considerations?
- What should be possible USFDA actions against untoward costs of drugs granted accelerated approvals?

Similarly, a questionnaire for Health Authority professionals has been designed to cover the same topics, but those questions have been portrayed more from the Agency directive and implementation perspective.

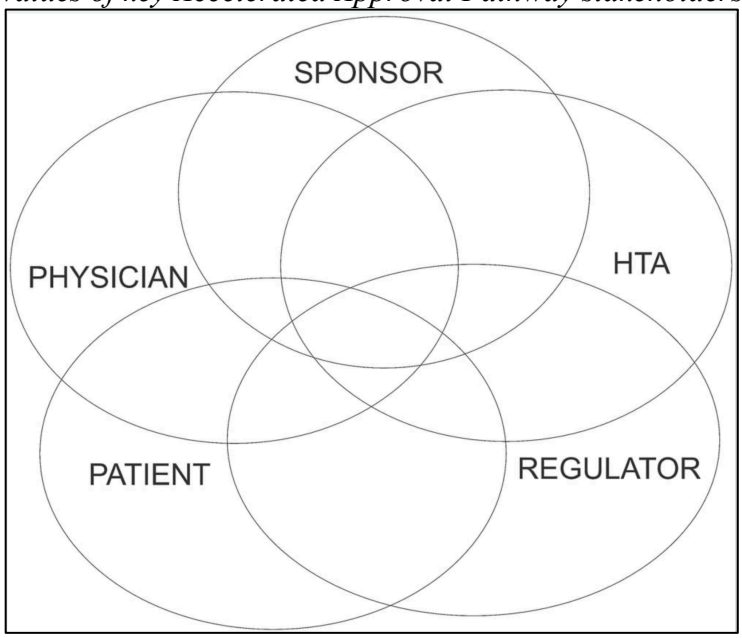
CHAPTER II:

REVIEW OF LITERATURE

2.1 Theoretical Framework

According to Gould et al, 2022, in a clinical study value chain, there are a series of stakeholders which are involved. These stakeholders are – patients, physicians, regulators, Health Technology Assessments (HTAs) and Sponsors. The value of any clinical study is determined by the benefits that it is offering to all these stakeholders involved. Accelerated Approval pathway is an approval appraoch that enables early availability of treatment modalities to patients suffering with diseases with unmet needs. Below are some expectations that are to be drawn and mapped for each of the stakeholders involved to get maximum benefits out of the clinical studies that form the basis of such Accelerated Approvals.

Figure 2.1
Unique and shared values of key Accelerated Approval Pathway stakeholders



Ref.: Published online 2022 Jun 24. doi: 10.1371/journal.pone.0265712

- **Patients:** Patients are always at the receiving ends of clinical trials and it is utmost critical that care needs to be taken to ensure that any trial, wherein they are involved, would render the highest order of benefit to them. Practically, any drug product that becomes a part of clinical trial, would not be free from harmful effects; yet the endeavor of scientific community, overall, remains to reduce the risk to the least possible. Hence, these risks are always evaluated aginst the benefits of drug products and the objective always remains to have a drug product with lowest risk-benefit ratio.
- **Physicians:** Physicians hold an important place in the clinical trial value chain, as they are the ones responsible for deciding the best treatment modality for their patients. There may be more than one such treatment option available at one point in time. Their expertise lies in choosing that one that would deliver maximum number of benefits for their patients – with respect to availbility, harmful effects, risk-benefit ratio, co-morbidities, cost of therapies, reimbursement options, etc. Thus, they would do a lot of screening on the overall benefit scale before they make an informed decision for their patients.
- **Regulators and Health Technology Assessments:** Regulators tend to remain at the other fag end of clinical trials value chain. They are the ultimate consumers of the data that has been produced as an outcome of those clinical trials and have huge responsibility of its assessment and then granting approvals to those treatment modalities. In case of drug products that have chosen conventional approval pathway to come into state commerce, the process still remains straightforward and they go by the

laid down regulations. But, in case of drug products that envision themselves as “early birds” into that unmet therapeutic need space and try to enter to state commerce through Accelerated Approval Pathway route, their assessment with a sharp eye holds the key. For such products, dynamics could be complex and there may be grey areas in their development. Hence, their role here is very crucial and that is the reason why they are always critical about the risk-benefit ratio. Similarly, the Health Technology Assessors belong to that discipline that examines and reports the attributes of an available or potential treatment modality on the parameters of safety, efficacy, feasibility and availability and its cost as well as cost effectiveness. Their assessments aid the Health Authorities take an informed decision on approvals; especially when there are grey areas in the drug development approaches.

- **Sponsors:** Sponsors are the entities who have a lot at stake in the whole value chain of clinical studies They tend to spend a lot of time, money and resources in bringing a safe, efficacious and quality product to market. Sponsors understand that products with conventional routes of approval would take their own time in realizations, but for products with accelerated routes of approval, they would intend to maximize as early as possible. Hence, they eye at early approvals from Health Authorities. There are Sponsors who follow the crux of accelerated approval approaches to their core, while there are some who do not, yet they intend to get considered for early approvals. The Sponsors who follow the premises of accelerated approval approach diligetly, they deserve some benefit/ s to be tranferred to them. The ways and means in which such a

transfer could occur need to be figured out; while for other class of Sponsors, the ways and means to deter them should also be looked into.

The core premise of this research work is to understand whether the benefits that have been envisaged or expected for all these stakeholders in this clincal study value chain are being realized or not. If not, what could be done to keep them in place. The literature review below tries to identify them and bring out some thoughts to get these challenges addressed.

2.2 Literature Review

Accelerated Approval Pathway is one such regulatory mechanism introduced by the USFDA in 1992 that allows faster approval of drugs that are needed to treat serious and life-threatening diseases and makes those treatment modalities available to the needy patient population earlier than those would have been approved through conventional approval pathway. The conventional pathway utilizes the evidence to measure of direct clinical benefit generated by that particular drug or its benefit upon a validated surrogate endpoint. This is a time-consuming process, as these studies and their outcomes take up to 10-15 years hence the approvals of such drugs as well. The Accelerated Approval Pathway utilizes the demonstration of the effect of a drug on its surrogate endpoint or on an intermediate clinical endpoint that is reasonably likely to predict a clinical benefit to approve drugs. As per this statute, the Sponsors should conduct post-approval studies to verify and ensure the expected clinical benefits of such drugs which have been approved through Accelerated Pathway. In case, the Sponsor is not able to establish the clinical benefit through these confirmatory trials or if there are any safety concerns, the approval so granted could be withdrawn (Beaver et al, 2020; Bilenker et al, 2020).

This literature review intends to assess around:

1. The evolutional aspects of the Accelerated Approval Pathway and its comparison with other similar approaches promulgated by the USFDA for Oncology Drugs
2. Adoption of Accelerated Approval Pathway for Oncology Drugs by industry & USFDA and benefits & challenges/ risks envisaged for patients
3. USFDA's current position on it and steps taken to strengthen it further

This literature review has been done utilizing the information gathered by scrolling through various electronic databases; viz. Google Scholar, ResearchGate, Springer, Elsvier, etc. Major keywords utilized for conducting these searches were: Accelerated Approval Pathway, USFDA drug approval approaches, fast-tracking approvals, oncology drug approvals, etc. Relevant citations from bibliographies of these articles, journals and dissertations were also evaluated to find additional sources.

Background

Though the Accelerated Approval Pathway was originally used for HIV drugs, over the last 10 years, 85% of accelerated approvals have been granted to Oncology drugs by the USFDA (Beaver and Pazdur, 2021). Even, research and development efforts across the industry have been concentrated in the area of Oncology. Over the years since its inception, Accelerated Approval Pathway has been utilized as a tool by Sponsors for begetting quicker approvals for their products by working around its tenets which have been quite well accepted by the scientific fraternity as well as beneficial for patients, at large. On the contrary side, it has also been seen that in many cases, the USFDA has approved the products following its similar principles, but the Sponsors have not been able to act up to the mark in conducting the confirmatory studies (Kaltenboeck et al, 2021) or the products have not been able to stand up to the study expectations and had to

be voluntarily withdrawn or have become critical discussion topics in several of the USFDA Oncologic Drug Advisory Committee meetings (Beaver and Pazdur, 2021). Along with these questions and challenges, henceforth, another big question that has always been raised is the cost of the availability of these treatment modalities. Risk-benefit balance profile and their cost trade-off have not always painted a greener picture of the Accelerated Approval Pathway. Sometimes voices have also taken rounds in the healthcare fraternity around the USFDA's inability to act against Sponsors not able to produce additional affirmatory evidence of drugs' efficacy and safety despite enjoying a considerable time post being granted Accelerated Approval or having worked on duplicative or similar indications, for which, the studies did not confirm a clinical benefit yet they continued to enjoy marketing authorization, resulting in "Dangling Accelerated Approvals" (Beaver and Pazdur, 2021; Kaltenboeck et al, 2021). These are some of the dichotomies associated with the Accelerated Approval Pathway that have motivated me to carry out this particular research.

Since Accelerated Approval Pathway is one of the most sought-after approaches to bringing therapeutic modalities quickly to the needy patient population and it has been a good 30 years since it came into existence, it is also important to see that while it addresses the timeliness and access aspects of treatment options of the unmet medical need, it should also be able to strike a right balance with safety and efficacy of them. If it should be able to incentivize the Sponsors who are following its tenets in their kith-and-kin, it should also be adequately able to restrain those who are fiddling around it. The cost of such therapies at which these are being made available to the patients in need should also be another area that should be critically looked into.

This literature review is trying to explore more into the journey that the Accelerated Approval System has traversed so far, its victories and challenges and what lies in future for it. A bit of a gist of this exploratory research is presented below:

The evolutional aspects of the Accelerated Approval Pathway and its comparison with other similar approaches promulgated by USFDA for Oncology Drugs

The modern safety and efficacy requirements that govern the FDA's review and approval of a new drug product evolved out of a series of legislative enactments over the years (Kepplinger, 2015). A major legislative breakthrough happened when in 1938, post the Sulfanilamide tragedy, the FDA enacted the Federal Food, Drug and Cosmetic Act of 1938 (abbreviated as FDCA). As per its then statutes, it not only required Sponsors to submit applications to the FDA for marketing of new drugs but also required them to prove that the subject product was safe. If the application submission by the Sponsor, the FDA did not act on it after a specific period, the application would be deemed to get automatically approved. Further, in 1962, there was another tragedy in Western Europe wherein it was discovered that due to a drug being marketed as a sleeping pill and subsequent to its ingestion by pregnant mothers, occurred several malformations in newborns. Taking cues from it, the FDA broadened the horizon of FDCA through the Kefauver-Harris Amendment by including both new drugs as well as biologics under it. Also, it quashed the automatic approval provision of the earlier statute and introduced an affirmative FDA approval for all drugs before those could be inducted into the US market. It did introduce the mandatory requirements of proving safety and efficacy for all drugs before approvals are granted to them, which set the stage for following the modern-day development and clinical trial process for all drugs. There have been multiple amendments to FDCA since 1962, but the basic crux of the Act has remained the same;

i.e. to receive marketing approval for a new drug, a Sponsor must show substantial evidence of safety and efficacy with the help of clinical trials (Drug Amendments of 1962) and Kulynych J (1999). When we say the safety of a product, it must be understood that the Sponsor needs to establish the safety of that product for use under the conditions mentioned in the proposed labelling of it. Per FDCA statutes, the USFDA assesses the safety of drug products through a risk-benefit framework, which means that the benefits rendered by the drug products must outweigh their risks (Draft PDUFA VI Implementation Plan (FY 2018-2022). The safety and efficacy of a drug product tend to be proved through a battery of one pre-clinical and three phases of clinical trials before the drug product application is submitted to the USFDA for its approval for marketing authorization.

Pre-clinical studies are conducted with the help of in vitro tests, computer-aided drug models and testing on live animals, scaling up from small species to large species to obtain a prediction around the drug's toxicity and its pharmacokinetics and pharmacodynamics.

Once these studies show promising results in animals, the Sponsor tends to reach out to the USFDA by filing an Investigational New Drug (IND) Application to seek permission to conduct clinical studies in human beings and also to obtain an exemption from the prohibition against bringing experimental drugs in interstate commerce in the US. These initial trials are known as Phase I clinical trials and are conducted in healthy human volunteers to assess the safety, toxicity, dosage and pharmacokinetics of investigational drugs. These trials are conducted in 20-80 subjects (21 CFR Part 312.21 and NIH Clinical Research Trials And You).

The drugs which have a successful Phase I clinical trial outcome, become candidates for the next level Phase II clinical trials. These trials are randomized &

controlled trials and are conducted on patients of that particular disease condition which generally tend to involve 80-200 subjects. The main objectives of these trials are to provide more information on safety, generate first of data on efficacy and establish dose-response relationships (21 CFR Part 312.21 and NIH Clinical Research Trials And You).

Safety and efficacy data generated through Phase I and Phase II clinical trials may not be sufficient to satisfy the USFDA's expectations of proving them to be substantial evidence of safety & efficacy or striking that apt balance between benefits and risks associated with that drug product. Hence, USFDA mandates conducting Phase III clinical trials which are more expanded controlled or uncontrolled studies. These clinical trials involve several hundred to several thousand subjects. These trials provide more comprehensive data on the safety and efficacy of that drug product with a special emphasis on the side effects associated with long-term usage of it. These artefacts together help the USFDA to ascertain the overall benefit-risk profile of the drug (21 CFR Part 312.21 and NIH Clinical Research Trials And You).

Once a drug product stands firm on this overall benefit-risk profile and has a robust Phase III clinical study outcome, the next step in the journey of the drug product lifecycle is to apply to the USFDA for drug approval by filing a New Drug Application (NDA). The USFDA reviews the NDA and grants marketing authorization approval to that drug product after a successful evaluation. In normal circumstances, this evaluation takes place in a review cycle of 6 to 10 months after the NDA validation stage, which spans 60 days (The Drug Development Process, Step 4: FDA Drug Review).

To determine the benefits associated with the drug product from these Phase III clinical trials, one of the most important parameters is the primary endpoint of the clinical trial. Under the regular approval mechanism, the USFDA grants approval to a drug product on the basis of a direct clinical efficacy endpoint or a validated surrogate

endpoint. A clinical endpoint ‘‘is a characteristic or variable that directly measures a therapeutic effect of a drug - an effect on how a patient feels (e.g., symptom relief), functions (e.g., improved mobility), or survives. Essential primary clinical endpoints include improved overall survival and symptomatic improvement (such as time to progression of cancer symptoms) (Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics). There may also be an intermediate clinical endpoint which measures how a patient feels or functions, but it is not an ideal endpoint that a drug product intends to achieve.

On the other hand, a surrogate endpoint is an alternative endpoint that measures the effect of a drug product on a distant biological marker that is predicted to relate with some degree of certainty to a clinical efficacy endpoint. A validated surrogate endpoint “is known to predict clinical benefit’’ for a certain disease state and for a certain type of intervention. It has been suggested that to be a validated surrogate endpoint, the biological marker ‘‘must be correlated with the clinical endpoint’’ and ‘‘must fully capture the net effect of the intervention on the clinical-efficacy endpoint’’ for a specific disease setting and class of interventions. Blood pressure reduction, for example, is a validated surrogate for the risk of stroke in patients with cardiovascular disease studied anti-hypertensive agents such as beta-blockers and low-dose diuretics with known favorable safety profiles (Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics)

Complexities in the process of drug development and the resources in terms of time, money and effort that it consumed had always been a compelling factor for the USFDA to bring reforms in the overall approach in which drug product applications should be handled. The increasing burden of diseases and the USFDA’s core objective of making treatment modalities available to patients in need have continuously fueled the

need to adopt measures that could expedite the drug product approval process. Alongside, pressure from the Industry was also one of the factors augmenting it.

In view of the above-mentioned challenges and leveraging on the ever-evolving scientific advancements that have taken place in the Industry, USFDA has been continuously putting efforts to come up with initiatives to bring treatment modalities quickly to the market. Some of them have been highlighted, as under.

The first of such initiatives was creating a matrix of chemical type and therapeutic potential of drugs to classify and prioritize the review of INDs and NDAs. It was created in 1974 and remained in use until 1992. As per this matrix, products were chemically classified and a fixed rating was assigned to active moieties already approved and marketed in the US. Any new product application having a relationship with these moieties would get reviewed on priority (CDER 4820.3 Drug Classification and Priority Review Policy).

Another such early initiative was for enabling treatment modalities for AIDS/ HIV in the 1980s. Being a disease condition that had no scientifically established or FDA-approved treatment to halt the progression of the virus, the FDA was criticized for lagging behind in being able to provide such a treatment option. FDA collaborated with Sponsors and came up with a focused development and review program that helped get the approval for Zidovudine (AZT) in 1987 in a two-year timeframe and, thus, an effective treatment modality became available to the US population (Huber 2013).

Based on a successful experience from AZT approval, the FDA moved ahead and introduced 21 CFR 312.80 Subpart E in 1988 in order to provide the broadest flexibility in their assessments and manoeuvring the risk-benefit considerations for those patients impacted with life-threatening or debilitating diseases. As per this new arrangement, the Sponsor could connect with USFDA for pre-IND and end-of-Phase I meetings to get an

early buy-in from USFDA on such drugs' development approaches. It would help the Sponsors in embedding FDA expectations early on in their development programs and quicker review and successful outcomes (21 CFR 312.80 and 21 CFR 312.84).

In January 1992, the FDA amended the prioritisation matrix and came up with two categories, Type P (Priority Review) and Type S (Standard Review), keeping the two earlier categories, i.e. Type AA (for drugs indicated for the treatment of AIDS/ HIV-related diseases) and Type E (for drug developed under the 21 CFR 312 Subpart E) intact. Here, FDA determines whether a drug product application would become a candidate for Priority Review or would fall under Standard Review criteria. To be a candidate for Priority Review, the drug product must be able to treat a life-threatening condition and be able to provide significant improvement in safety and effectiveness as compared to the available treatment modalities. If a product is granted a Priority Review status, there tends to be a reduction of four months in the projected review time by the USFDA. FDA tend to put additional resources to review such applications and tends to complete the review expeditiously. (Guidance for Industry, Expedited Programs For Serious Conditions - Drugs and Biologics and Grabowski & Wang (2008)).

To address the issues of the FDA's challenges in faster approvals and to aid quick patient access to drugs, in October 1992, congress passed the Prescription Drug User Fee Act (PDUFA) 1992. It mandated the Sponsors to pay the user fees for review of their NDAs. Funds so collected would be used of hire new reviewers and other FDA staff to expedite the review processes. Through this, an FDA review and response charter was also put in place that a mandated FDA to finish the reviews in a stipulated and time-bound manner. It further codified the review categories into two - Priority Review and Standard Review for NDAs.

As another headway to reforms, in December 1992, the Accelerated Approval Pathway was introduced by the USFDA for NDA approvals. This mechanism was meant for drugs indicated for life-threatening conditions that would be able to provide a therapeutic benefit over the existing therapeutic modalities. Under this mechanism, approval is granted by the USFDA when the efficacy of the drug product is demonstrated through clinical trials that involve the effect on an unvalidated surrogate endpoint or an intermediate endpoint that would have the most likelihood of predicting a clinical benefit, instead of involving a validated surrogate endpoint or an ultimate clinical efficacy endpoint. This usage of an unvalidated surrogate endpoint would shorten the time duration of the clinical study that it would take to reach the ultimate clinical efficacy endpoint, but without compromising the efficacy and safety of the drug. Another important requirement associated with this pathway that the USFDA expects is that, post obtaining approval under the Accelerated Approval Pathway, the Sponsor must diligently complete the confirmatory clinical trials and their outcomes should positively reflect the safety and efficacy expectations as predicted through surrogate or intermediate clinical efficacy endpoints. (Guidance for Industry, Expedited Programs For Serious Conditions - Drugs and Biologics).

In 1997, USFDA codified another important approach to expeditiously approve drugs which is known as Fast Track designation. It evolved out of Subpart E regulations and came into force when the US Congress passed the Food and Drug Administration Modernization Act of 1997 (FDAMA). According to this approach, a drug product could be a candidate for Fast Track review if it is meant for a serious and life-threatening condition and it has been able to demonstrate a potential to address that unmet medical need for that disease condition. If a drug is designated under the Fast Track review category, FDA facilitates various ways and means to expedite the development and

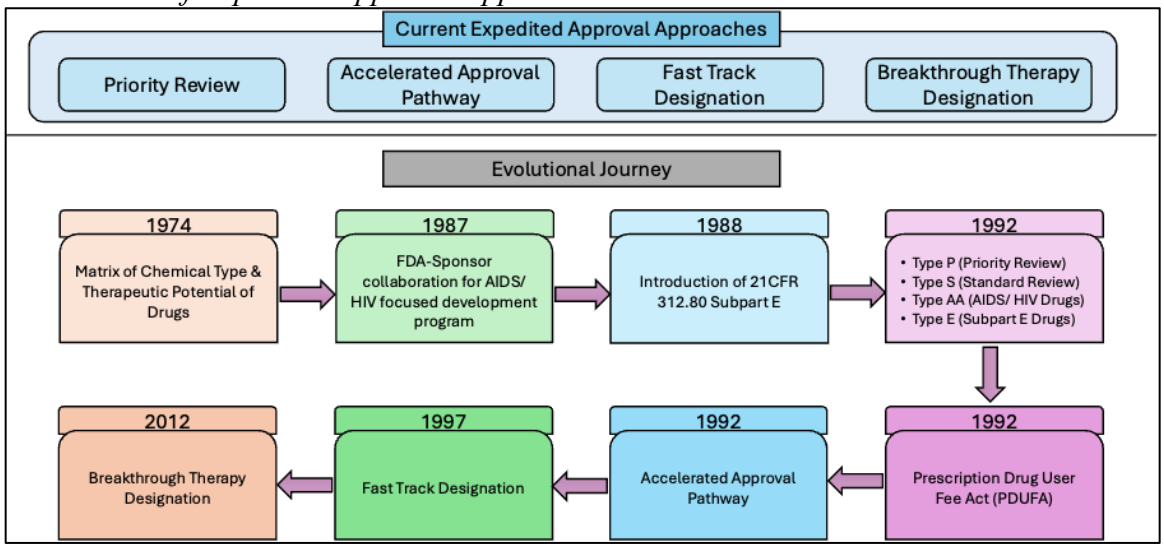
approval of that product. It provides opportunities for frequent interactions with the FDA in the form of pre-IND meetings, end-of-phase 1 meetings, and end-of-phase 2 meetings to discuss study design, the extent of safety data required to support approval, dose-response concerns, and the use of biomarkers. There may also be more meetings that could be arranged to discuss the structure and content of the application. The product may also be eligible for priority review if the application is supported by clinical data at the time of its submission. There may also be opportunities provided for a "Rolling Review," which means before a complete application is submitted, FDA may entertain review of portions of that application on a rolling basis, as and when data is available and submitted. (Guidance for Industry, Expedited Programs For Serious Conditions - Drugs and Biologics).

Further in 2012, the US Congress came up with the Breakthrough Therapy designation through the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA). Under this designation, if a drug or a combination of drugs that is intended for serious or life-threatening disease conditions has undergone clinical trials and has been able to show strong evidence of improvement over currently available treatment modalities even in early-stage through preliminary clinical efficacy and safety, it could be granted a Breakthrough Therapy status. If this evidence is not sustained through further data, FDA may revoke the status granted. This evidence should at least be shown through promising Phase I and /or Phase II clinical trials. The clinical performance may also be corroborated with non-clinical data and should involve a sufficient number of patients. The preliminary evidence must be shown through substantial improvement over one or more available treatment modalities on one or more clinically significant endpoints. Substantial improvement here could be considered if the improvement in symptoms is more sustained and complete instead of transient and partial as compared

with the currently available treatment options. There must be either a complete reversal or inhibition of symptoms or there is an important safety advantage as compared with currently available therapies. If a drug product is granted Breakthrough Therapy status, the FDA would help the Sponsor in expediting the development process by designing the clinical trials with the help of adaptive approaches, taking the help of an interim data analysis monitoring committee, facilitating frequent interactions at various phases of development, involving a cross-functional review team of experienced reviewers who would perform "Rolling Review" on partial data submissions. (Guidance for Industry, Expedited Programs For Serious Conditions - Drugs and Biologics).

Below figure summarizes about the evolutional journey of these Expedited Programs and as a time-and-motion depiction.

Figure 2.2:
USFDA - Evolution of Expedited Approval Approaches



A brief comparison depicting these expedited programs has also been presented in the below table.

Table 2.1:
Comparison of FDA's Expedited Programs for Serious Conditions

	Fast Track	**Breakthrough Therapy**	**Accelerated Approval**	**Priority Review**
Nature of program	Designation	Designation	Approval Pathway	Designation
Reference	• Section 506(b) of the FD&C Act, as added by section 112 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) and amended by section 901 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA)	• Section 506(a) of the FD&C Act, as added by section 902 of FDASIA	• 21 CFR part 314, subpart H • 21 CFR part 601, subpart E • Section 506(c) of the FD&C Act, as amended by section 901 of FDASIA	• Prescription Drug User Fee Act of 1992
Qualifying criteria	• A drug that is intended to treat a serious condition AND nonclinical or clinical data demonstrate the potential to address unmet medical need OR • A drug that has been designated as a	• A drug that is intended to treat a serious condition AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant	• A drug that treats a serious condition AND generally provides a meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a	• An application (original or efficacy supplement) for a drug that treats a serious condition AND, if approved, would provide a significant improvement in safety or

	Fast Track	**Breakthrough Therapy**	**Accelerated Approval**	**Priority Review**
Nature of program	Designation	Designation	Approval Pathway	Designation
	qualified infectious disease product	endpoint(s) over available therapies	clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)	effectiveness OR • Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505A OR • An application for a drug that has been designated as a qualified infectious disease product OR • Any application or supplement for a drug submitted with a priority review voucher

	Fast Track	**Breakthrough Therapy**	**Accelerated Approval**	**Priority Review**
Nature of program	Designation	Designation	Approval Pathway	Designation
When to submit request	• With IND or after • Ideally, no later than the pre-BLA or pre-NDA meeting	• With IND or after • Ideally, no later than the end-of-phase 2 meeting	• The sponsor should ordinarily discuss the possibility of accelerated approval with the review division during development, supporting, for example, the use of the planned endpoint as a basis for approval and discussing the confirmatory trials, which should usually be already underway at the time of approval	• With original BLA, NDA, or efficacy supplement
Timelines for FDA response	• Within 60 calendar days of receipt of the request	• Within 60 calendar days of receipt of the request	• Not specified	• Within 60 calendar days of receipt of original BLA, NDA, or efficacy supplement

	Fast Track	**Breakthrough Therapy**	**Accelerated Approval**	**Priority Review**
Nature of program	Designation	Designation	Approval Pathway	Designation
Features	• Actions to expedite development and review • Rolling review	• Intensive guidance on efficient drug development • Organizational commitment • Rolling review • Other actions to expedite review	• Approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit	• Shorter clock for review of marketing application (6 months compared with the 10-month standard review)
Additional considerations	• Designation may be rescinded if it no longer meets the qualifying criteria for fast track	• Designation may be rescinded if it no longer meets the qualifying criteria for breakthrough therapyg	• Promotional materials • Confirmatory trials to verify and describe the anticipated effect on IMM or other clinical benefit • Subject to expedited withdrawal	• Designation will be assigned at the time of original BLA, NDA, or efficacy supplement filing

Ref.: Final Guidance - Guidance for Industry, Expedited Programs For Serious Conditions - Drugs and Biologics

Adoption of Accelerated Approval Pathway for Oncology Drugs by industry & USFDA and benefits & challenges/ risks envisaged for patients

Initially, Accelerated Approval Pathway was used for drug approval meant for AIDS/ HIV-related drugs, but it has been observed that over the last decade or so, this pathway has made way for predominantly oncology drugs, with cancer drugs being granted around 85% of approvals through Accelerated Approval Pathway. While the

Sponsors have quite efficiently used this pathway to submit applications and seeking approvals, the USFDA has also been considerate within the realms of data and confidence and supportive in granting those approvals for Oncology drugs.

Eli Lilly is one such Sponsor company has been quite vocal about it and used this pathway diligently and they are committed to following FDA's guidance in its kith and kin. They have also come up with their own Principles on Accelerated Approval that conspicuously outline the transparency, commitment and actions to be taken in the event of a failure to comply with FDA expectations (Lilly's Principles on Accelerated Approval).

Accelerated Approval applications received and their approvals granted by the USFDA are a testament to its usage by other Sponsors over the last three decades. FDA has granted 300 approvals till June 2023 under this category and most of them have been Oncology products. (AV Health Policy Brief). Another review work by Beaver et al (2018) also puts forth that, from its inception in 1992 till 2017, the usage of Accelerated Approval Pathway has considerably increased and 64 Oncology approvals have been granted by USFDA for 93 indications over this period. Out of these total 64 approvals, 53 have been for New Molecular Entities (Beaver et al (2018)). There is another review article by Beakes-Read et al (2022) that evaluated the performance of the Accelerated Approval program in the last three decades, i.e. from 1992 to 2022 and, based on their research, inferred that overall the program was working fine and broadly meeting its objective of enabling treatment options to be made available for patients, at large. USFDA granted 278 approvals under the Accelerated Approval Pathway. In the first 10 years, 65% of the approvals (52 approvals) were granted to drugs intended for infectious diseases. In the next 20 years, most approvals have been granted to Oncology drugs through this approval pathway (with 59 approvals in the second 10 years). In the last 10

years, this number has significantly increased and 83% of approvals (167 approvals) that were granted were granted for Oncology drugs. The average median time to confirm clinical benefit has also been seen to be drastically decreased from 3.9 years in the first decade to 2.3 years in the last decade. Also, till December 31, 2021, the FDA has granted traditional/ full approval status to 50% of accelerated approvals (139 drugs) with a median time from accelerated approval to full approval of 3.2 years. In the last decade itself, 51 accelerated approvals have been converted to traditional approval with a median time of 2.3 years (Beakes-Read G et al (2022)). Ortendhal and Broder (2022) in a study conducted by the Partnership for Health Analytic Research found out that the Accelerated Approval program is critical for patients ailing from life-threatening diseases and also aids in improving the clinical outcomes. They compared the real-world outcomes of five drugs that were granted approval through the Accelerated Approval Pathway - two of them meant for Non-small Cell Lung Cancer, one for Lymphomatous Meningitis, one for HIV and one for Crohn's Disease - and highlighted that Accelerated Approval not only helped patients getting early access to these drugs but also could help their Sponsor organizations in early realization of the return on investment of these candidate drugs.

While there have been considerable benefits of the Accelerated Approval Pathway for the patients at large who look towards gaining early access to treatment modalities for diseases with unmet medical needs, there have been challenges and associated risks as well. Gyawali et al (2023) have tried to highlight some of the challenges; viz., use of unvalidated surrogate endpoints in clinical trials, long waits for completion of confirmatory clinical trials, delays in FDA action for not completing these trials and for these trials not able to show the expected benefit, some of the benefits shown by drugs not as good clinically as them being statistically projected and drugs treatments being

exorbitantly costly for drugs that have been approved under Accelerated Approval Pathway.

Table 2.2:
Endpoints Commonly Used in Trials of Drugs for Advanced Cancer

Endpoint	**Definition**
Overall survival	Time from randomization (or treatment initiation in single-arm trials) to death from any cause.
Progression-free survival	Time from randomization to disease progression (defined as a ≥20% increase in the sum of the diameters of target lesions, with an absolute increase of at least 5 mm, or any new lesion) or death.
Complete response rate	Percentage of patients who have a complete response, defined as the disappearance of all target lesions.
Partial response rate	Percentage of patients who have a partial response (tumor shrinkage), defined as a ≥30% decrease in the sum of the diameters of target lesions but not the disappearance of all target lesions.
Overall response rate	Percentage of patients who have a response, usually defined as a ≥30% decrease in the sum of the diameters of target lesions. The overall response rate is the sum of complete and partial response rates.
Stable disease	A change in target lesions that doesn't meet the definition of response or disease progression (i.e., a change in the sum of the diameters of target lesions between a decrease of 30% and an increase of 20%).

Ref: The Accelerated Approval Program for Cancer Drugs - Finding the Right Balance

Another article by Grabowski H. and Wang R.Y. (2008) analyzed the effects of FDA review time, drug novelty and US launch lag on the serious adverse events in the US from 1993 to 2003 and found out that while the introduction of newer drugs and shorter US launch lag has led to more adverse events but faster FDA review times had no association with side effects and any compromise on patient safety. There is another thought that has been put forth by AV Health Policy Brief (AV Health Policy Brief (2023)) that mentions inadequate incentives for Sponsors to complete the confirmatory trials. It asserts that one of the reasons the Sponsors tend not to complete the confirmatory trials could be that the Sponsors do not want to lose the commercial pie that

they get when an Accelerated Approval is granted, as products that receive such approvals, command high prices due to the scale of investment and being the niche treatment modality for that disease condition. They tend to prolong this status quo to remain drawing the premium price from consumers. If they complete the confirmatory trials quickly, they would be squeezing the opportunity to be more profitable and encash it. Hence, there is a need to look into options by USFDA to incentivize the Sponsors to complete the confirmatory trials, either in cash or in kind. There is another article in Health Affairs Forefront (Lederer and Dusetzina pinpoints towards a distinct kind of challenge that the pricing of products being granted accelerated approvals has not based product-based, rather it has based indication-based. A single product may be granted approvals for several indications, some of them may be traditional approvals and for some, it may be through the Accelerated Approval Pathway. There are instances when a single and high price has been set for a certain product basis a particular accelerated approval. It does not really reflect the value of the pricing when the certainty of benefit is unclear. Also, in such situations, there is a need for uniform pricing for these multi-variate accelerated approval indications and this has especially been a problem in resource-constrained government programs; like, Medicaid, in which most outpatient products tend to be covered in the US. A data snapshot from the Office of Inspector General of US Department of Health and Human Services from September 2022 shows that since 1992 till December 31, 2021, 104 of all 278 accelerated approvals granted have incomplete confirmatory trials and 139 drugs with confirmatory trials took an average of 48 months to complete these confirmatory trials since the time FDA granted them accelerated approvals. Up to May 30, 2022, 35 of these 278 (a total of 13 percent) drugs approved using the accelerated approval system have been withdrawn and a little more than half of these withdrawals (precisely 18 of them) have been withdrawn after January

2021. FDA staff has observed two common and peculiar challenges of the Sponsor's inability to complete the required confirmatory trials. One of the challenges is the availability of an advanced standard of care than that particular drug in today's scenario and changes in ownership of drug molecules. Due to advanced treatment options available today as compared to the drug product which was approved earlier, it is becoming difficult for those Sponsors to prove that their drug products are superior to these current standards of care. Also, changing hands on these drug products is a big show-stopper. The new owner/ Sponsor of the drug product takes more time to conduct those confirmatory trials, as it has to further start from scratch with the USFDA in establishing that desired connection US Department of Health and Human Services, Office of Inspector General - Data Snapshot (2022)).

USFDA's current position on it and steps taken to strengthen it further

Though; the FDA has reformulated and introduced other expedited review systems; viz., Priority Review, Fast Track Designation and Breakthrough Therapy Designation, in addition to Accelerated Approval Pathway, it does not mean that there is a threat to the existence of any one of them due to each other. Each one of them has its own significance and application. Hence, the Accelerated Approval Pathway is there to stay more steadfastly. The FDA has always taken cognizance of the challenges and associated risks that have evolved since its inception and it is committed to doing so in future as well to keep the health and safety of the human population, superseding everything. To meet the demands of these progressions, the US Congress has come up with some reforms and the FDA has come up with newer guidance and recommendations that have strengthened the Accelerated Approval Pathway. One such reform is the introduction of the Food and Drug Omnibus Reform Act (FDORA) of 2022 which has

laid down significant necessities to help strengthen the Accelerated Approval Pathway. It has mandated the Sponsors to keep confirmatory trials in progress while they apply for approval of drug products through the Accelerated Approval pathway. As per this reform, there will be a need for a Sponsor to submit a half-yearly status and progress report to USFDA on confirmatory trials. It also prompts the FDA to withdraw a drug product if it has ceased to confirm the clinical benefit during its confirmatory trials. This will also help address the issue of dangling approvals. To emphasize FDORA enactments, USFDA has also come up with a couple of guidance documents. One such guidance circulated is the FDA draft guidance for Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics in March 2023. It has stressed upon conducting randomized controlled clinical trials to support the accelerated approvals. It also recommends conducting a single arm trial to support accelerated approval. As per this guidance, "Sponsors can conduct separate randomized controlled trials – one trial with an early endpoint (e.g., response rate) to support the accelerated approval of the drug and a second trial powered for a longer-term clinical endpoint (e.g., progression-free survival (PFS) or overall survival (OS)) to verify clinical benefit. Alternatively, sponsors could design a single randomized controlled trial to support accelerated approval, that is also powered for the longer-term clinical endpoint with follow-up in the same trial to verify clinical benefit (i.e., "one-trial" approach)" (Guidance for Industry - Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics (2023)). To support this guidance, there is another guidance from the USFDA that provides key recommendations around the clinical trial endpoints. It clearly demarcates families of endpoints, types of multiple endpoints, individual components of composite and multiple endpoints and methodological considerations in the selection and evaluation of an endpoint from a statistical perspective. (Guidance for Industry - Multiple Endpoints in

Clinical Trials (2022)). There is another such guidance specific to Oncology trials which recommending around the endpoints to be considered for Oncology drugs. (Guidance for Industry - Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018)). In addition to these efforts by the USFDA, there are some recommendations that have been put forth by the industry and academia to Congress and the USFDA to help strengthen the Accelerated Approval Pathway. AV Health Policy Brief recommends certain policy modifications in this regard and some of them are described here. It asks to automatically withdraw accelerated approval drugs or indications when the confirmatory trial does not show clinically relevant, direct benefits for patients. It recommends to restrict the use of accelerated approval so that it does not become a regulatory pathway for acute diseases. It asks to ensure manufacturers comply with requirements for post-market studies in a timely manner. It does recommend FDA to seek medical and scientific consensus regarding the use of clinician reported outcomes or other surrogate endpoints in any type of disease before it is used in drug development and drug approval (e.g., FDA advisory committee on the evidence supporting the use of candidate surrogate outcomes), including how surrogate endpoints are chosen and what features allow them to serve as the basis for accelerated approval. It mandates confirmatory trials use direct measures of patient outcomes. It does ask to revise product labeling to ensure providers and patients know whether a surrogate endpoint was used to convert a drug from accelerated approval to traditional approval. It also requires confirmatory trial protocols to be finalized as a condition of accelerated approval. Also, it recommends FDA to publicly display a standardized accelerated approval review template that includes a structured explanation for why accelerated approval was deemed necessary and the justification for the use of the chosen surrogate endpoint (AV Health Policy Brief (2023)). There is another paper from Health Affairs Forefront from 2021 that

recommends, as here. It recommends developing and implementing a publicly available framework for identifying and validating surrogate endpoints. It mandates reasonable timeframes for generating confirmatory evidence and keeps a standard process for review to not allow dangling approvals. It asks to create a process for accelerated approval revocations so that harm to patients can be minimized and there is less impact on patient care. It recommends keeping the price of accelerated approved products to reflect the drug's value at the time of approval. It does recommend to use indication-based pricing for products approved through the Accelerated Approval Pathway. It also puts forth to link reimbursement to confirmatory evidence to incentivize rapid confirmatory clinical trials. It also mentions to implement value-based payment arrangements and real-world data & evidence that can be utilized along with data from clinical trials. (Lederer NM and Dusetzina SB (2021)).

Hence, it can be inferred that there have been a great deal of forward-looking actions and recommendations by Congress, USFDA and Industry bodies. Accelerated Approval Pathway offers a great opportunity for patients who need therapeutic options for diseases with unmet needs and the actions taken by government stakeholders are in the right direction to enable it to stand firm on its expectations. These efforts have also been augmented by constant constructive criticism and rational recommendations by the Industry and Scientific Community.

2.3 Summary

The burden of cancer has seen a significant upward trend over the last 3-4 decades and so do the scientific and research & development efforts in this area. Patients with cancerous conditions need treatment options to be made available to them at the shortest time possible.

Accelerated approval is a component of the Code of Federal Regulations that provides the FDA authority to grant marketing approval for a new drug product on the basis of adequate and well-controlled studies establishing that the drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The Accelerated Approval Pathway was added to the Federal Regulations in 1992 and was intended for diseases that are serious and life-threatening and when no other therapy is available for them. Approval for marketing can be withdrawn by USFDA if post-marketing studies fail to confirm the clinical benefit. A surrogate endpoint is generally accepted to mean a laboratory measurement or physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions or survives. The accelerated approval can be granted on the basis of a surrogate endpoint that is reasonably likely to predict clinical benefit but that is not established to the level that would support regular approval. Though the Accelerated Approval Pathway is an instrument put forth by the USFDA to benefit the patients, at large, by enabling them to utilize the newer treatment options, the true essence of it has been marred by some challenges. A few of these challenges are - the Sponsors not committing to complete the confirmatory trials, hence questioning the risk-benefit aspects of the new drug, selection and usage of surrogate endpoints and their validity, dangling approvals, withdrawal of drugs due to not being able to withstand confirmatory trials, exorbitantly high cost of available therapies, etc.

This literature review covers understanding various kinds of expeditious approval mechanisms available through the USFDA and their evolutional journey, what is industry's take on Accelerated Approval Pathway, its benefits and challenges & risks for patients and how has USFDA addressed these challenges so far and what lies in future from the Health Agency, Industry and patient perspective keeping in view of the questions that have been raised by varied stakeholders on the validity of it.

An array of research papers, health authority guidance, and thought papers have been referred and studied to understand the dimensions of these questions that have been raised. Federal statutes and Health Authority guidance have also been studied and Industry and Scientific Community recommendations have also been looked into thoroughly to understand if Accelerated Approval Pathway and its tenets would be able to withstand the turbulence that is being felt its way.

2.4 Conclusion

Through this Literature Review, it can be concluded that the Accelerated Approval Pathway has strong backing from the Federal Structure within the US, the USFDA, Industry and the Scientific Community. Though there have been some apprehensions around its future, considering the challenges that it has been going through, it is a firm understanding that it is going to pass the test of time and will keep on extending greater benefits for the patients in utmost need of such a mechanism. With the US federal government and USFDA working hand-in-hand to sail it through, it is going to meet its desired expectations.

With this research, it is intended that in addition to the recommendations put forth by the Scientific Community and Industry to USFDA that have been highlighted through this Literature Review; after seeking further inputs on the applicability of those recommendations from my own sources within global health authorities, Industry and academia/ scientific community, a recipe would be able to come up with to augment this mechanism so that patients, at large, would keep benefitting from it.

CHAPTER III:

METHODOLOGY

3.1 Overview of the Research Problem

Despite of USFDA's introduction of other assessment and approval approaches, like, Priority Review, Fast track Approval and Breakthrough Therapy Designation, Accelerated Approval Pathway has been and likely to remain the most sought-after approval approaches for Oncology drugs by the Sponsors. The USFDA has not only embraced and accepted drug product applications for assessment and review but also has been approving them with complete positive intent that the Sponsors would follow the tenets of this pathway with utmost diligence.

A literature review of studies around it suggests that the implementation of the Accelerated Approval Pathway has not been that smooth in recent years. Time and again, there have been some pertinent issues that have been highlighted by these studies, which tend to revolve around design of clinical studies and selection of surrogate endpoints that are used for approval decisions, delays in conductance of confirmatory clinical studies by the Sponsors after accelerated approvals have been granted, usage of non-validated surrogate endpoints instead of clinical endpoints while conducting confirmatory clinical studies, inaction or delayed action by USFDA when a confirmatory clinical study has not been conducted by a Sponsor even after passage of a considerable amount of time, inaction or delayed action by USFDA when a drug product does not show an evidence of predicted clinical benefit upon conductance of a confirmatory clinical study or the treatment outcomes could be statistically good but are not clinically significant, or high cost of availability of such therapeutic options to cancer patients after obtaining accelerated approval and, more so, after obtaining traditional approval, post conductance of confirmatory clinical trials.

The USFDA has been able to put forth regulations in the form of the introduction of the Food and Drug Omnibus Reform Act (FDORA) of 2022 which has laid down significant necessities to help strengthen the Accelerated Approval Pathway and has also come up with a couple of forward-looking guidance documents; viz., FDA draft guidance for Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics in March 2023; FDA Guidance for Industry - Multiple Endpoints in Clinical Trials (2022); and FDA Guidance for Industry - Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018), there is still a good deal of work that needs to be done, both at the USFDA end from an implementation perspective and at Industry end from their adoption perspective, so that existence of Accelerated Approval Pathway remain as stout as it is expected and it should keep delivering the cancer patients with the best possible safe and efficacious treatment modalities.

Post building an understanding through a literature search around the current efforts that have already been underway by the USFDA and other statutory bodies in The US and that have been able to address some of the issues above, this research work would intend to seek a path forward broadly to below unaddressed or under-addressed issues:

- Time-boxing conductance of confirmatory studies by Sponsors and the possibility of automatic expiration of accelerated approval if confirmatory studies are not completed in that fixed duration of time
- Possibilities of incentivization or penalization of Sponsors in case of non-conductance or non-conformance of confirmatory clinical studies
- Possibility of introducing changes/ modifications of information on Labels for drugs approved under accelerated approval pathway
- Ways and means to keep checks and balances on costs of treatment modalities that have been approved through the Accelerated Approval Pathway

3.2 Operationalization of Theoretical Constructs

The theoretical framework and a broader construct of this study revolves around a study that was performed by Gould et al, 2022, wherein it was postulated that the stakeholders involved in a clinical trial value chain are uniquely correlated with each other and they all do share a common spaces of this value chain with each other. Accelerated Approval Pathway is an enabler in this value chain and they all deserve to get maximum benefit for themselves in this value chain due to interventions of Accelerated Approval Pathway. There are five primary stakeholders in a clinical trial value chain – the patients, the physicians, the health authorities (in this particular case, it is USFDA), the health technology assessments and the Sponsors. Ideally and theoretically, all five of them should get benefitted through a clinical trial. In this quest, as an enabler, it is also expected that Accelerated Approval Pathway should also act as a value creator and augment these benefits.

Through this research, an attempt has been made, first of all, to understand what could be those benefits for these stakeholders and, secondly, whether the expected benefits have really been getting translated or not. Further, it is also be to assessed that if these benefits are not getting translated, what could be the ways and means to achieve the pivotal objectives of clinical trials for all these stakeholders.

To begin with, in context of these stakeholders, through secondary research, it was tried to identify the variables that would get impacted with introduction of Accelerated Approval Pathway in the drug approval process and that would ultimately bring benefits to all these stakeholders involved. Out of these identified variables, then a classification was done to see which of them were perpetually getting addressed by the USFDA and for which of them, there were still some gaps. Then, the ones for which

there existed gaps, were picked up and became candidates for conducting primary research with the help of a structured questionnaire.

There were primarily gaps identified on timeboxing of confirmatory clinical studies, possibility of incentivization or penalization of Sponsors for conducting or not conducting confirmatory clinical studies respectively, possibility of introduction of changes to labels of drugs approved through this pathway and ways and means to keep checks and balances on the cost of products approved through Accelerated Approval Pathway.

For each of the stakeholder, benefits were sought through possible addressal of these gaps. Corroboration of it was done with the help of responses of the questionnaire and, thus, arriving at some possible recommendations. Below are some envisaged benefits that each of these stakeholders should receive through addressal of the identified gaps.

- **Patients:** Timeboxing of confirmatory clinical studies will lead to conductance of these studies in a timebound manner and thus bringing affirmed treatment modalities with stronger evidence of scucceses for the patients. Incentivization or penalization of Sponsors for conducting or not conducting confirmatory clinical studies will beget an indirect benefit to patients. Incentivization will be a boon for availability of more stronger therapeutic options for patients and penalization will help reducing the risks associated with drugs with unconfirmed therapeutic benefits. Label modifications will directly help patients in becoming more inclusive in the therapeutic modality selection process, in conjunction with the physicians. Similarly, any reduction on costs will have a direct benefit for the patients, at large.

- **Physicians:** Physicians are the decision makers for their patients. Timeboxing of confirmatory clinical studies will help them understanding around the availabilty of treatment modality with robust clinical outcomes and help taking them an informed decision for the patients. Incentivization or penalization of Sponsors might not have a direct benefit to them, but these will surely indirectly benefit them, as these would ensure Sponsors to carry on with clinical studies more enthusiatically, incorporating measures to complete them in agreed timeframe. Drug product label modifications will extend a direct benefit to physicians, as they would come to know about the salient aspects of drug product and it will also yield them in making informed decisions about those drug products for their patients. Any impacts on costs of drug products will directly benefit the treating physicians, as by being so closely involved in decision-making process for their patients, they would be able to figure out and guide their patients around the possible treatment alternatives available at the same point in time.
- **Health Authorities i.e. USFDA:** Timeboxing of confirmatory clinical studies will provide a significant benefit to USFDA, as with the introduction of timeboxing, the clinical studies would get confined into their timeframes and it would be easier for USFDA to conclude on a go or no-go for the clincal study and, hence, the drug product. Thus, it would make decision-making for USFDA simpler. Incentivization or penalization would create an indirect benefit to USFDA, as incentivization would lead to greater transparency in conductance of clinical studies and penalization would clearly demarcate inaction at the part of such a Sponsor. Also, in

turn, these approaches would enhance and elevate USFDA's image as health authority acting with equality. Label modifications will further strengthen USFDA's image as a health authority observing utmost transprency in dissemination of facts and figures about a drug product to its series of stakeholders. Rationalization of costs of drug products is not a USFDA jurisdiction and prices of drug products are decided by the manufacturers, retailers and distributors of drug products. Federal Trade Commission (FTC) is one such authority who could be reached out in case there are concerns about drug product costs. The FTC enforces antiturst and consumer protection laws in The US and they ensure that the markets are free from any unwarranted competition or undue restrictions. To help patients obtain drugs at a no cost or at a reasonable cost, there are several patient assistance programs that are run by several Sponsor organizations. In order for a drug product reach the patients in the most economic manner, there are financial assistance provided to needy patients through Center for Medicare and Medicaid Services (CMS). Thus, any reduction or rationalization of drug product costs will not have a direct bearing on USFDA, except that such efforts would lead to easy and economic access drug products to patients, which is also an ultimate objective of USFDA.

- **Health Technology Assessments (HTAs):** Health Technology Assessments comprise of the evaluation of a drug product's clinical effectiveness, safety aspects and cost and economic effectiveness. Timeboxing of confirmatory clinical studies will have an important but indirect benefit in HTAs, as it would lead to a clincally sound drug product with some impact on drug's overall development costs that may

ultimately boil down to final drug product cost. Incentivization or penalization would again have an indirect benefit on HTAs, as incentivization would inculcate a forward-looking research environment while penalization would serve as a deterrant for bringing less value-deriving drug products into market. Drug label modifications would yet again be an indirect benefactor as the information so extracted out of modified labels would serve as a helping hand in making informed decisions around drug product safety, efficacy and compliance. Rationalization of costs will directly help in conducting robust HTAs with respect to drug product costs.

- **Sponsors:** Timeboxing of confirmatory clinical studies will directly benefit the Sponsors from the perspective that there would not only be quick realilzation of development efforts, but also an encouragement to pour more efforts into further research. Incentivization or penalization approaches would also have a direct impact on Sponsors in the sense that the former one will lead to more encouraged delvings into research and the latter one would help reduce clutter of under-rated drug products from market. Drug label modifications will indirectly benefit Sponsors, as the labels would become more inclusive and path-finding for other stakeholders, like patients, physicians and HTAs. Cost rationalization of drug products will directly benefit the Sponsors from the perspective of prospective wider outreach of patient population and access to drug products, strong positive image- and trust-building of Sponsors for provisioning cost-effective treatment modalities, early accrual of investments made, etc.

3.3 Research Purpose and Questions

The purpose of this research is to conduct a deep-dive study to understand the challenges that Accelerated Approval Pathway, as an approval mechanism, has been facing; how patients, at large, are being impacted by those challenges; what value Industry and Sponsors are deriving out of it; and what it brings up for the USFDA.

In this research, these multi-faceted aspects are being explored with the help of secondary research as well as primary research. Questions or challenges with respect to clinical trial design, selection of trial endpoints or measures to strike the apt risk-benefit balance have been explored with the help of secondary research and these would be reinforced by conducting primary research as well, but the questions or challenges pertaining to time-boxing of confirmatory clinical studies, incentivization or penalization of Sponsors, drug product label modifications and checks and balances of drug product costs have either been under-answered or unanswered through secondary research - these would be explored with the help of primary research. Below are some of these probable explorations through primary research:

A. Time-boxing of confirmatory clinical studies: To understand what time-boxing practices could be adopted for the conductance of confirmatory clinical studies, how much time could be granted to a Sponsor to conduct such a trial after accelerated approval has been granted

B. Incentivization or penalization of Sponsors: To assess the conduct practices that could make the potential for either incentivization of Sponsors for conducting confirmatory clinical trials or penalize them for not conducting them, what could be the magnitude of these incentives or penalties

C. Drug product label modifications: To assess what distinct and discrete type of additional information should make way for putting on labels of products that have

been granted accelerated approvals, how this information should look different from labels of traditionally approved products vs products approved under accelerated approval pathway

D. Checks and balances of drug product costs: To understand the practices that would be able to help in decision-making of cost of drug products that have been approved using accelerated approval mechanism, what approaches could be adopted to keep the costs of such products justified and under control, what measures USFDA could take in keeping these costs balanced vis-à-vis the research efforts

To delve further into above four identified areas of exploration, the primary research questionnaire has been designed for various Industry Stakeholders to seek answers to the below questions.

A. Time-boxing (mandatory confining of a time limit) of confirmatory clinical studies:

There were a total of five sub-questions designed in this area for further exploration.

1. *In your opinion, should time-boxing of confirmatory clinical studies, post grant of an accelerated approval of a drug product for an indication, be made mandated and fixed?*

   This question was a closed-ended question and had five choices for the respondents to make, ranging from "Strongly Disagree," "Disagree," "Neutral," "Agree," and "Strongly Agree."

2. *Should there be a blanket time-boxing duration mandated for every confirmatory clinical study?*

   This question was also a closed-ended question and had five choices for the respondents to make, ranging from "Strongly Disagree," "Disagree," "Neutral," "Agree," and "Strongly Agree."

3. *Should this time-boxing be different for below different possible variables of confirmatory clinical studies?*

   This question was again a closed-ended question, wherein, four variables, viz. Therapeutic Area, Disease Area, Patient Population and Patient Enrolment were provided and the respondents were supposed to respond on five choices, as above, viz. "Strongly Disagree," "Disagree," "Neutral," "Agree," and "Strongly Agree" against each of these variables.

4. *What should be the time-boxing range for below different possible variables of confirmatory clinical studies*?

   This question was again a closed-ended question, wherein, four variables, viz. Therapeutic Area, Disease Area, Patient Population and Patient Enrolment were provided and the timeboxing ranges of "1 to 3 years," "3 to 5 years," "5 to 6 years" and "Beyond 6 years" the respondents were supposed to respond to these choices against each of these variables.

5. *In your opinion, what could be other possible variables that have a significant impact on time-boxing of confirmatory clinical studies?*

   This question was kept as an open-ended question and the respondent was provided a choice of responding to it in a maximum of 150 words as a running text or a bulletted list.

B. Incentivization or penalization of Sponsors:

For this area as well, there were a total of five sub-questions designed for further exploration.

1. *Should there be an incentivization provided or penalization exercised for timely completion or not able to complete the confirmatory clinical studies, respectively, for Sponsors, post accelerated approvals are granted for their drug products?*

   This question was a closed-ended question and had five choices for the respondents to make, ranging from "Strongly Disagree," "Disagree," "Neutral," "Agree," and "Strongly Agree."

2. *Should incentivization be provided to eligible Sponsors in the form of below different possible incentivization variables upon successful and speedy conductance of confirmatory clinical studies?*

This question was also a closed-ended question, but had four variables, viz. Exclusivity Provisions, Pricing Preferences, Review Acceleration and Speedy Reimbursement Options, for each of which the respondents had five choices to make, ranging from "Strongly Disagree," "Disagree," "Neutral," "Agree," and "Strongly Agree."

3. *Should penalization be exercised on eligible Sponsors in the form of below different possible penalization variables upon delayed conductance or non-conductance of confirmatory clinical studies?*

   This question was also a closed-ended question, but had four variables, viz. Stringent Financial Penalties, Debarment, Review Delayes of Subsequent Trials and Issuance of 483s, for each of which the respondents had five choices to make, ranging from "Strongly Disagree," "Disagree," "Neutral," "Agree," and "Strongly Agree."

4. *In your opinion, what could be other possible variables to incentivize a Sponsor for conducting confirmatory clinical trials with due diligence?*

   This question was kept as an open-ended question and the respondent was provided a choice of responding to it in a maximum of 150 words as a running text or a bulletted list.

5. *In your opinion, what could be other possible variables to penalize a Sponsor for not conducting confirmatory clinical trials with due diligence?*

   This question was also kept as an open-ended question and the respondent was provided a choice of responding to it in a maximum of 150 words as a running text or a bulletted list.

C. Drug product label modifications:

For this area, there were a total of four sub-questions designed for further exploration.

1. *In your opinion, should there be a differentiated label/ prescribing information of a product that has been granted an accelerated approval than a product that has been approved traditionally?*

   This question was a closed-ended question and had five choices for the respondents to make, ranging from "Strongly Disagree," "Disagree," "Neutral," "Agree," and "Strongly Agree."

2. *Should key information highlighting accelerated drug approval be distinctly displayed on the label/ prescribing information; viz. in different color or as a boxed text?*

   This question was also a closed-ended question and had five choices for the respondents to make, ranging from "Strongly Disagree," "Disagree," "Neutral," "Agree," and "Strongly Agree."

3. *Information pertaining to which of the below different possible variables should be displayed on the label/ prescribing information (either in a box or in different color) of a product that has been granted accelerated approval?*

   This question was also a closed-ended question, but had five variables, viz. Approval Pathway (Traditional or Accelerated), Surrogate Marker Details, Tentative Confirmatory Clinical Study Timeline, Approval in Other Countries and Post-approval Committments, for each of which the respondents had five choices to make, ranging from "Strongly Disagree," "Disagree," "Neutral," "Agree," and "Strongly Agree."

4. *In your opinion, what could be other possible variables that could be included on the label/ prescribing information of a drug product that has been granted approval through accelerated approval pathway?*

   This question was kept as an open-ended question and the respondent was provided a choice of responding to it in a maximum of 150 words as a running text or a bulletted list.

D. Checks and balances of drug product costs:

For this area, there were a total of four sub-questions designed for further exploration.

1. *Do you think there is a need to rationalize the cost of drug products that have been granted accelerated approvals?*

   This question was a closed-ended question and had five choices for the respondents to make, ranging from "Strongly Disagree," "Disagree," "Neutral," "Agree," and "Strongly Agree."

2. *Which of the below variables could be the drivers of cost decisions of the drug products that have been granted accelerated approvals?*

This question was also a closed-ended question, but had five variables, viz. Therapeutic Area, Indication of Use, Disease Condition, Patient Population and Development Costs, for each of which the respondents had five choices to make, ranging from "Strongly Disagree," "Disagree," "Neutral," "Agree," and "Strongly Agree."

3. *In your opinion, what could be other possible variables to have an impact on cost of drug products that have been approved through accelerated approval pathway?*

   This question was kept as an open-ended question and the respondent was provided a choice of responding to it in a maximum of 150 words as a running text or a bulletted list.

4. *What could be possible measures by USFDA to contain inflated cost of drug products that have been approved through accelerated approval pathway?*

   This question was kept as an open-ended question and the respondent was provided a choice of responding to it in a maximum of 150 words as a running text or a bulletted list.

In a similar manner, for above four identified areas of exploration, the primary research questionnaire was also has been designed for USFDA Stakeholders to seek guidance on below questions. Though; it was already considered that getting a response from USFDA officials on such promulgations was a bleak possibility, yet the questionnaire was prepared and floated to a few relevant USFDA office bearers.

A. Time-boxing (mandatory confining of a time limit) of confirmatory clinical studies:

There were a total of two sub-questions designed in this area for further exploration.

1. *Despite USFDA's Food and Drug Omnibus Reform Act (FDORA) of 2022 and The Consolidated Appropriations Act of 2023 (CAA) being in place, is time-boxing of confirmatory clinical studies, post grant of an accelerated approval of a drug product for an indication, still a challenge?*

This question was a closed-ended question and had five choices for the respondents to make, ranging from “Strongly Disagree,” “Disagree,” “Neutral,” “Agree,” and “Strongly Agree.”

2. *Are there any other provisions being promulgated by USFDA that could make time-boxing of confirmatory clinical studies further mandated and fixed? If those could be disclosed at this point in time, what are those?*

   This question was kept as an open-ended question and the respondent was provided a choice of responding to it in a maximum of 150 words as a running text or a bulletted list.

B. Incentivization or penalization of Sponsors:

For this area as well, there were a total of two sub-questions designed for further exploration.

1. *Should there be a reasonable incentivization provided or penalization exercised for timely completion or not able to complete the confirmatory clinical studies, respectively, for Sponsors, post accelerated approvals are granted for their drug products?*

   This question was a closed-ended question and had five choices for the respondents to make, ranging from “Strongly Disagree,” “Disagree,” “Neutral,” “Agree,” and “Strongly Agree.”

2. *Under USFDA’s current or futuristic regulatory framework, are there any provisions available or envisaged for incentivization or penalization of Sponsors for completing confirmatory studies or not completing them in a genuinely agreed timeframe, respectively, post accelerated approvals are granted to them?*

   This question was kept as an open-ended question and the respondent was provided a choice of responding to it in a maximum of 150 words as a running text or a bulletted list. The two heads provided to respond were – a. Incentivization options and b. Penalization options.

C. Drug product label modifications:

For this area as well, there were a total of two sub-questions designed for further exploration.

1. *To benefit the physicians and potential patients at large, should there be a differentiated label/ prescribing information of a product that has been granted an accelerated approval than a product that has been approved traditionally?*

   This question was a closed-ended question and had five choices for the respondents to make, ranging from "Strongly Disagree," "Disagree," "Neutral," "Agree," and "Strongly Agree."

2. *Under the current gamut of USFDA regulations, could variables; like, surrogate marker details, tentative confirmatory clinical study timeline, approval in other countries, post-approval commitments, if any, be included on the label/ prescribing information of a drug product that has been granted approval through accelerated approval pathway?*

   This question was kept as an open-ended question and the respondent was provided a choice of responding to it in a maximum of 150 words as a running text or a bulletted list.

D. Checks and balances of drug product costs:

For this area also, there were a total of two sub-questions designed for further exploration.

1. *Do you think there is a need to rationalize the cost of drug products that have been granted accelerated approvals?*

   This question was a closed-ended question and had five choices for the respondents to make, ranging from "Strongly Disagree," "Disagree," "Neutral," "Agree," and "Strongly Agree."

2. *What are various measures currently being exercised by USFDA or from a futuristic perspective to contain inflated cost of drug products that have been approved through accelerated approval pathway?*

   This question was kept as an open-ended question and the respondent was provided a choice of responding to it in a maximum of 150 words as a running text or a bulletted list.

The research involved responses to questionnaires & interviews to gather data from relevant Research & Development professionals, Regulatory Affairs professionals,

Clinical Healthcare professionals & Key Opinion Leaders (KOLs) [jointly referred to as, Industry professionals, erstwhile in this document] primarily. Efforts were also made to reach out to Health Authority stakeholders and seek their viewpoints on these issues. Through this comprehensive study, the research aimed to shed light on the impact that the accelerated approval mechanism has on the availability of treatment modalities to patients and whether it is justified for its existence. The findings could inform Industry and healthcare professionals of some probable efforts that could enhance the drug product research and Health Authority of probable feasibility of policy amendment which would help this approval pathway to achieve its objective of swift patient access with the utmost balanced risk-benefit profile and at a better-justified cost.

3.4 Research Design

This research has been conducted through a literature review (secondary research) and seeking inputs from respective stakeholders on questionnaires designed for this study (primary research or survey research). As desribed above, a questionnaire for Industry and Healthcare professionals has been designed to cover questions on challenges and dependencies in time-boxing of confirmatory clinical studies, boundaries for automatic revocation of approval, probable and justified time duration for completion of confirmatory clinical study, need of incentivization or penalization in conductance of confirmatory studies and their boundaries, probable ways to incentivize or penalize, labelling information to be included for products granted accelerated approval, ways to make labels distinct from traditional labels and cost-ceiling decision factors and preferences for cost-ceiling.

Similarly, a questionnaire for Health Authority professionals has also been designed to cover the same topics, but those questions have been portrayed more from the Agency directive and implementation perspective.

There have been, both, qualitative and quantitative approaches exercised for this research. A qualitative approach is a naturalistic, interpretative approach concerned with understanding the meanings which people attach to phenomena (actions, decisions, beliefs, values, etc.) within their social worlds (Snape and Spencer, 2003). The descriptive approach used to collect information from or about people to describe, compare, or explain their feelings, knowledge, values and behaviours is known as survey research (Fink, 2019). To explore the research questions, a "Mixed Methods Approach" has been adopted. The inclusion of the mixed method approach leverages and combines quantitative and qualitative methods, both, (Morgan, 2014) and provides the benefits of generality and particularity. It is very relevant to use a mixed methods approach for this research study because the study here is being performed revolving around the challenges due to this regulatory approach where it is needed to investigate the application, implementation and impact on the entities, i.e. the Industry, the Patients and the Health Authority, which orbit around it in close proximity. It was planned that in this research, out of a set of 50 participants chosen, particularity would be achieved by conducting qualitative semi-structured interviews with a set of Industry and Healthcare professionals (15 subjects) and generality by conducting questionnaires surveys with set of Industry and Healthcare professionals (35 subjects). This would help achieve a balance between generality & particularity and quantitative & qualitative research.

Practically, when participants for interviews were approached, most of them chose to respond to questionnaire survey as an alternate instead, due to their occupacny

and mutual unavailability. Hence, it was decided to reach out to all 50 participants through a survey questionnaire.

Though it was not assured to get a response from them owing to their neutral allegiance and being a guiding lighthouse, but efforts were made to seek inputs on the Health Authority direction and implementation stance from three Health Authority (USFDA) professionals with the help of an email survey. It was decided that data analysis would be performed only on responses obtained from Industry professionals and responses received, if any, from Health Authority stakeholders would be treated as guiding principles.

3.5 Population and Sample

Population: The population for this study comprises professionals from the domains of pharmaceutical and biopharmaceutical Research & Development, Clinical Research & Development, Regulatory Affairs, Medical Affairs, Clinical Research Organizations (CROs), Medical Oncologists and Clinical Physicians involved in clinical trials, Healthcare, Health Economics and Outcomes Research, Pharmaceutical and Clinical Academics, etc. These sets of individuals are from the lot who understand the intricacies of conductance of clinical trials and their regulations in The USA and have been envisaged to provide right insights required to take this research to a logical conclusion. The professionals so chosen for this study have a strong experience in their respective fields, average in the range of 15-20 years, who have handled Oncology products in their past or current assignments. Some of them are retired professionals who have spent around 35-40 years in the industry. Most of them are from global multinational pharmaceutical/ biopharmaceutical organizations and have been in the senior management in their respective functions, at the levels of Associate Directors/

General Mangers/ Directors and above. Some of the individuals are renowned independent Consultants who have contributed a lot to Industry in their past associations and are continuing to do so in their current engagements. There are also individuals who have been associated with USFDA in their past assignments but now have taken over roles in organizations in industry.

Sample: The sample size for any study depends on several factors; viz., the level of confidence required, the margin of error and the diversity and heterogenicity of the population.

Generally, to obtain relevant, meaningful statistically, significant and valid results, a representative sample should be large enough. Considering the particularity of the kind of Oncology experience and skill-set required from the pharmaceutical/ biopharmaceutical industry to be able to participate in this study, obtaining a very large sample size could be challenging. Hence, it was considered that a sample size of 50 Industry participants could be appropriate. Also, from a Health Authority stakeholder perspective, it should be kept in mind that these stakeholders might not like to respond to such surveys, considering their neutral allegiance and being guiding authorities. Thus, it was difficult to have a lot many Health Authority stakeholders and, hence, it was considered to involve not more than 2-3 Health Authority stakeholders for this study and was factored that, if any response is obtained from them, it would be considered as a boon. Else, their responses would not be considered for analysis purposes.

3.6 Participant Selection

Criteria for Participant Selection: Participants should be industry professionals, as described above. A few factors that needed to be weighed in before a participant was roped in for this study, were:

a. **Domain:** The participants should be from Pharmaceutical and biopharmaceutical Research & Development, Clinical Research & Development, Regulatory Affairs, Medical Affairs, Clinical Research Organizations (CROs), Medical Oncologists and Clinical Physicians involved in clinical trials, Healthcare, Health Economics and Outcomes Research, Pharmaceutical and Clinical Academics, etc.
b. **Experience:** The participant should possess at least an average of 15-20 years of work experience and exposure to end-to-end conduct, managing, overseeing and/ or advising and regulating Oncology clinical trials in The USA.
c. **Role:** The participant should be from global multinational pharmaceutical/ biopharmaceutical organizations. They should have been in the senior management in their respective functions, at the levels of Associate Directors/ General Mangers/ Directors and above. They may be independent Consultants who have contributed a lot to the Industry in their past associations and are continuing to do so in their current engagements. They could also be individuals who have been associated with USFDA in their past assignments, but now have taken over roles in discrete organizations in industry.
d. **Free from Bias:** The participant should be one who is free from any bias pertaining to any past associations with organizations evaluating the sanctity of Accelerated Approval Pathway.
e. **Informed Consent:** Every participant would be informed of the purpose and envisaged outcomes of the study and would need to affirm to an informed consent agreeing to their voluntary participantion in this study and share their inputs, as deemed necessary.

Random sampling techniques will be employed to ensure representativeness.

3.7 Instrumentation

1. Questionnaires: Major instruments that form the backbone of this study are the questionnaires that have been prepared and disseminated to participants from Industry as well as the Health Authority, i.e. The USFDA, for seeking their responses on the gaps identified that have been the crux of this study. The questionnaires contain close-ended, Likert scale derived and open-ended questions on the four gap areas, viz. Timeboxing of confirmatory clinical studies, Incentivization and penalization of Sponsors, Drug product label modifications and Checks and balances of drug product costs.

2. Informed Consent: Before these questionnaires are administered to the relevant stakeholders, there is an Informed Consent that has been taken from all participants that their participation is voluntary and they are agreeing to share their inputs in response to these questions.

3. Accessibility Options: Any accessibility preferences on as to whether the respondants would like to have the questionnaire administered or would like to have an interview conducted or any other method, whatsoever, should also be taken beforehand.

4. Data Verification and Assurance of Quality: Data so received from the dissemination exercise should be ensured for completeness and integrity. Any incomplete or erroneous responses should be flagged.

5. Maintaining Confidentiality and Anonymity: Care should be taken to ascertain that confidentiality and anonymity of the participant data should always be maintained.

6. Record-keeping of Data: Participant records and their responses should be kept securely in compliance with data protection and data privacy requirements.

7. Data Presentation and Visualization: Data gathered from the responses should be presented in the best presentable form, viz. in the form of tables, charts, graphs, visuals, etc. and inferences so drawn from them should also be explained diligently.

3.8 Data Collection Procedures

Collecting data from both Industry and Health Authority professionals requires not only a thoughtful and inclusive approach but also an understanding of thoughts from two groups which are separated by their own vested interests of effort optimization and implementation & compliance. Since both of these target audience face unique challenges, it's essential to use data collection methods that cater to their needs.

Here are the administered methods:

1. **Face-to-Face Interviews:** Conducted a few face-to-face interviews with interested participants to gather in-depth insights into their opinions, preferences, and challenges related to the Accelerated Approval Pathway, but most of them insisted on having responses made through questionnaires.
2. **Telephonic Interviews:** Telephonic interviews were also offered as an alternative for those who may find it challenging to participate in person. However, respondents preferred to respond to the online questionnaire. Care was taken to provide any necessary assistive technologies or resources during the phone call to accommodate the participants' needs.
3. **Online Surveys:** Designed and distributed accessible online surveys tailored for both Industry and Health Authority professionals separately.
4. **Mixed-Methods Approach:** Using a combination of data collection methods to ensure receiving comprehensive insights and validated findings across different approaches.

The surveys were administered to participants both in the Industry and in the Health Authority. Interviews with Industry participants were also scheduled separately with willing parties.

The deployed methods were both quantitative and qualitative methods. The quantitative method involved the use of primary data obtained from the administration of a structured questionnaire through an opinion survey questionnaire as below:

Industry or Healthcare professionals	Health Authority professionals
50	2-3

The obtained data has been analysed using statistical tools. Also, the qualitative method involved obtaining data from diverse secondary data sources including government released documents, published literature and conference material.

The opinion survey results & interviews have been recorded and option was provided to respondents that those could be shared with the respondent and interviewee, if they wished to have access. After the survey and interviews were concluded, an abductive approach was applied to derive the conclusions and valuable insights.

Ethical Considerations:

- **Informed Consent:** Participants have been informed about the study's purpose, their rights, and the confidentiality of their responses. Consents will be obtained from all participants.
- **Anonymity and Confidentiality:** The data collected will be kept confidential, and participants will remain anonymous.

3.9 Data Analysis

Below data analysis techniques have been employed for the analysis of the data obtained from respondents.

- **Quantitative Data:** The closed-ended questionnaire responses have been analysed using descriptive statistics to derive frequencies and percentages.
- **Qualitative Data:** Responses from open-ended questions and interviews have been subjected to thematic analysis using Natural Language Processing (NLP) to identify recurring themes and patterns.

The collected data has been analysed using appropriate statistical tools for quantitative data and thematic analysis for qualitative data.

Data analysis for this opinion survey requires careful planning and execution. Below are the proposed possible steps for data analysis process. Responses received on the circulated questionnaires will be the decision factor of application of steps for data analysis.

1. **Data Collection:**
    a) Gather survey responses from all stakeholders
    b) Ensure the survey includes both closed- and open-ended questions related to the Accelerated Approval Pathway
    c) Consider using online surveys, phone interviews, or in-person interviews based on the accessibility needs of the participants
2. **Data Pre-processing:**
    a) Clean the data to remove any incomplete or inaccurate responses.

b) Ensure the data is anonymized and follows ethical guidelines for data handling.

3. **Data Coding:**
    a) If needed assign numerical codes to categorical responses, such as "Strongly Agree"- 5, "Agree" -4, "Neutral"- 3, "Disagree" -2, "Strongly Disagree" -1.
    b) If there are open-ended questions, consider using sentiment analysis or thematic coding to categorize responses.
4. **Descriptive Statistics:**
    a) Calculate basic descriptive statistics, such as mean, median, mode, standard deviation, and range, to summarize the responses.
    b) Use visualizations like bar charts, pie charts, or histograms to present the data clearly.

Here are some explanations around the basic descriptive statistical teminologies.

Mean (Average):

- **What It Is:** The mean is the average value of a dataset. It's calculated by adding up all the values and then dividing by the number of values.
- **What It Suggests:** It gives you an overall idea of the central tendency of the data. For example, if you're looking at test scores, the mean tells you the average score of all students.
- **Interpretation:** A high mean indicates that the average value is high, while a low mean indicates a lower average value. However, it can be affected by extremely high or low values (outliers).

Median:

- **What It Is:** The median is the middle value in a dataset when the values are sorted in ascending order. If there is an even number of values, it's the average of the two middle numbers.
- **What It Suggests:** It provides a measure of central tendency that is not affected by outliers or skewed data. It's useful for understanding the middle point of your data.
- **Interpretation:** The median is especially helpful when the data is skewed, as it gives a better representation of the "typical" value than the mean.

25th Percentile (First Quartile, Q1):

- **What It Is:** The 25th percentile is the value below which 25% of the data falls. It's also known as the first quartile (Q1).
- **What It Suggests:** It shows the lower end of the data distribution. For instance, if you're looking at income data, the 25th percentile indicates the income level below which 25% of the population earns.
- **Interpretation:** It helps to understand where the lower quarter of the data lies and can be useful for assessing the spread and distribution of the data.

50th Percentile (Median, Q2)

- **What It Is:** The 50th percentile is the middle value in the data set (the same as the median). It divides the data into two equal halves.
- **What It Suggests:** It represents the middle point of the data, providing a central reference for data distribution.
- **Interpretation:** It's a key measure for understanding the central tendency of your data, and it divides your dataset into two equal parts.

75th Percentile (Third Quartile, Q3):

- **What It Is:** The 75th percentile is the value below which 75% of the data falls. It's also known as the third quartile (Q3).
- **What It Suggests:** It shows the upper end of the data distribution. For instance, if you're looking at test scores, the 75th percentile indicates the score below which 75% of the students fall.
- **Interpretation:** It helps to understand where the higher quarter of the data lies and can be useful for identifying high-end outliers and assessing the spread of the data.

Standard Deviation

- Standard deviation is a measure of how spread out the values in a dataset are around the mean. It tells you how much individual data points deviate from the average value.
- **What It Is:** Standard Deviation (SD) quantifies the amount of variation or dispersion in a set of values. A low standard deviation means that the values tend to be close to the mean, while a high standard deviation means that the values are spread out over a wider range.

5. **Sentiment Analysis (if applicable):**
    a) If there are open-ended responses, conduct sentiment analysis to gauge the overall sentiment and identify key themes in the participants' comments with the help of Natural Language Processing (NLP).
6. **Recommendations and Insights:**
    a) Based on the analysis, provide meaningful insights into the opinions of stakeholders from both Industry as well as Health Authority.

b) Suggest potential improvements or policy changes that could benefit or improvise Accelerated Approval Pathway.

3.10 Research Design Limitations

Below are some of the limitations of this study.

a) **Sample Size:** Sample size may not truly represent the whole industry.

b) **Limited Generalizability:** The study's findings may not be fully generalizable to the whole Industry and all the Health Authority stakeholders.

c) **Social Desirability Bias:** Participants might provide socially desirable responses, affecting the study's validity.

d) **Interpretation of Open-ended Responses:** Thematic anlaysis tends to be subjective and at times represent an individual’s viewpoint instead of a population’s. Applicabilty of Natural Language Processing also has limiations, as there might be responses which may not be aligned with each other and act as completely discrete response.

3.11 Conclusion

Within the boundaries of limitation that this study and that its associated artefacts have, considering the research methodology that has been applied and analysis techniques employed, this study looks slated to provide valuable insights to fill the identified research gaps of Accelerated Approval Pathway. With the application of statistical techniques, it is indicating to produce a good corroboration to the hypotheses and the theoretical construct of extending overall benefit to all stakeholders involved in the clincal trial value chain.

Outcomes of responses to questionnaire, connect with and are strong indicative of the value the Accelerated Approval Pathway is brining to Oncology drug products.

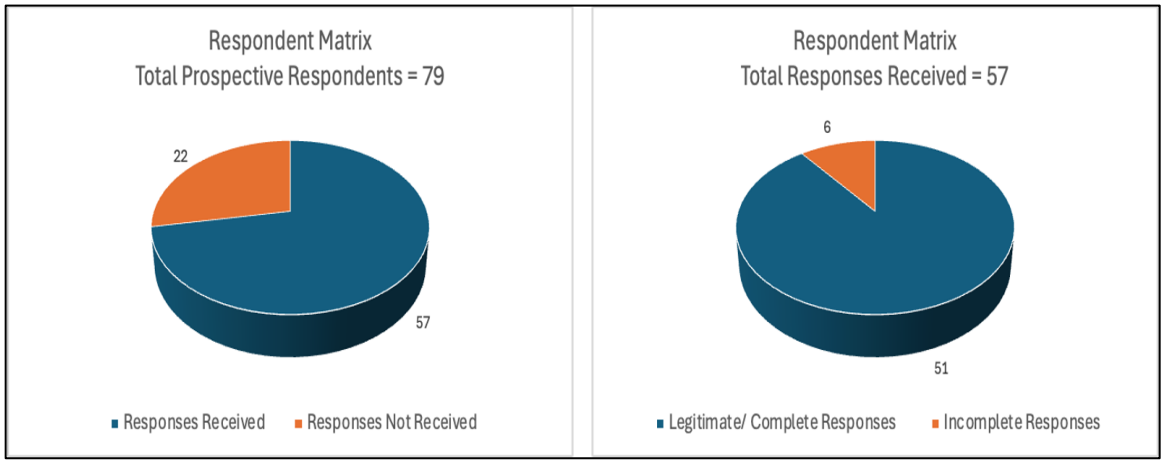
Hence, there is a great need to pick this research as a base and delve on it to further build on recommendations to stakeholders involved, and most importantly to Health Authority, i.e. The USFDA and other federal agencies in The US.

CHAPTER IV:

RESULTS

For the Industry respondents, there were a total of 89 prospective respondents with whom the connection was tried to be established through the means of face-to-face connects, telephonic connects, emails and social media connects, viz. LinkedIn and WhatsApp. Out of those 89 prospective respondents, connections were established with 79 of such respondents and the questionnaires were sent out to all of them. Out of these 79 respondents, responses were received from a total of 57 respondents. Responses received from these 57 respondents were analyzed and validated and it was found out that six of such responses were either incomplete or redundant. Hence, for the sake of this study, a total of 51 responses have been considered. As per the plan, it was required to have 50 responses for this study and, thus, these 51 responses have been adequately poised to provide the desired results for this study.

Figure 4.1
Respondent Matrix



Demographics of the validated Industry respondents has been provided, as under.

Table 4.1
Demographics of Respondents

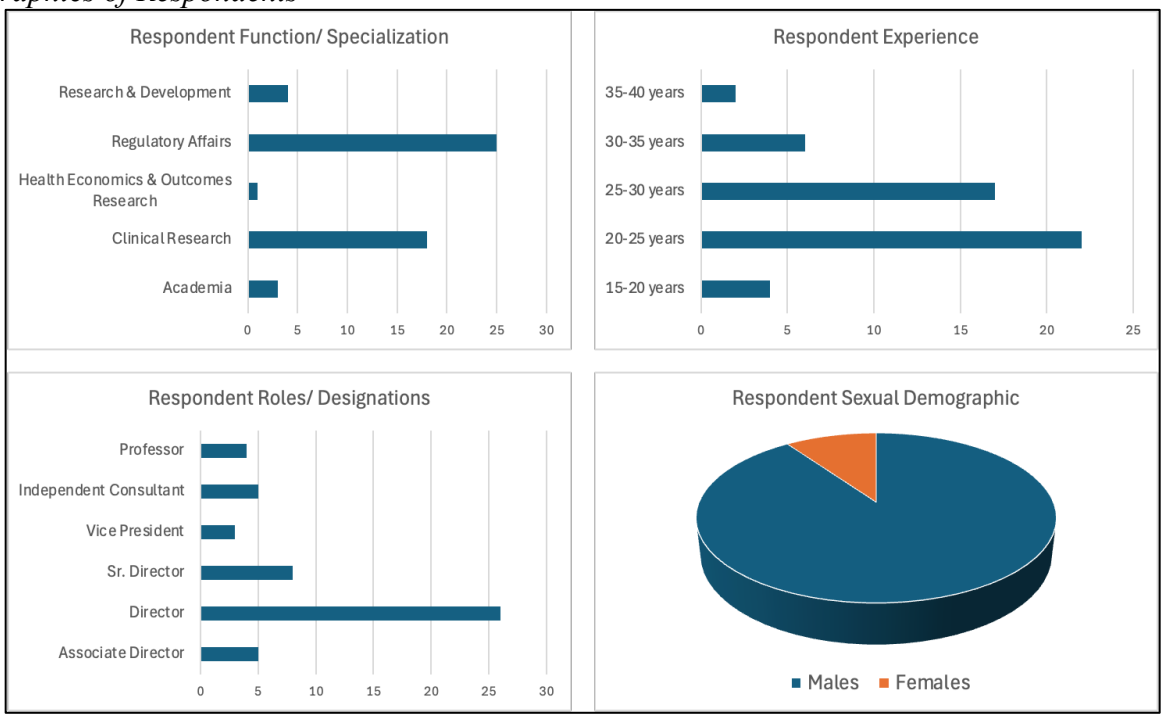
Function/ Specialization	No. of Respondents
Academia	3
Clinical Research	18
Health Economics & Outcomes Research	1
Regulatory Affairs	25
Research & Development	4

Range of Experience	No. of Respondents
15-20 years	4
20-25 years	22
25-30 years	17
30-35 years	6
35-40 years	2

Role/ Designation	No. of Respondents
Associate Director	5
Director	26
Sr. Director	8
Vice President	3
Independent Consultant	5
Professor	4

Sexual Demographic	No. of Respondents
Males	46
Females	5

Figure 4.2
Demographics of Respondents



For Health Authority respondents, there were a total of 3 respondents selected and questionnaires were sent to all of them through email after establishing connects over LinkedIn. As it was envisaged, none of them responded. Hence, their responses have not been considered while evaluating the outcomes of this study.

The outcomes of this study pertaining to main four questions were subjected to two kinds of statistical analysis. Questions which had closed-ended response options were subjected to statistical techniques, like, calculating the mean values, median values, the 25th percentile (first quartile, Q1), the 50th percentile (median, Q2), 75th percentile (third quartile, Q3) and standard deviation. The mean provides an overall idea of central tendency of the data. The median provides the measure of central tendency that is not affected by any outliers or skewed data. The 25th percentile, 50th percentile and 75th percentile suggest the lower end, middle value and upper end of the data distribution respectively. The standard deviation tells us as to how much individual data points deviate from the average or mean value. A Chi-square test is another technique that has been applied to this data to determine if there is a significant association between two categorical variables. There are also Heat Maps plotted for various results. Heat map is a data visualization tool that uses color to represent the magnitude of values in a matrix grid. It is a graphical representation where individual values are shown in a matrix and are coded according to their magnitude with different colors, indicating different levels of intensity. Further, Cramer's V test is yet another statistical measure that has been used to assess the strength of association between two categorical variables. It is an extension of Chi-square test for nominal (categorical) data and provides a value between 0 and 1, where 0 indicates no association between the variables and 1 indicates a perfect association such that knowing the value of one variable perfectly predicts the value of the other. Like heat maps of Chi-square test, heat maps of Cramer's V test were also plotted to visualize the strength of association between multiple pairs of categorical values. In addition to the above-described statistical approaches, there is yet another statistical approach that has been applied in this study. It is Paired T-Test. It is a statistical method used to determine whether there is a significant difference between the means of two

related groups. It is specifically designed to compare two sets of observations that are paired or matched in some way.

For questions which had open-ended responses, thematic analysis was performed, and their analysis was done using a couple of Natural Language Processing (NLP) techniques. The first such technique was Sentiment Analysis. It is a process of determining the emotional tone behind series of words and is valuable for measuring the sentiment of texts to see how people feel about a particular subject. It was utilized to assess the responses pertaining to first problem statement, i.e. timeboxing of confirmatory clinical studies. For this assessment, this technique was used because the responses so obtained were sounding like "sentiments" over this issue of timeboxing. For the thematic analysis of questions pertaining to rest of the three broad topics, viz. incentivization and penalization of Sponsors, drug product label modifications and checks and balances of drug product costs, another Natural Language Processing technique was utilized, which is known as Topic Modeling through a method called Latent Dirichlet Allocation (LDA). This technique is used to automatically discover the hidden themes in a large collection of documents or large database of text or for researching trends.

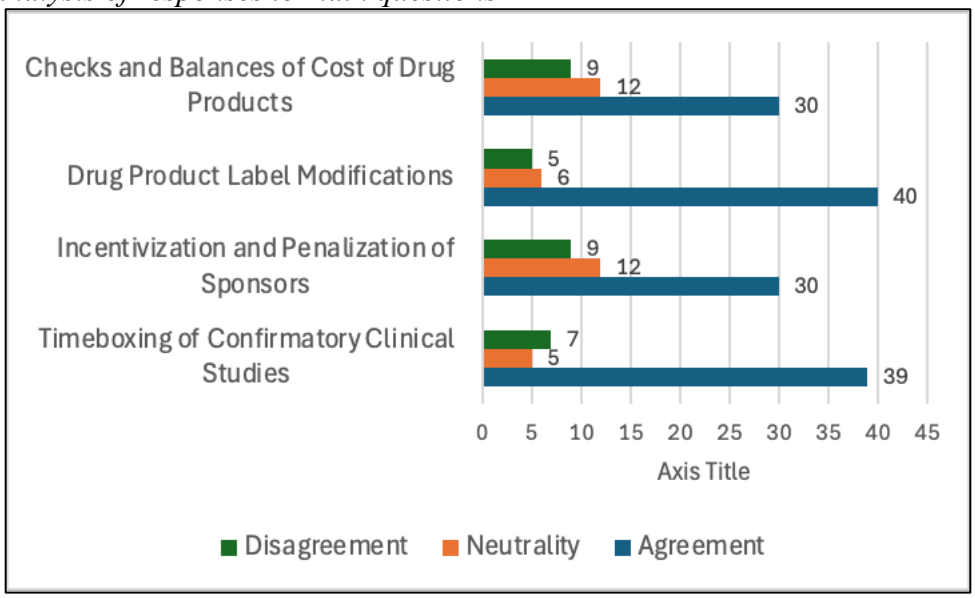
An overall trend analysis from the responses to main questions indicate a positive inclination of respondents. Below table and figure provide an overarching idea of it.

Table 4.2
Overall trend analysis from responses

Main Research Question	Agreement	Neutrality	Disagreement
Timeboxing of Confirmatory Clinical Studies	39	5	7
Incentivization or Penalization of Sponsors	30	12	9

Drug Product Label Modifications	40	6	5
Checks and Balances of Costs of Drug Products	30	12	9

Figure 4.3
Trend analysis of responses to main questions



Detailed statistical analysis was performed on each of the broad topics and questions associated with them has been detailed, as under.

4.1 Research Question One: Time-boxing (mandatory confining of a time limit) of confirmatory clinical studies

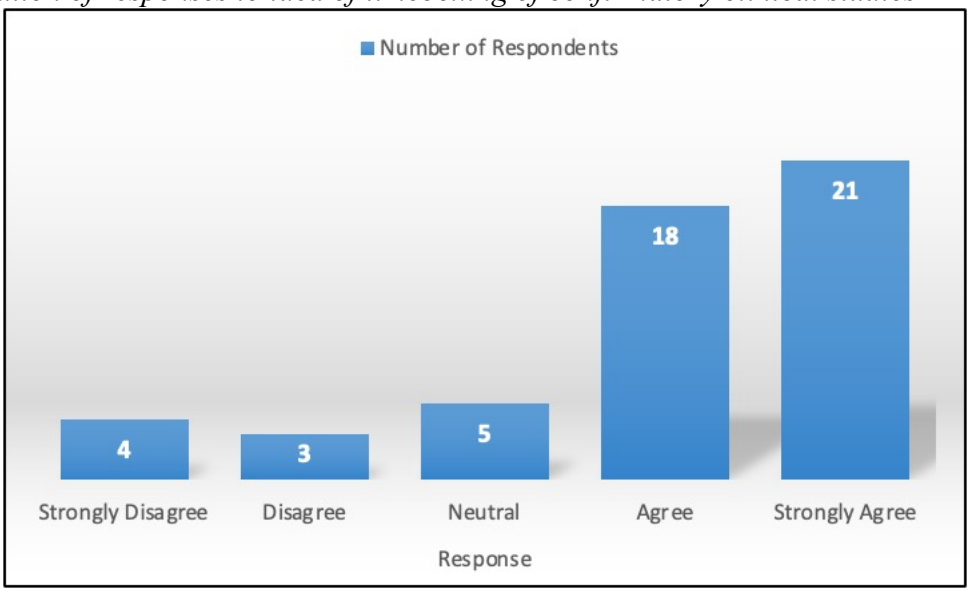
Sub-questions with closed-ended response options:

1. *In your opinion, should time-boxing of confirmatory clinical studies, post grant of an accelerated approval of a drug product for an indication, be made mandated and fixed?*

Out of 51 legitimate responses, a total of 39 responses indicated an agreement to timeboxing of confirmatory clinical studies (with 21 respondents strongly agreeing to it

and 18 agreeing to it). There were 5 of them who were neutral to this idea and 3 of them disagreeing to it, while 4 of them strongly disagreeing to it.

Figure 4.4
Distribution of responses to idea of timeboxing of confirmatory clinical studies



The descriptive statistic for this sub-question shows below results.

- Mean response: 3.96
- Standard deviation: 1.22
- Median: 4
- Minimum: 1
- Maximum: 5

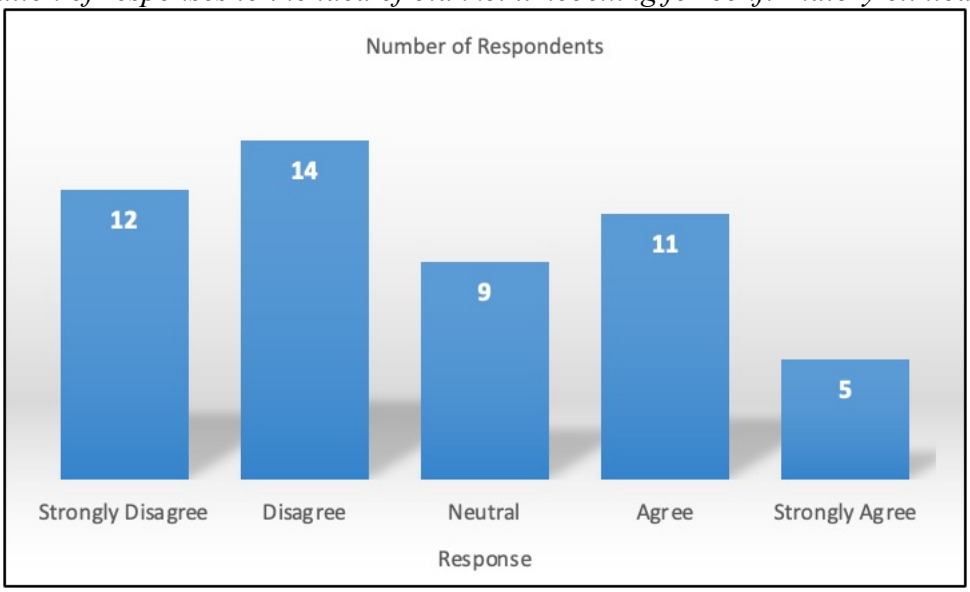
Here, the distribution plot of the responses shows that the majority of responses are concentrated around 4 and 5, indicating a strong agreement with the statement.

2. *Should there be a blanket time-boxing duration mandated for every confirmatory clinical study?*

Out of 51 legitimate responses, a total of 16 responses indicated an agreement to blanket timeboxing of confirmatory clinical studies (with 5 respondents strongly agreeing

to it and 11 agreeing to it). There were 9 of them who were neutral to this idea and 14 of them disagreeing to it, while 12 of them strongly disagreeing to it.

Figure 4.5
Distribution of responses to the idea of blanket timeboxing for confirmatory clinical trials



The descriptive statistic for this sub-question is depicted, as under.

- Mean response: 2.67
- Standard deviation: 1.32
- Median: 2
- Minimum: 1
- Maximum: 5

Here, the distribution plot of the responses shows that the responses are more spread out, with a significant number of respondents choosing 2, indicating a more mixed opinion on having a blanket time-boxing duration.

A correlation between the responses received to these questions was also evaluated. The correlation coefficient between these two sub-questions (Q1 and Q2) is

0.28, indicating a weak positive correlation. This suggests that respondents who agree with timeboxing for confirmatory clinical studies (Q1) are slightly more likely to also agree with having a blanket time-boxing duration (Q2).

Figure 4.6
Heat map of correlation between Q1 and Q2

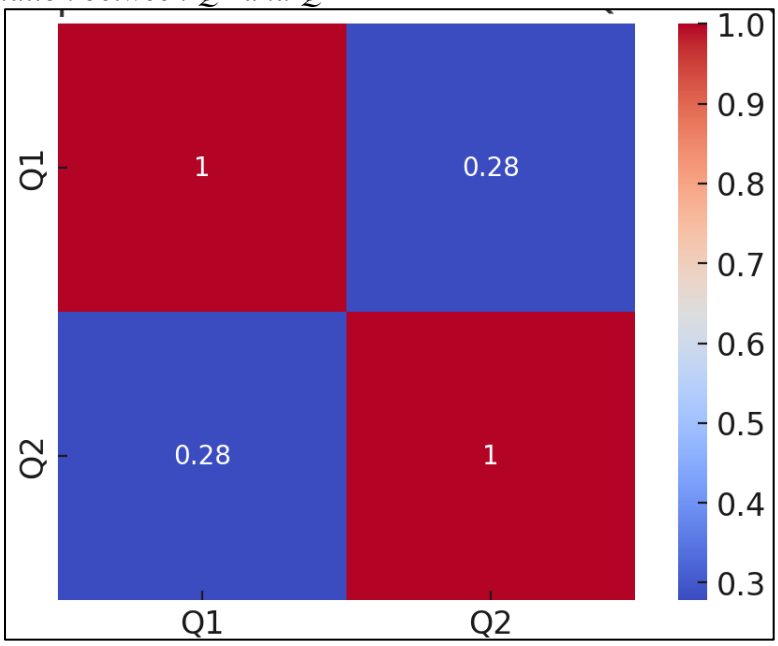
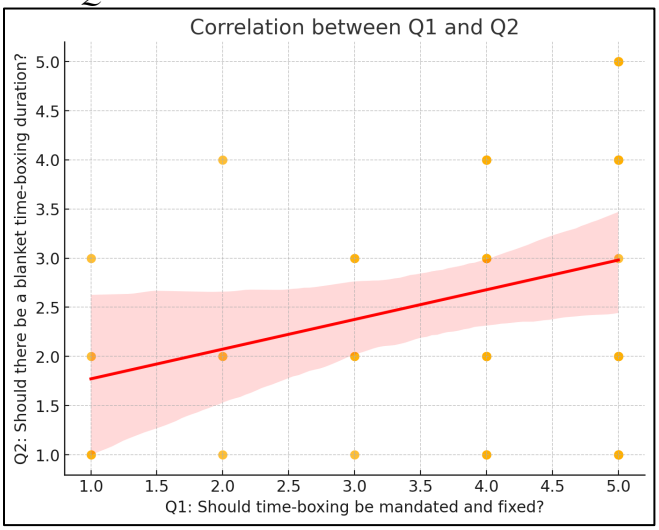


Figure 4.7
Correlation between Q1 and Q2



The responses of next two closed-ended questions were taken up together, analysed and evaluated.

3. *Should this time-boxing be different for below different possible variables of confirmatory clinical studies?*

   Below is the frequency distribution of responses for this question.

   Therapeutic Area: Here, out of 51 legitimate responses, a total of 40 responses indicated an agreement to have different timeboxing considering 'Therapeutic Area' as one of the discrete variables for confirmatory clinical studies (with 18 respondents strongly agreeing to it and 22 agreeing to it). There were 5 of them who were neutral to this idea and 4 of them disagreeing to it, while 2 of them strongly disagreeing to it.

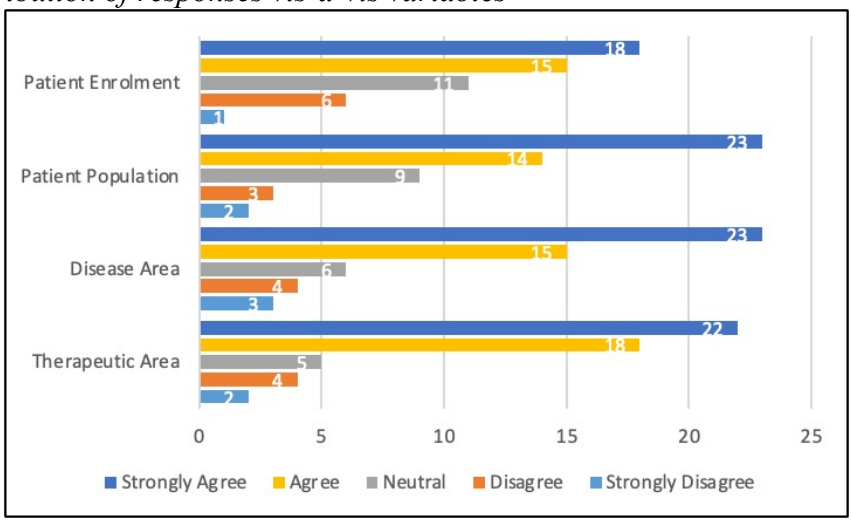
   Disease Area: For this variable, out of 51 legitimate responses, a total of 38 responses indicated an agreement to have different timeboxing considering 'Disease Area' as one of the discrete variables for confirmatory clinical studies (with 15 respondents strongly agreeing to it and 23 agreeing to it). There were 6 of them who were neutral to this idea and 4 of them disagreeing to it, while 3 of them strongly disagreeing to it.

   Patient Population: Here, out of 51 legitimate responses, a total of 37 responses indicated an agreement to have different timeboxing considering 'Patient Population' as one of the discrete variables for confirmatory clinical studies (with 14 respondents strongly agreeing to it and 23 agreeing to it). There were 9 of them who were neutral to this idea and 3 of them disagreeing to it, while 2 of them strongly disagreeing to it.

   Patient Enrolment: Here, out of 51 legitimate responses, a total of 33 responses indicated an agreement to have different timeboxing considering 'Patient

Enrolment' as one of the discrete variables for confirmatory clinical studies (with 15 respondents strongly agreeing to it and 18 agreeing to it). There were 11 of them who were neutral to this idea and 6 of them disagreeing to it, while 1 of them strongly disagreeing to it.

Figure 4.8
Frequency distribution of responses vis-à-vis variables



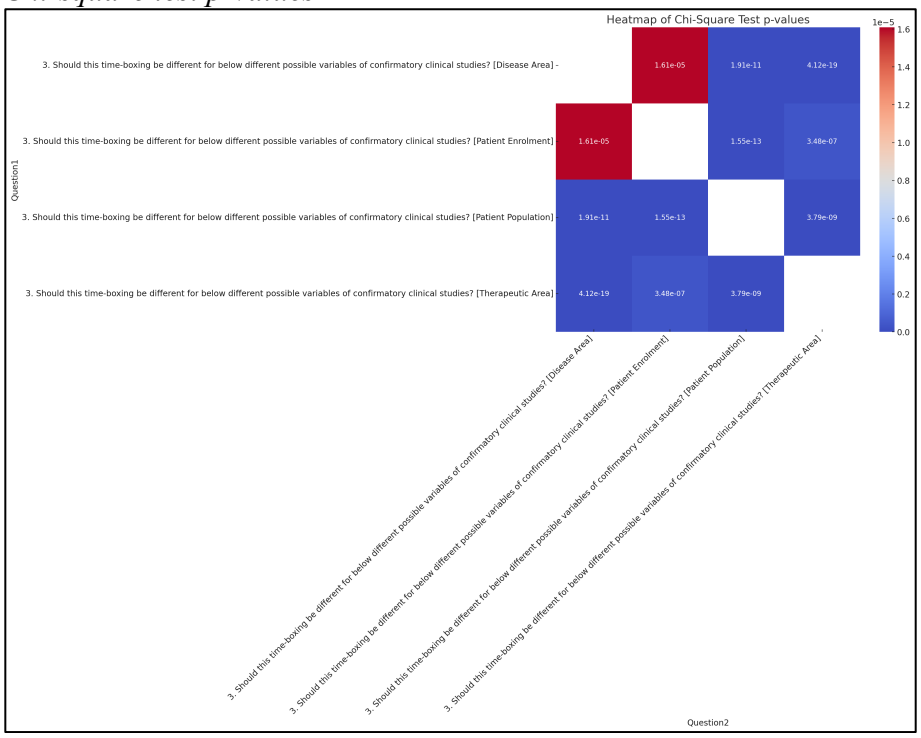
A Chi-square analysis was also performed on the dataset of responses that have been received for this question to understand if the variables being tested had any dependence on each other. Below are the values obtained after performing Chi-square analysis.

Figure 4.9
Chi-square analysis of responses obtained for different possible variables of timeboxing

	3. Should this time-boxing be different for below different possible variables of confirmatory clinical studies? [Therapeutic Area]			3. Should this time-boxing be different for below different possible variables of confirmatory clinical studies? [Disease Area]			3. Should this time-boxing be different for below different possible variables of confirmatory clinical studies? [Patient Population]			3. Should this time-boxing be different for below different possible variables of confirmatory clinical studies? [Patient Enrolment]		
	3. Should this time-boxing be different for below different possible variables of confirmatory clinical studies? [Disease Area]	3. Should this time-boxing be different for below different possible variables of confirmatory clinical studies? [Patient Population]	3. Should this time-boxing be different for below different possible variables of confirmatory clinical studies? [Patient Enrolment]	3. Should this time-boxing be different for below different possible variables of confirmatory clinical studies? [Therapeutic Area]	3. Should this time-boxing be different for below different possible variables of confirmatory clinical studies? [Patient Population]	3. Should this time-boxing be different for below different possible variables of confirmatory clinical studies? [Patient Enrolment]	3. Should this time-boxing be different for below different possible variables of confirmatory clinical studies? [Therapeutic Area]	3. Should this time-boxing be different for below different possible variables of confirmatory clinical studies? [Disease Area]	3. Should this time-boxing be different for below different possible variables of confirmatory clinical studies? [Patient Enrolment]	3. Should this time-boxing be different for below different possible variables of confirmatory clinical studies? [Therapeutic Area]	3. Should this time-boxing be different for below different possible variables of confirmatory clinical studies? [Disease Area]	3. Should this time-boxing be different for below different possible variables of confirmatory clinical studies? [Patient Population]
0	125.830834	72.389685	61.051699	125.830834	85.179529	50.96043	72.389685	85.179529	96.522542	61.051699	50.96043	96.522542
1	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

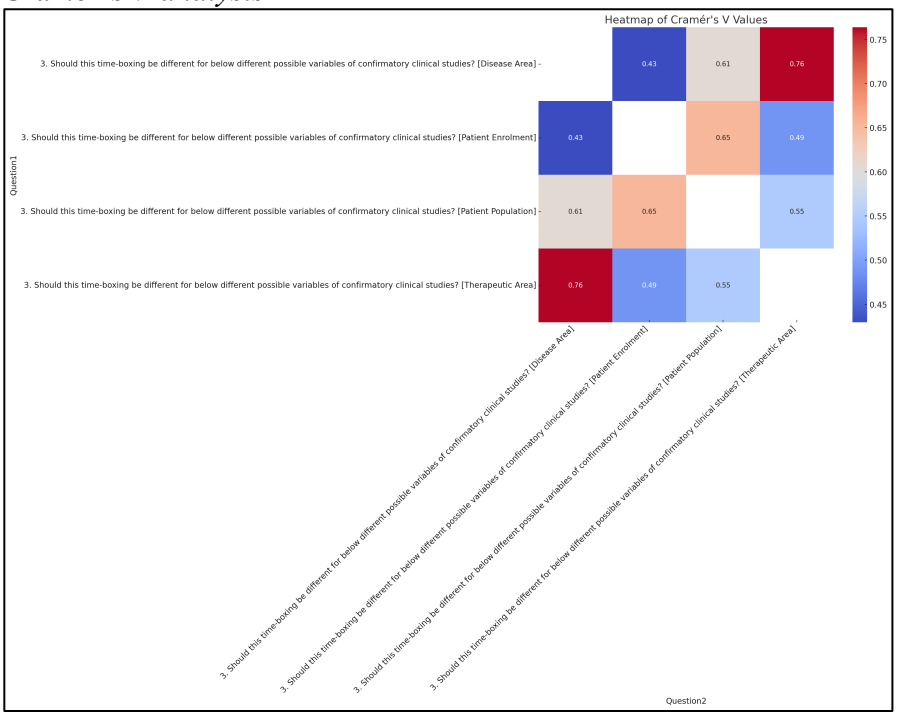
The p-values obtained for all the pairs were extremely low (significantly below 0.05), indicating that the responses to the two questions are not independent of each other, which means that the respondent's opinion in one area are related to their responses in other areas, taken pairwise. Heat maps so plotted are depicted in figures, as under.

Figure 4.10
Heat map of Chi-square test p-values



Further, to understand the strength of association between these categorical variables in numerical terms, Cramer's V analysis was also performed on the data values obtained for this question. Cramer's V values range from 0 to 1, where 0 indicates no association between variables and 1 indicates a very strong association between them. The heat map plotted for Cramer's V analysis is depicted, as under.

Figure 4.11
Heat map for Cramer's V analysis

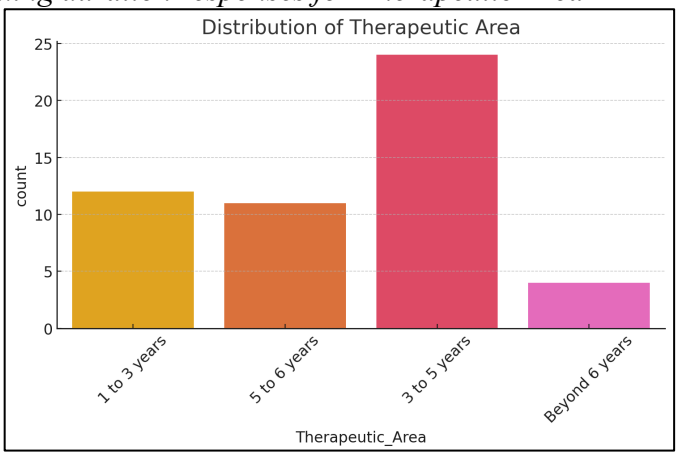


4. *What should be the time-boxing range for below different possible variables of confirmatory clinical studies?*

For the question of duration ranges vis-à-vis these four variables, viz. Therapeutic Area, Disease Area, Patient Population and Patient Enrolment, some very interesting outcomes were obtained from the responses so received.

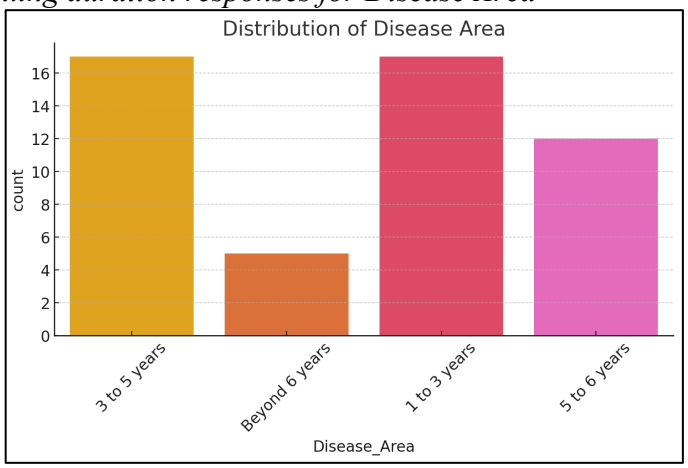
Therapeutic Area: Out of 51 legitimate responses, a total of 12 respondents supported the duration range of 1 to 3 years for timeboxing, 24 respondent supported for 3 to 5 years, 11 respondents supported for 5 to 6 years and 4 respondents supported for beyond 6 years. Below figure depicts the results in a graphical format.

Figure 4.12
Distribution of timeboxing duration responses for Therapeutic Area



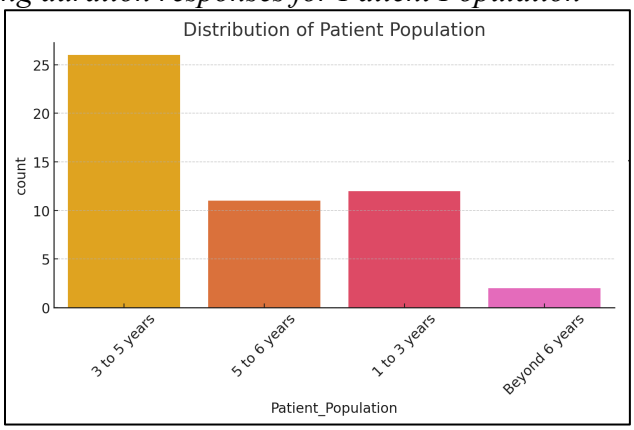
Disease Area: Out of 51 legitimate responses, a total of 17 respondents supported the duration range of 1 to 3 years for timeboxing, 17 respondent supported for 3 to 5 years, 12 respondents supported for 5 to 6 years and 5 respondents supported for beyond 6 years. Below figure depicts the results in a graphical format.

Figure 4.13
Distribution of timeboxing duration responses for Disease Area



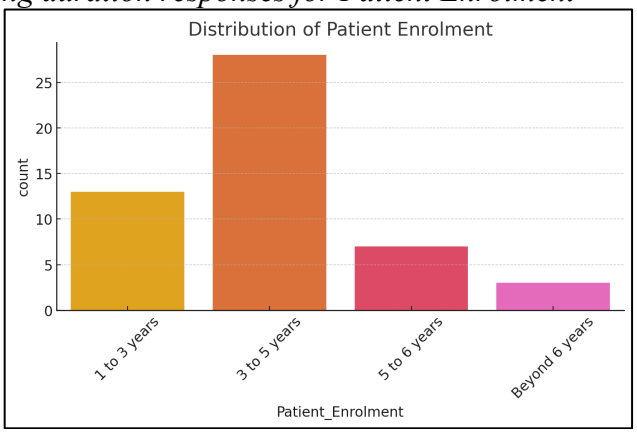
Patient Population: Out of 51 legitimate responses, a total of 12 respondents supported the duration range of 1 to 3 years for timeboxing, 26 respondent supported for 3 to 5 years, 11 respondents supported for 5 to 6 years and 2 respondents supported for beyond 6 years. Below figure depicts the results in a graphical format.

Figure 4.14
Distribution of timeboxing duration responses for Patient Population



Patient Enrolment: Out of 51 legitimate responses, a total of 23 respondents supported the duration range of 1 to 3 years for timeboxing, 18 respondent supported for 3 to 5 years, 7 respondents supported for 5 to 6 years and 3 respondents supported for beyond 6 years. Below figure depicts the results in a graphical format.

Figure 4.15
Distribution of timeboxing duration responses for Patient Enrolment



Sub-question with open-ended response options:

The last sub-question in this category of questions was an open-ended question for which responses obtained were analysed with the help of one of the Natural Language Processing (NLP) technique, which is known as Sentiment Analysis. Sentiment analysis

is a vital aspect of NLP that aims to determine the emotional tone embedded within a text. In this analysis, it was sought to examine the overall sentiment expressed in the subjective responses related to time boxing in clinical studies. The purpose of this analysis was to identify key trends in participant feedback and uncover any underlying emotional patterns that could provide insights into the challenges, expectations, and experiences within this domain.

This report systematically breaks down the sentiment distribution and the topics associated with each sentiment category: positive, neutral, and negative.

5. *In your opinion, what could be other possible variables that have a significant impact on time-boxing of confirmatory clinical studies?*

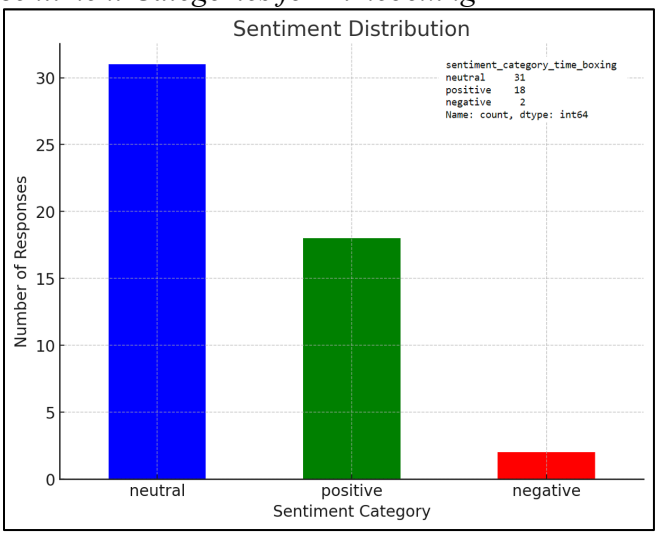
   For this question, the sentiment distribution among the 51 responses is as follows:

   - Neutral Sentiment: 31 responses (61%)
   - Positive Sentiment: 18 responses (35%)
   - Negative Sentiment: 2 responses (4%)

The majority of responses were neutral, indicating that most participants discussed clinical studies in an objective or factual manner without expressing strong emotions. A significant portion of the responses leaned towards positive sentiment, suggesting that many participants held a favourable or optimistic view of certain aspects of time-boxing in clinical studies. A small number of responses were classified as negative, highlighting specific areas of concern or dissatisfaction. Some of the key topics that emerged from the positive responses revolved around impact, disease management, sponsorship, and the overall structure of clinical studies. Similarly, the key topics in neutral responses were generally descriptive and centred around clinical operations, patient needs, study protocols, and disease management. These responses tended to be

more factual, with participants describing processes, challenges, and outcomes without strong emotional undertones. The key topics raised in negative sentiments included tight timelines, extra pressures, and difficulties associated with the overall structure of the studies. While these responses were few, they highlighted significant concerns related to the scheduling and operational efficiency of clinical studies.

Figure 4.16
Distribution of Sentiment Categories for Timeboxing



4.2 Research Question Two: Incentivization or penalization of Sponsors

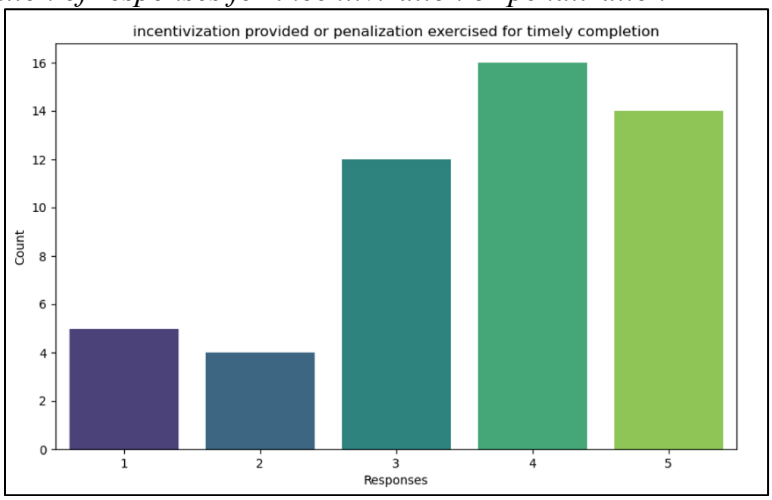
Sub-questions with close-ended response options:

1. *Should there be an incentivization provided or penalization exercised for timely completion or not able to complete the confirmatory clinical studies, respectively, for Sponsors, post accelerated approvals are granted for their drug products?*

Out of 51 legitimate responses, a total of 30 responses indicated an agreement to incentivization or penalization of Sponsors if they are or they are not able to complete confirmatory clinical studies respectively (with 14 respondents strongly agreeing to it and

16 agreeing to it). There were 12 of them who were neutral to this idea and 5 of them disagreeing to it, while 4 of them strongly disagreeing to it. A frequency distribution of these responses so obtained has been depicted, as under.

Figure 4.17
Frequency distribution of responses for incentivization or penalization



Descriptive statistics for these responses has been provided, as below.

- Count: 51 responses
- Mean: 3.59
- Standard Deviation: 1.25
- Minimum Value: 1
- 25th Percentile: 3
- Median (50th Percentile): 4
- 75th Percentile: 5
- Maximum Value: 5

The bar chart shows the distribution of responses is clustered around neutral, agree and strongly agree. There are fewer responses which are there for disagree and

strongly disagree. The trend of response is indicative towards a general agreement and high support for incentivization and penalization of Sponsors if they diligently complete or do not complete the confirmatory clinical studies in time, respectively.

2. *Should incentivization be provided to eligible Sponsors in the form of below different possible incentivization variables upon successful and speedy conductance of confirmatory clinical studies?*

This question was around possible incentivization options that could be provided to eligible Sponsors. There were four such options provided to the respondents – Exclusivity Provisions, Pricing Preferences, Review Acceleration and Speedy Reimbursement Options. Frequency distribution of the responses obtained is provided as under.

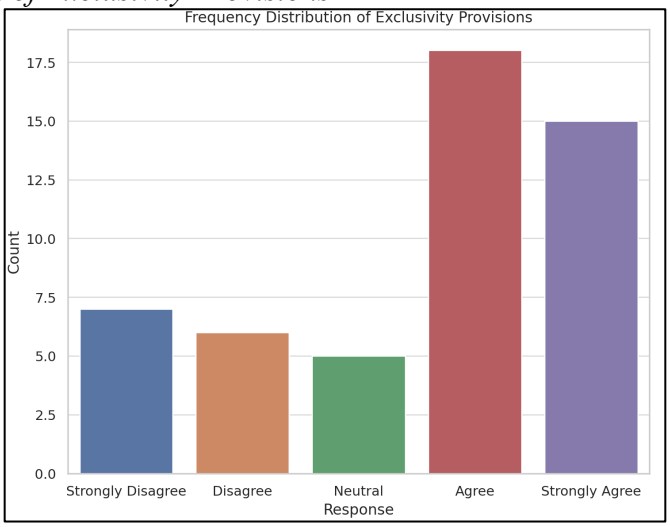
Figure 4.18
Frequency distribution of incentivization options

	Agree	Disagree	Neutral	Strongly Agree	Strongly Disagree
Exclusivity Provisions	18	6	5	15	7
Pricing Preferences	13	11	17	5	5
Review Acceleration	18	3	7	21	2
Speedy Reimbursement Options	17	5	14	13	2

Below are the responses that have been received against these options.

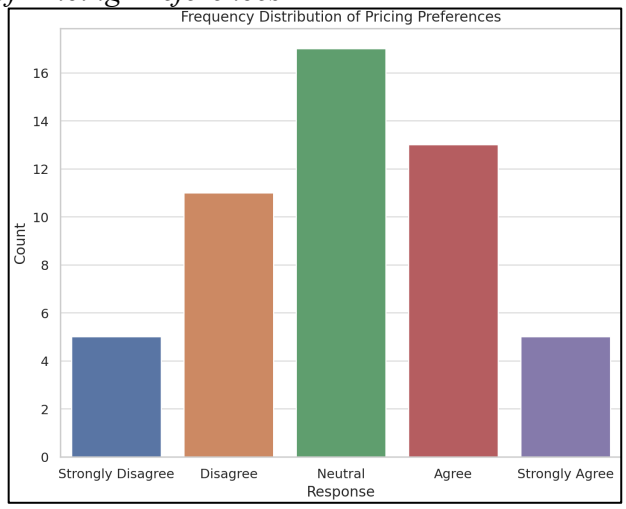
Exclusivity Provisions: Out of 51 legitimate responses, a total of 33 responses indicated an agreement to incentivize Sponsors by providing Exclusivity Provisions, if they are able to complete confirmatory clinical studies respectively (with 15 respondents strongly agreeing to it and 18 agreeing to it). There were 5 of them who were neutral to this idea and 6 of them disagreeing to it, while 7 of them strongly disagreeing to it. A frequency distribution of these responses so obtained has been depicted, as under.

Figure 4.19
Frequency distribution of Exclusivity Provisions



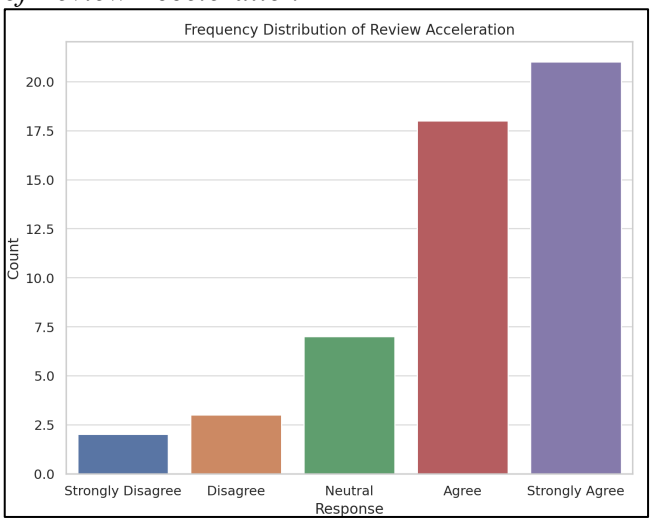
Pricing Preferences: Out of 51 legitimate responses, a total of 18 responses indicated an agreement to incentivize Sponsors with certain Pricing Preferences, if they are able to complete confirmatory clinical studies respectively (with 13 respondents strongly agreeing to it and 5 agreeing to it). There were 17 of them who were neutral to this idea and 11 of them disagreeing to it, while 5 of them strongly disagreeing to it. A frequency distribution of these responses so obtained has been depicted, as under.

Figure 4.20
Frequency distribution of Pricing Preferences



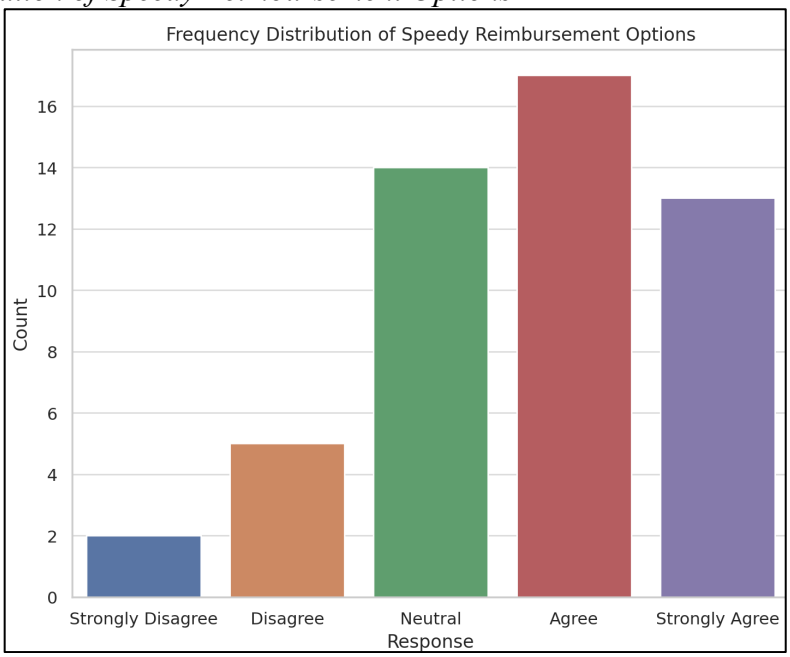
Review Acceleration: Out of 51 legitimate responses, a total of 39 responses indicated an agreement to incentivize Sponsors with Review Acceleration, if they are able to complete confirmatory clinical studies respectively (with 21 respondents strongly agreeing to it and 18 agreeing to it). There were 7 of them who were neutral to this idea and 3 of them disagreeing to it, while 2 of them strongly disagreeing to it. A frequency distribution of these responses so obtained has been depicted, as under.

Figure 4.21
Frequency distribution of Review Acceleration



Speedy Reimbursement Options: Out of 51 legitimate responses, a total of 30 responses indicated an agreement to incentivize Sponsors with Speedy Reimbursement Options, if they are able to complete confirmatory clinical studies respectively (with 13 respondents strongly agreeing to it and 17 agreeing to it). There were 14 of them who were neutral to this idea and 5 of them disagreeing to it, while 2 of them strongly disagreeing to it. A frequency distribution of these responses so obtained has been depicted, as under.

Figure 4.22
Frequency distribution of Speedy Reimbursement Options



Further to the distribution analysis, Chi-square test was also performed on the datasets received to assess if there was a significant association between the responses to different questions. Below are the results of the Chi-square analysis.

Figure 4.23
Results of Chi-square test for independence of variables

Variables Compared	**Chi2 Value**	**p-value**
Exclusitivity Provisions Vs Pricing Preferences	57.72435564	1.25934E-06
Exclusitivity Provisions Vs Review Acceleration	48.87724868	3.45521E-05
Exclusitivity Provisions Vs Speedy Reimbursement Options	39.74243851	8.48E-04
Pricing Preferences Vs Review Acceleration	33.86646687	5.66E-03
Pricing Preferences Vs Speedy Reimbursement Options	49.42090326	2.83385E-05
Review Acceleration Vs Speedy Reimbursement Options	107.2214286	1.50E-15

The Chi-square analysis indicated that the responses to different questions were related. For example, if someone agreed with Exclusivity Provisions, they were also likely to agree with other incentivization strategies. The strongest positive relationship and correlation were observed between Review Acceleration and Speedy Reimbursement Options.

3. *Should penalization be exercised on eligible Sponsors in the form of below different possible penalization variables upon delayed conductance or non-conductance of confirmatory clinical studies?*

This question was around possible penalization options that could be exercised on eligible Sponsors. There were four such options provided to the respondents – Stringent Financial Penalties, Debarment, Review Delays of Subsequent Trials and Issuance of 483s. Frequency distribution of the responses obtained is provided as under.

Figure 4.24
Frequency distribution of penalization options

Frequency Distribution

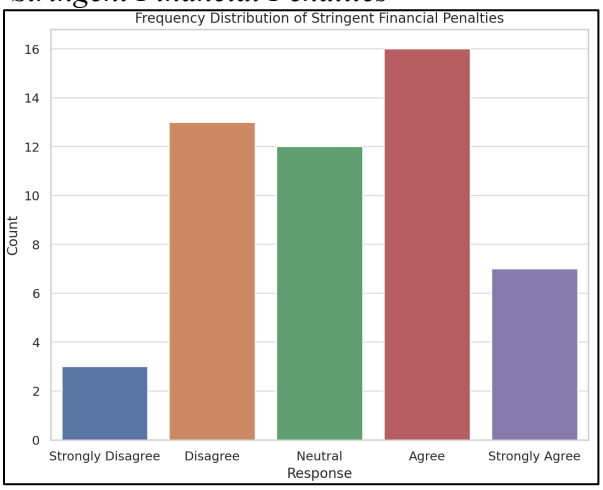
	Agree	Disagree	Neutral	Strongly Agree	Strongly Disagree
Stringent Financial Penalties	16	13	12	7	3
Debarment	8	15	18	1	9
Review Delays of Subsequent Trials	17	8	10	3	13
Issuance of 483s	17	12	10	6	6

Below are the responses that have been received against these options.

Stringent Financial Penalties: Out of 51 legitimate responses, a total of 23 responses indicated an agreement to penalize Sponsors by extending Stringent Financial Penalties, if they are not diligently able to complete confirmatory clinical studies

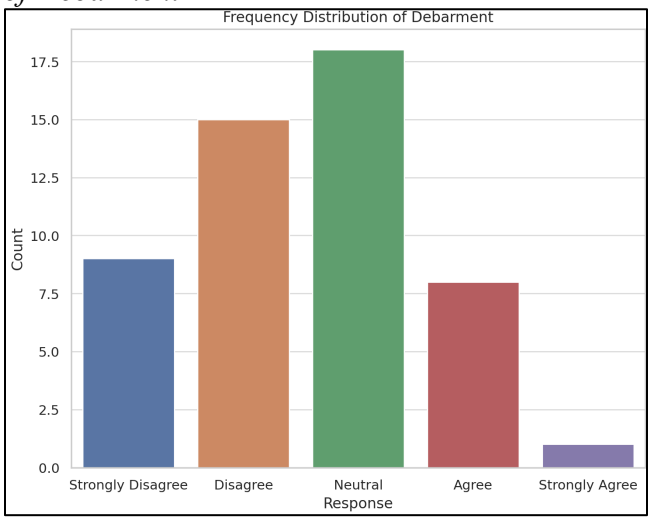
respectively (with 7 respondents strongly agreeing to it and 16 agreeing to it). There were 12 of them who were neutral to this idea and 13 of them disagreeing to it, while 3 of them strongly disagreeing to it. A frequency distribution of these responses so obtained has been depicted, as under.

Figure 4.25
Frequency distribution of Stringent Financial Penalties



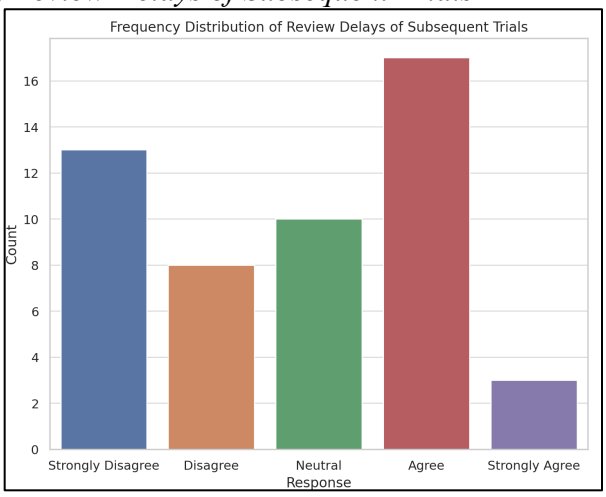
Debarment: Out of 51 legitimate responses, a total of 9 responses indicated an agreement to penalize Sponsors by extending Debarment, if they are not diligently able to complete confirmatory clinical studies respectively (with 1 respondent strongly agreeing to it and 8 agreeing to it). There were 18 of them who were neutral to this idea and 15 of them disagreeing to it, while 9 of them strongly disagreeing to it. A frequency distribution of these responses so obtained has been depicted, as under.

Figure 4.26
Frequency distribution of Debarment



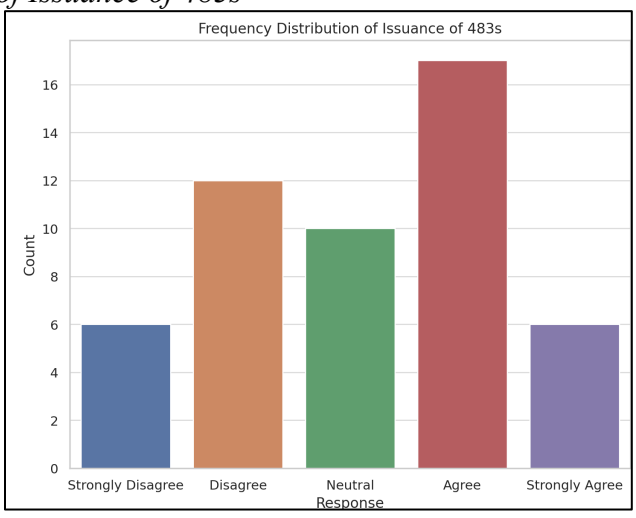
Review Delays of Subsequent Trials: Out of 51 legitimate responses, a total of 20 responses indicated an agreement to penalize Sponsors by extending Review Delays of Subsequent Trials, if they are not diligently able to complete confirmatory clinical studies respectively (with 3 respondents strongly agreeing to it and 17 agreeing to it). There were 10 of them who were neutral to this idea and 8 of them disagreeing to it, while 13 of them strongly disagreeing to it. A frequency distribution of these responses so obtained has been depicted, as under.

Figure 4.27
Frequency distribution of Review Delays of Subsequent Trials



Issuance of 483s: Out of 51 legitimate responses, a total of 23 responses indicated an agreement to penalize Sponsors by Issuing 483s, if they are not diligently able to complete confirmatory clinical studies respectively (with 6 respondents strongly agreeing to it and 17 agreeing to it). There were 10 of them who were neutral to this idea and 12 of them disagreeing to it, while 6 of them strongly disagreeing to it. A frequency distribution of these responses so obtained has been depicted, as under.

Figure 4.28
Frequency distribution of Issuance of 483s

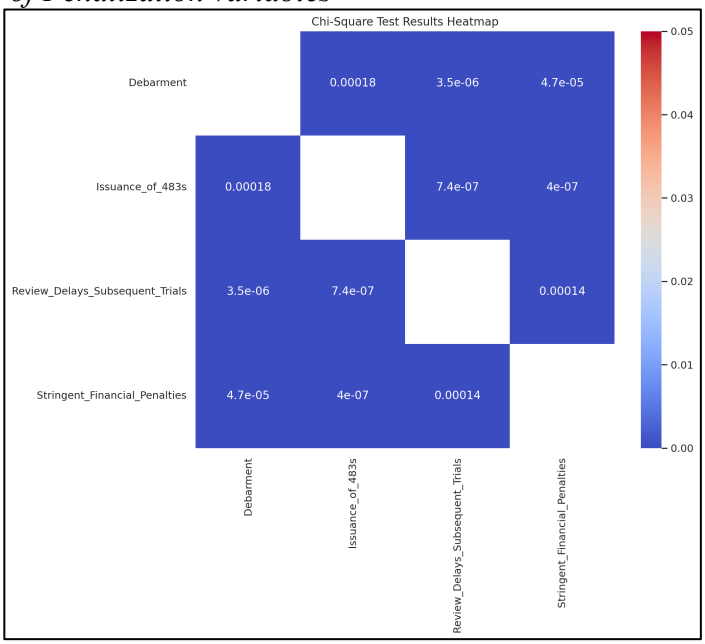


Further to the distribution analysis, Chi-square test was also performed on the datasets received to assess if there was a significant association between the responses to different questions on Penalization variables. Below are the results of the Chi-square analysis for responses obtained for variables of suggested Penalization.

Figure 4.29
Results of Chi-square test for independence of variables of Penalization

Variables Compared	Chi-Square
Stringent Financial Penalties vs Debarment	48.0351515
Stringent Financial Penalties vs Review Delays of Subsequent Trials	44.9836221
Stringent Financial Penalties vs Issuance of 483s	60.6830357
Debarment vs Review Delays of Subsequent Trials	55.0112179
Debarment vs Issuance of 483s	44.2794444
Review Delays of Subsequent Trials vs Issuance of 483s	59.1055788

Figure 4.30
Heat map of p-values of Penalization variables



The Chi-square analysis as well as the heat map indicated that the responses to different questions have correlation and association. The significant associations between responses to different penalization variables suggest that respondents who agree with one

form of penalization are likely to agree with others. The strongest associations were observed between Review Delays of Subsequent Trials and Issuance of 483s.

Sub-questions with open-ended response options:

As described above, these questions were analyzed using an NLP technique called Topic Modeling through the method of Latent Dirichlet Allocation (LDA). It scans through texts and groups them into clusters based on common topics to automatically discover the hidden themes in a large collection of documents. This helps in understanding and categorizing content quickly, which is useful for managing large databases of text or for researching trends.

4. In your opinion, what could be other possible variables to incentivize a Sponsor for conducting a confirmatory clinical trials with due diligence?

Based on LDA analysis, below are some common themes that have been identified in all the responses for possible Incentivization options.

Figure 4.31
Thematic outcomes for Incentivization, post LDA Analysis

```
incentive_themes = {
    'Topic 1': ['Prioritize Review', 'Exclusivity', 'Future Studies', 'Clinical Provisions'],
    'Topic 2': ['Accelerated Approvals', 'Faster Trials', 'Quick Data Submission'],
    'Topic 3': ['Priority Vouchers', 'Market Recognition', 'Speedy Review']
}
```

The main themes emerged out of this analysis could be divided into three broad topics:

- Prioritizing Review and Exclusivity for Future Studies
- Accelerated Approvals and Faster Data Submissions
- Market Recognition and Speedy Review

5. In your opinion, what could be other possible variables to penalize a Sponsor for not conducting a confirmatory clinical trials with due diligence?

Based on LDA analysis, below are some common themes that have been identified in all the responses for possible Penalization options.

Figure 4.32
Thematic outcomes for Penalization, post LDA Analysis

```
penalty_themes = {
    'Topic 1': ['Delayed Trials', 'Withdrawal of Approval', 'Review Results', 'Clinical Requirements'],
    'Topic 2': ['FDA Involvement', 'Holding Approvals', 'Debarnment', 'Withdrawal of Rights'],
    'Topic 3': ['Financial Penalties', 'Product Recall', 'Enforcement Actions', 'Holding/Delaying Trials']
}
```

The main themes emerged out of this analysis could be divided into three broad topics:

- Delayed Trials and Withdrawal of Approval
- FDA Involvement and Withdrawal of Sponsor's Rights
- Financial Penalties and Product Recall

4.3 Research Question Three: Drug Product Label Modifications

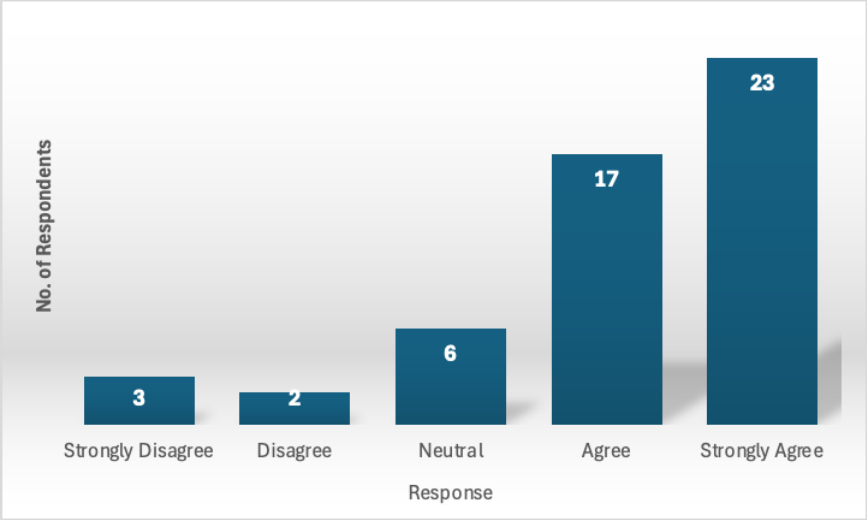
Sub-questions with close-ended response options:

1. *In your opinion, should there be a differentiated label/ prescribing information of a product that has been granted an accelerated approval than a product that has been approved traditionally?*

Out of 51 legitimate responses, a total of 40 responses indicated an agreement to have a differentiated label/ prescribing information of a drug product with accelerated approval (with 23 respondents strongly agreeing to it and 17 agreeing to it). There were 6 of them who were neutral to this idea and 2 of them disagreeing to it, while 3 of them

strongly disagreeing to it. A frequency distribution of these responses so obtained has been depicted, as under.

Figure 4.33
Frequency distribution of responses for differentiated label/ prescribing information



Descriptive statistics for these responses has been provided, as below.

Figure 4.34
Descriptive statistics for differentiated label/ prescribing information responses

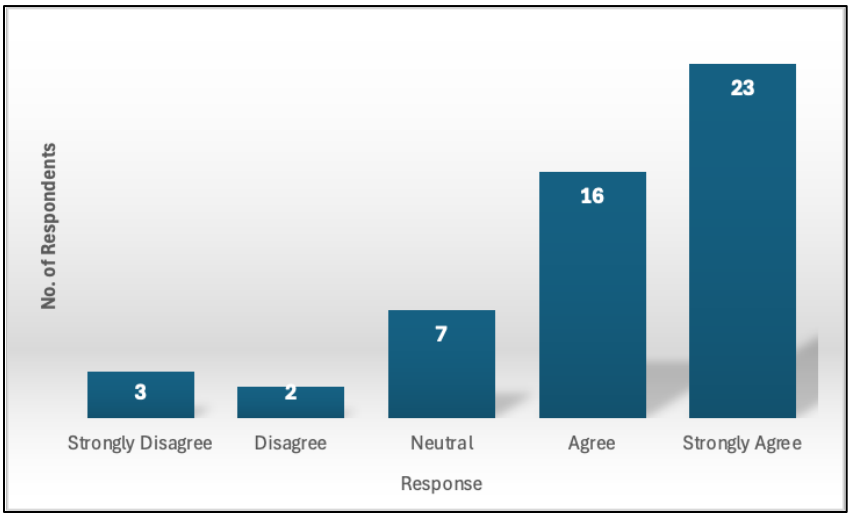
count	mean	std	min	25%	50%	75%	max
51.0	4.078431	1.128594	1.0	4.0	4.0	5.0	5.0

The distribution shows that the responses are clustered around agree and strongly agree. There are fewer responses which are there for disagree and strongly disagree. The trend of response is indicative towards a general agreement and high support for differentiated label/ precribing information for products which have been granted approval through Accelerated Approval Pathway.

2. *Should key information highlighting accelerated drug approval be distinctly displayed on the label/ prescribing information; viz. in different colour or as a boxed text?*

Out of 51 legitimate responses, a total of 39 responses indicated an agreement to have a distinctly displayed information on the label of a drug product with accelerated approval (with 23 respondents strongly agreeing to it and 16 agreeing to it). There were 7 of them who were neutral to this idea and 2 of them disagreeing to it, while 3 of them strongly disagreeing to it. A frequency distribution of these responses so obtained has been depicted, as under.

Figure 4.35
Frequency distribution of responses for distinct display of information on label/ prescribing information



Descriptive statistics for these responses has been provided, as below.

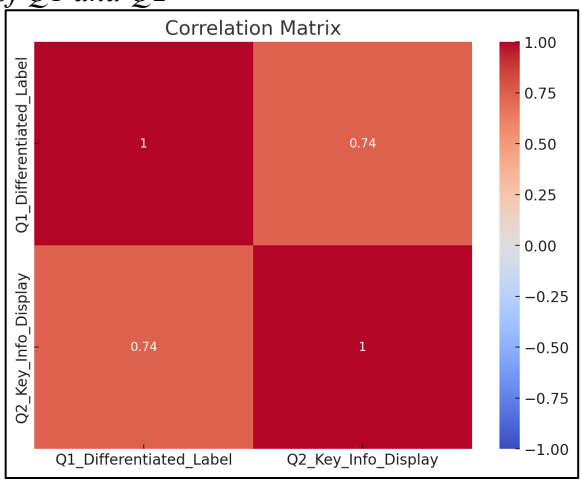
Figure 4.36
Descriptive statistics for distinct display of information on label/ prescribing information

count	mean	std	min	25%	50%	75%	max
51.0	4.058824	1.138627	1.0	4.0	4.0	5.0	5.0

The distribution shows that the responses are clustered around agree and strongly agree. There are fewer responses which are there for disagree and strongly disagree. The trend of response is indicative towards a general agreement and high support distinct display of information on label/ prescribing information for products which have been granted approval through Accelerated Approval Pathway.

Further to assess a correlation between the responses obtained for above two questions, a correlation analysis was also performed. It was found out that there was a strong positive correlation coefficient of 0.74 between the responses of two questions. This suggests that respondents who agree with one statement are likely to agree with the other.

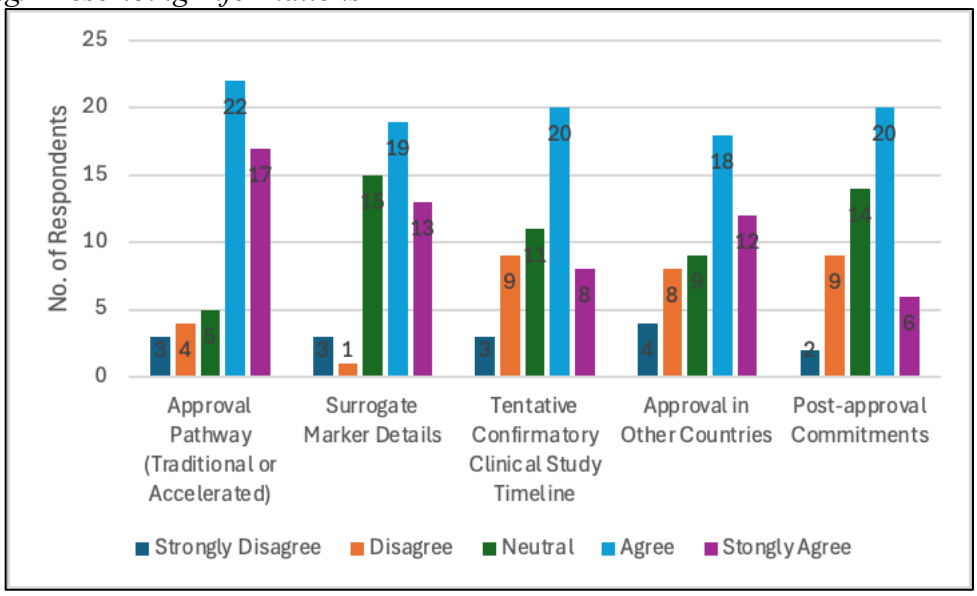
Figure 4.37
Correlation of responses of Q1 and Q2



3. *Information pertaining to which of the below different possible variables should be displayed on the label/ prescribing information (either in a box or in different color) of a product that has been granted accelerated approval?*

For this question, some of the variables were assigned, which were proposed to get included on the labels/ prescribing informations of the drug products, viz., Approval Pathway of drug product (whether the product was approved by following traditional approval pathway or by following Accelerated Approval Pathway), Surrogate Marker Details, Tentative Confirmatory Clinical Study Timeline, Approval in Other Countries and Post-approval Commitments. Below are the overall responses received for these set of variables from all 51 respondents.

Figure 4.38
Responses received for discrete variables to be included as prospective modifications on Labeling/ Prescribing Informations



Approval Pathway (Traditional or Accelerated): Out of 51 legitimate responses, a total of 39 responses indicated an agreement to include approval pathway details on label/ prescribing information of drug products (with 17 respondents strongly agreeing to it and 22 agreeing to it). There were 5 of them who were neutral to this idea and 4 of them disagreeing to it, while 3 of them strongly disagreeing to it.

Surrogate Marker Details: Out of 51 legitimate responses, a total of 32 responses indicated an agreement to include Surrogate Marker Details on label/ prescribing information of drug products (with 13 respondents strongly agreeing to it and 19 agreeing to it). There were 15 of them who were neutral to this idea and 1 of them disagreeing to it, while 3 of them strongly disagreeing to it.

Tentative Confirmatory Clinical Study Timeline: Out of 51 legitimate responses, a total of 28 responses indicated an agreement to include Tentative Confirmatory Clinical Study Timeline details on label/ prescribing information of drug products (with 8 respondents strongly agreeing to it and 20 agreeing to it). There were 11 of them who were neutral to this idea and 9 of them disagreeing to it, while 3 of them strongly disagreeing to it.

Approval in Other Countries: Out of 51 legitimate responses, a total of 30 responses indicated an agreement to include Approval in Other Countries details on label/ prescribing information of drug products (with 12 respondents strongly agreeing to it and 18 agreeing to it). There were 9 of them who were neutral to this idea and 8 of them disagreeing to it, while 4 of them strongly disagreeing to it.

Post-approal Commitments: Out of 51 legitimate responses, a total of 26 responses indicated an agreement to include Post-approval Commitment details on label/ prescribing information of drug products (with 6 respondents strongly agreeing to it and 20 agreeing to it). There were 14 of them who were neutral to this idea and 9 of them disagreeing to it, while 2 of them strongly disagreeing to it.

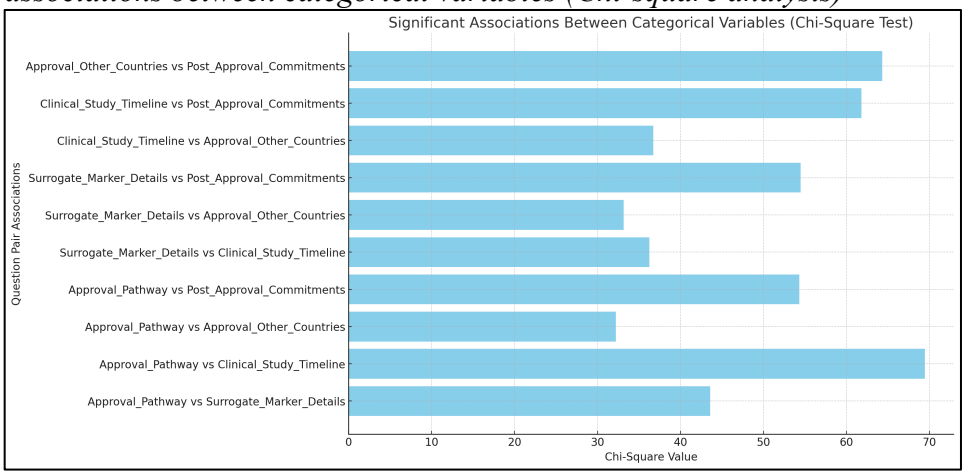
Further, to assess the correlation and association of these variables, a Chi-square analysis was also performed. Below are the results of this analysis.

Figure 4.39
Results of Chi-square analysis to study the association of variables

Variables	Chi2	p-value
Approval Pathway (Traditional or Accelerated) Vs Surrogate Marker details	43.5952	0.0002
Approval Pathway (Traditional or Accelerated) Vs Tentative Confirmatory Clinical Study Timeline	69.4495	0.0000
Approval Pathway (Traditional or Accelerated) Vs Approval in other countries	32.2244	0.0093
Approval Pathway (Traditional or Accelerated) Vs Post-approval Commitments	54.3194	0.0000
Surrogate Marker details Vs Tentative Confirmatory Clinical Study Timeline	36.2600	0.0027
Surrogate Marker details Vs Approval in other countries	33.1511	0.0071
Surrogate Marker details Vs Post-approval Commitments	54.4694	0.0000
Tentative Confirmatory Clinical Study Timeline Vs Approval in other countries	36.7067	0.0023
Tentative Confirmatory Clinical Study Timeline Vs Post-approval Commitments	61.8269	0.0000
Approval in other countries Vs Post-approval Commitments	64.3133	0.0000

Chi-square analysis results indicate significant associations between the responses of different variables.

Figure4.40
Significant associations between categorical variables (Chi-square analysis)



This bar chart was also plotted to indicate the Chi-Square values of the significant associations.

Sub-question with close-ended response options:

4. *In your opinion, what could be other possible variables that could be included on the label/ prescribing information of a drug product that has been granted approval through accelerated approval pathway?*

For this question, responses from individuals who provided suggestions for other possible variables that could be included on the label or prescribing information of a drug products that have been granted approval through the accelerated approval pathway were analyzed. Key themes and patterns in their suggestions were identified using Topic Modeling (LDA) [a Natural Language Processing (NLP) technique] and word cloud visualizations.

This details outline the most important themes and the potential variables that the respondents suggested to be included in drug labeling. The goal was to better understand what information the respondents feel was essential for ensuring safety, efficacy, and clarity in prescribing of these drugs.

Below are the key themes that have been identified after the analysis of all the responses.

- Theme 1: Approval Process and Criteria
- Theme 2: Risks and Side Effects
- Theme 3: Benefits and Efficacy
- Theme 4: Study Outcomes and Efficacy Measures
- Theme 5: Patient Information and Eligibility

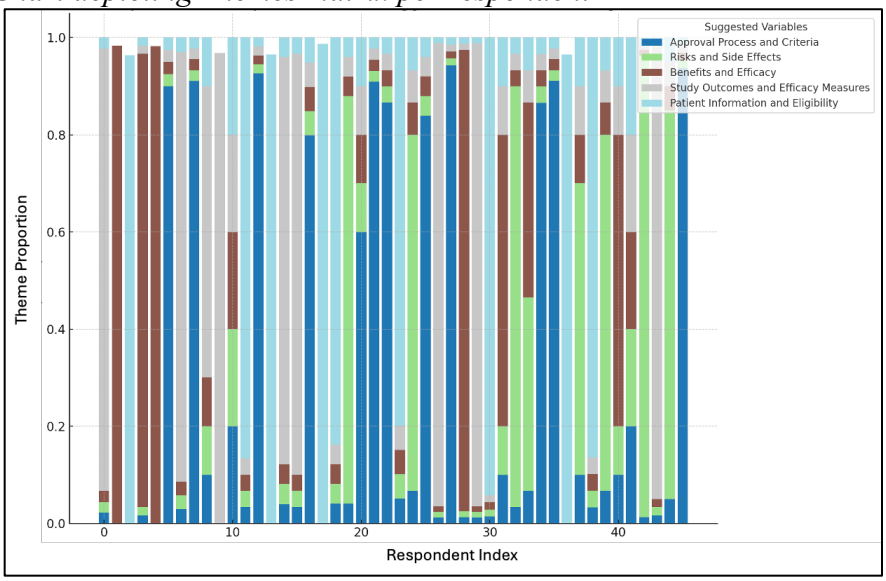
Figure 4.41
Themes based upon Topic Modeling of Label modification related question

	Topic Number	Theme	Key Words	Suggested Variables
0	1	Approval Process and Criteria	approval, pathway, product, date	Approval criteria, accelerated approval pathwa...
1	2	Risks and Side Effects	risk, effects, possible, add, black-box	Side effects, risk factors, black-box warnings
2	3	Benefits and Efficacy	benefit, drug, accelerated, effective	Benefits of the drug, effectiveness in patients
3	4	Study Outcomes and Efficacy Measures	outcome, efficacy, results, data	Outcome measures, clinical trial results, effi...
4	5	Patient Information and Eligibility	patients, eligibility, label, approval	Patient eligibility, specific patient groups

These responses so obtained vis-à-vis each of the themes were plotted on a Stacked Bar Chart. The stacked bar chart is a way of visually showing how the different

themes (topics) that were identified from the respondents' suggestions appear across various responses. Each bar represents one response from a participant who gave suggestions about what variables should be included on drug labels. In total, there are several bars lined up next to each other. Each bar corresponds to a different person's response. The different colors in each bar represent the different themes or topics that were identified from the suggestions. These colors show which themes are present in each person's response and how much they talk about each theme. From the stacked bar chart, it can be depicted that Risks and Side Effects are themes that appears in many responses, which tell us that respondents are particularly concerned about safety. Approval Process and Criteria also appear frequently, indicating that people want to know more about how the drug was approved. Benefits and Efficacy appear often, but in some responses, they are discussed less than risks, showing that people may prioritize safety over benefits. The Study Outcomes and Patient Information themes are present, but they tend to be smaller in some bars, indicating that not everyone discusses them at length.

Figure 4.42
Stacked Bart Chart depicting Themes matrix per respondent



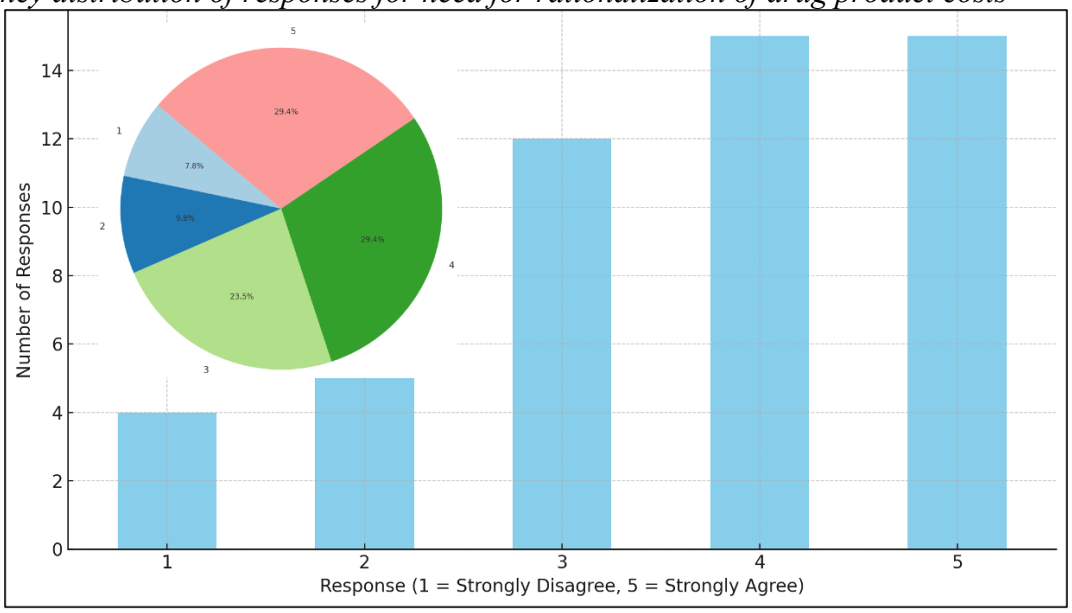
4.4 Research Question Four: Checks and Balances of Drug Product Costs

Sub-questions with close-ended response options:

1. *Do you think there is a need to rationalize the cost of drug products that have been granted accelerated approvals?*

Out of 51 legitimate responses, a total of 30 responses indicated an agreement to the need to rationalize the cost of a drug product that has been approved through accelerated approval route (with 15 respondents strongly agreeing to it and 15 agreeing to it). There were 12 of them who were neutral to this idea and 5 of them disagreeing to it, while 4 of them strongly disagreeing to it. A frequency distribution of these responses so obtained has been depicted, as under.

Figure 4.43
Frequency distribution of responses for need for rationalization of drug product costs



Descriptive statistics for these responses has been provided, as below.

Figure 4.44
Descriptive statistics of responses for need for rationalization of drug product costs

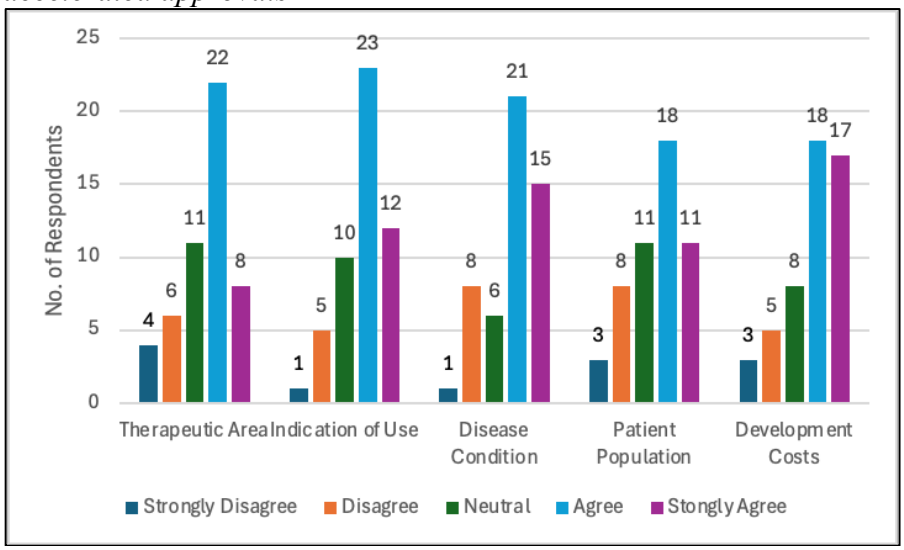
- **Count**: 51 responses
- **Mean**: 3.63
- **Standard Deviation**: 1.23
- **Minimum**: 1
- **25th Percentile**: 3
- **Median (50th Percentile)**: 4
- **75th Percentile**: 5
- **Maximum**: 5
- **Mode**: 4 (most common response)

The distribution shows that the responses are clustered around agree and strongly agree (roughly 60%). The mean response is 3.63, which is reinforcing the trend towards agreement. There are fewer responses which are there for disagree and strongly disagree (nearly 18%). The trend of response is indicative towards a general agreement and high support for rationalization of costs for products which have been granted approval through Accelerated Approval Pathway.

2. *Which of the below variables could be the drivers of cost decisions of the drug products that have been granted accelerated approvals?*

For this question, some of the variables were assigned, which were proposed to be important for deriving the costs of drug products, viz., Therapeutic Area, Indication of Use, Disease Condition, Patient Population and Development costs. Below are the overall responses received for these set of variables from all 51 respondents.

Figure 4.45
Responses received for discrete variables to be key drivers of cost of products that have been granted accelerated approvals



Therapeutic Area: Out of 51 legitimate responses, a total of 30 responses indicated an agreement for Therapeutic Area being one of the drivers of costs of drugs approved through Accelerated Approval Pathway (with 8 respondents strongly agreeing to it and 22 agreeing to it). There were 11 of them who were neutral to this idea and 6 of them disagreeing to it, while 4 of them strongly disagreeing to it.

Indication of Use: Out of 51 legitimate responses, a total of 35 responses indicated an agreement for Indication of Use being one of the drivers of costs of drugs

approved through Accelerated Approval Pathway (with 12 respondents strongly agreeing to it and 23 agreeing to it). There were 10 of them who were neutral to this idea and 5 of them disagreeing to it, while 1 of them strongly disagreeing to it.

Disease Condition: Out of 51 legitimate responses, a total of 36 responses indicated an agreement for Disease Condition being one of the drivers of costs of drugs approved through Accelerated Approval Pathway (with 15 respondents strongly agreeing to it and 21 agreeing to it). There were 6 of them who were neutral to this idea and 8 of them disagreeing to it, while 1 of them strongly disagreeing to it.

Patient Population: Out of 51 legitimate responses, a total of 29 responses indicated an agreement for Patient Population being one of the drivers of costs of drugs approved through Accelerated Approval Pathway (with 11 respondents strongly agreeing to it and 18 agreeing to it). There were 11 of them who were neutral to this idea and 8 of them disagreeing to it, while 3 of them strongly disagreeing to it.

Development Costs: Out of 51 legitimate responses, a total of 35 responses indicated an agreement for Development Costs being one of the drivers of costs of drugs approved through Accelerated Approval Pathway (with 17 respondents strongly agreeing to it and 18 agreeing to it). There were 8 of them who were neutral to this idea and 5 of them disagreeing to it, while 3 of them strongly disagreeing to it.

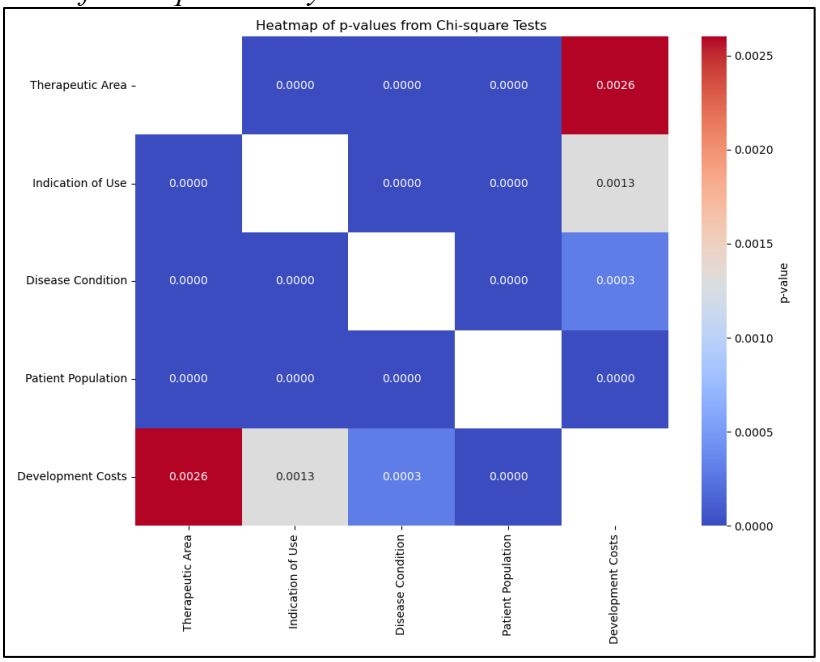
Further, to assess the correlation and association of these variables, a Chi-square analysis was also performed. Below are the results of this analysis.

Figure 4.46
Results of Chi-square analysis to study the association of variables

Variable Pair	Chi-square	p-value
Therapeutic Area vs Indication of Use	95.4877	0
Therapeutic Area vs Disease Condition	83.6532	0
Therapeutic Area vs Patient Population	54.0587	0
Therapeutic Area vs Development costs	36.3911	0.0026
Indication of Use vs Disease Condition	127.3336	0
Indication of Use vs Patient Population	61.6486	0
Indication of Use vs Development costs	38.4124	0.0013
Disease Condition vs Patient Population	71.5601	0
Disease Condition vs Development costs	42.7407	0.0003
Patient Population vs Development costs	65.8307	0

Chi-square analysis results indicate significant associations between the responses of different variables.

Figure 4.47
Heat map of p-values of Chi-square analysis



The heat map also visualized the p-values from the Chi-Square analysis. This provided a visual representation of how strongly the variables were associated.

To affirm the strength of association between these variables, a Cramer's V test for variable association strength was performed. The heat map, as under, visualized these associations.

Figure 4.48
Results of Cramer's V association of strengths

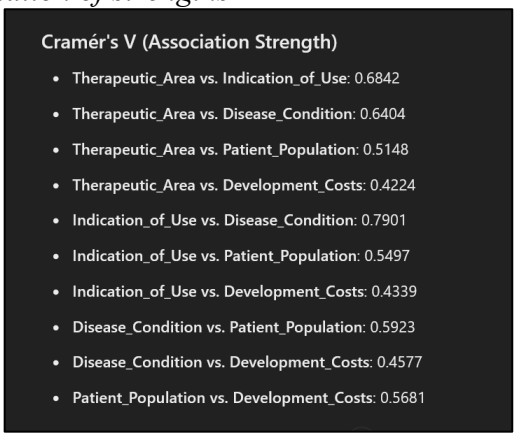
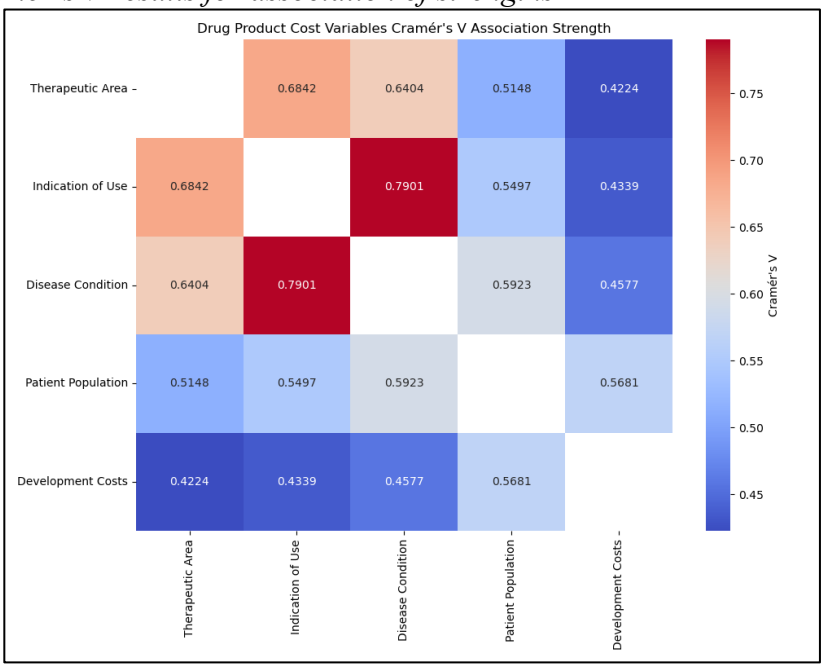


Figure 4.49
Heat map of Cramer's V results for association of strengths



Sub-question with open-ended response options:

There were two open-ended sub-questions under this main question which were responded by the respondents. The responses have been analysed thoroughly with the help of a Natural Language Processing (NLP) technique called Topic Modeling (especially with the utilization of LDA) to identify common themes, suggestions, and factors related to drug pricing and cost containment.

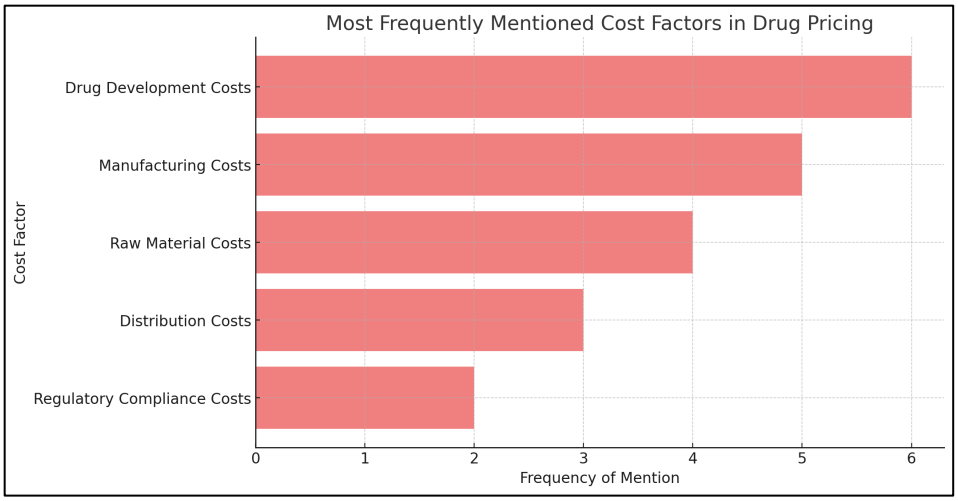
3. *In your opinion, what could be other possible variables to have an impact on cost of drug products that have been approved through accelerated approval pathway?*

With application of NLP technique, below are some of the commnly identified themes that have emerged out of the responses received. These have been highlighted by most of the respondents as the variables that constitute the substrates that tend to have an impact on overall cost of the drug products and to the costs of drug products that have been approved following Accelerated Approval Pathway.

- Drug Development Costs
- Manufacturing Costs
- Raw Material Costs
- Disease and Patient Demographics
- Distribution Costs

A plot of most frequently discussed cost factors in the respondent narratives has been provided, as under. It highlighted drug development costs as most prominent factor impacting the cost of drug products.

Figure 4.50
Most frequently mentioned cost factors in drug pricing



4. What could be possible measures by USFDA to contain inflated cost of drug products that have been approved through accelerated approval pathway?

The second question focused on the respondents' suggestions for how the USFDA could help control the rising costs of drug products. Although USFDA neither does directly control nor has much say in pricing endeavors of drug products, as these topics are at the helm of Sponsors or Manufacturers and distributors/ payers and largely with the Centre for Medicare and Medicaid Services (CMS). The USFDA can indirectly impact the prices of drugs by exercising a more stringent post-approval monitoring of drug products approved through Accelerated Approval Pathway. There is a forward-looking step that has been taken by US Federal Government in 2022 in the form of Inflation Reduction Act (IRA) that has given the US Health and Human Services (HHS), especially the Medicare, to do pricing negotiations with the Sponsor companies. Though, it is meant for a select drugs now, but this could bring a breakthrough for drugs that have been approved under the Accelerated Approval Pathway.

Responses received in lieu of this question were also analysed using NLP technique through Topic Modeling. Based on the responses received, several potential

measures were identified, ranging from price regulation strategies to more stringent post-approval monitoring. Below are some of the broad propositions suggested by the respondents. Some of them may not be practically possible for USFDA in the current regulatory environment, as they are not directly concerned with regulating costs of drug products in the US, but they may be recommendations of future, for which foundations are being laid down in the form of Inflation Reduction Act (IRA).

- Differential Pricing Based on Economic Status
- Disease-Based Pricing
- Competitive/Reference Pricing
- Adjusted Pricing During Accelerated Approval
- Technology-Based Pricing Adjustments

The respondents have also mentioned, discussed and recommended about various kinds of pricing models in their narratives that could help containing costs of drug products approved through Accelerated Approval Pathway. Some of these models are presented, as under.

Figure 4.51
Most discussed pricing models for regulating drug product costs

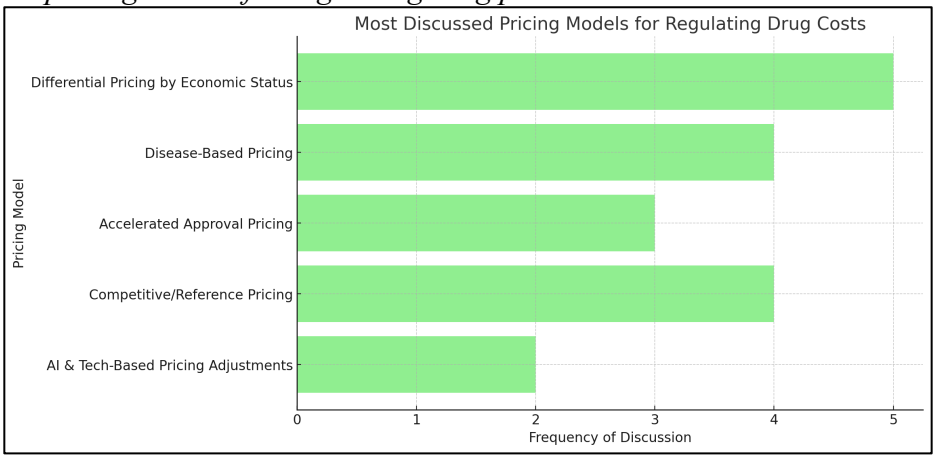
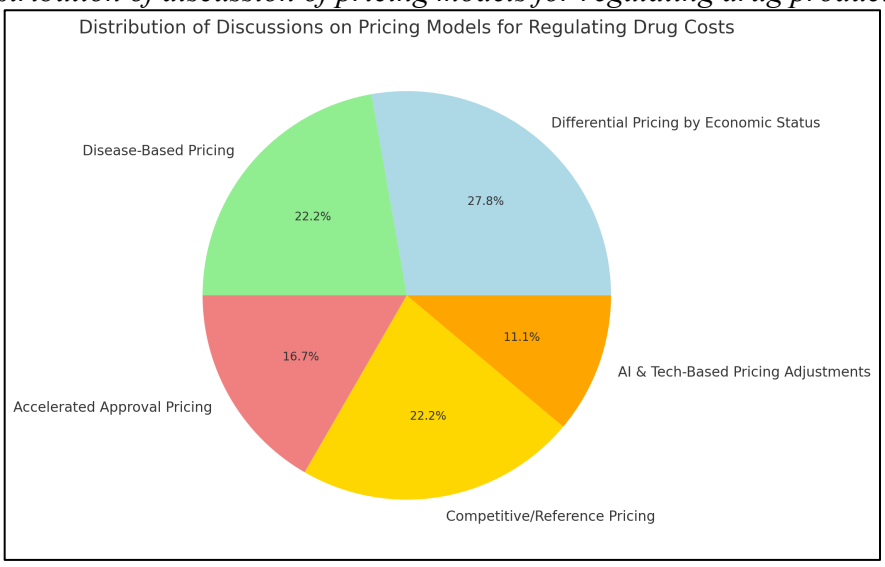


Figure 4.52
Percentage distribution of discussion of pricing models for regulating drug product costs



4.3 Summary of Findings

Research Question One: Time-boxing (mandatory confining of a time limit) of confirmatory clinical studies

Sub-questions with close-ended response options:

- On the questions of mandatory timeboxing and blanket timeboxing durations, responses were showing a strong agreement and mixed opinion, respectively, towards both the aspects. There was a weak correlation, with correlation coefficient of 0.28, between both the aspects, which showed that the respondents who who agree with timeboxing for confirmatory clinical studies are slightly more likely to also agree with having a blanket time-boxing duration.
- On the question of opinion on timeboxing for various variables, upon conducting a Chi-square test for assessment of independence of responses,

it was found out that the p-values for all the pairs are extremely low (significantly below 0.05), indicating that the responses to the different questions are not independent of each other. There is a significant association between responses to different questions. Responses to "Therapeutic Area" are significantly associated with responses to "Disease Area", "Patient Population", and "Patient Enrolment." Responses to "Disease Area" are significantly associated with responses to "Therapeutic Area", "Patient Population", and "Patient Enrolment." Responses to "Patient Population" are significantly associated with responses to "Therapeutic Area", "Disease Area", and "Patient Enrolment." Responses to "Patient Enrolment" are significantly associated with responses to "Therapeutic Area", "Disease Area", and "Patient Population." These associations suggest that respondents' opinions about time-boxing for different variables are closely related.

- Strength of these assocations were determined by Cramer's V test. Cramér's V values range from 0 to 1, where 0 indicates no association and 1 indicates a very strong association. Cramer's V values for different variables were - Therapeutic Area and Disease Area (Cramér's V = 0.76), Therapeutic Area and Patient Population (Cramér's V = 0.55), Disease Area and Patient Population (Cramér's V = 0.61), Disease Area and Patient Enrolment (Cramér's V = 0.43) and Patient Population and Patient Enrolment (Cramér's V = 0.65). These results indicate that respondents' opinions about time-boxing are closely related across different contexts, with some associations being particularly strong.

- On the question of probable duration of mandatory timeboxing for different variables, for Therapeutic Area, most common range was 3 to 5 years; for Disease Area, most common range was 1 to 3 years; for Patient Population, most common range was 3 to 5 years; for Patient Enrolment, most common range was 3 to 5 years. The Chi-square test performed on these variable results to see if there was an association between them. It was found out that there were strong connections between Therapeutic Area and Disease Area; Therapeutic Area and Patient Population; Therapeutic Area and Patient Enrolment; Disease Area and Patient Population; Disease Area and Patient Enrolment; and Patient Population and Patient Enrolment.
- These strong connections tell us that the time needed for one part of the study can predict the time needed for other parts. So, if we know it usually takes 3 to 5 years to complete studies in a particular therapeutic area, we can expect similar time frames for related disease areas, patient populations, and patient enrolment periods. In simple terms, if one part of the study takes a certain amount of time, other related parts will probably take the same amount of time. This helps us plan better and set realistic expectations for the overall time needed for clinical studies.

Sub-question with open-ended response options:

- For this question, Sentiment Analysis was performed to determine key trends in respondent feedback and uncover any underlying emotional patterns that could provide insights into the challenges, expectations, and experiences within this domain. This analysis systematically breaks down

the sentiment distribution and the topics associated with each sentiment category: **positive, neutral, and negative**.

- **Positive sentiment** accounted for 35% of the responses. The key topics that emerged from the positive responses revolved around impact, disease management, sponsorship, and the overall structure of clinical studies. These responses highlighted the beneficial aspects of time-boxing in clinical studies, with participants often appreciating the role of sponsors and the effectiveness of well-designed studies. Terms like "impact," "confirmatory," and "new" suggest that participants viewed the approach as bringing positive changes to clinical trials, particularly in areas such as study timelines, product development, and safety protocols. Key Words in Positive Sentiment Responses were: impact, disease, sponsor, clinical, studies, variables, timeboxing. These words indicate that positive responses focused on the constructive influence of time-boxing on clinical trial outcomes, sponsor involvement, and improved management of study timelines.
- **Neutral sentiment** was the most prevalent category, comprising 61% of the responses. The topics in neutral responses were generally descriptive and centered around clinical operations, patient needs, study protocols, and disease management. These responses tended to be more factual, with participants describing processes, challenges, and outcomes without strong emotional undertones. The focus here was on operational details, including patient enrollment, population variability, and the need for availability and proper protocol adherence. Key Words in Neutral Sentiment Responses were: clinical, patient, disease, need, population,

availability, studies. Neutral responses frequently described the logistics of clinical trials, such as patient demographics, population impacts, and study availability. These responses reflect a neutral tone, with the authors focusing on the procedural aspects of clinical studies rather than expressing personal opinions or emotions.

- **Negative sentiment** was the least common, making up only 4% of the responses. The negative responses predominantly expressed concerns about time constraints and industry challenges. The key issues raised included tight timelines, extra pressures, and difficulties associated with the overall structure of the studies. While these responses were few, they highlighted significant concerns related to the scheduling and operational efficiency of clinical studies. Key Words in Negative Sentiment Responses were: time, extra, industry, patient, tight, threatening. The primary focus of negative responses was on time pressures and threats to study efficacy, particularly in relation to tight deadlines and the additional stress placed on study participants and staff.

Research Question Two: Incentivization or penalization of Sponsors

Sub-questions with close-ended response options:

- On the question of excercising incentivization or penalization on Sponsors, majority of responses were clustered around Strongly Agree, Agree and Neutral options. There were very few which were revolving around Disagree or Strongly Disagree options. The analysis indicated that most respondents were in favor of providing incentives or penalizing sponsors based on the timely completion of confirmatory clinical studies.

This suggested a consensus that such measures could be beneficial in ensuring the timely completion of these studies.

- This question asked participants to express their level of agreement with different incentivization strategies, including, Exclusivity Provisions, Pricing Preferences, Review Acceleration, and Speedy Reimbursement Options. Most respondents either agreed or strongly agreed with the incentivization strategy of Exclusivity Provisions. For Pricing Preferences, responses were more varied, with many people feeling neutral and others agreeing or disagreeing. Review Acceleration had the highest agreement, with a significant number of respondents strongly agreeing. Similar to Exclusivity Provisions, most responses were either neutral or in agreement for Speedy Reimbursement Options. Correlation of different variables was evaluated. For instance, agreeing with one incentivization strategy often meant agreeing with others. The strongest positive correlation was between "Review Acceleration" and "Speedy Reimbursement Options," indicating that respondents who liked one often liked the other as well. It was evident from the results that respondents generally favored incentivization strategies, with "Review Acceleration" receiving the most support. There was a noticeable pattern where agreement with one strategy tended to correlate with agreement with others, especially between "Review Acceleration" and "Speedy Reimbursement Options."
- On the question of penalization options, respondents were supposed to respond to different options, like, Stringent Financial Penalties, Debarment, Review Delays of Subsequent Trials and Issuance of 483s. Many respondents agreed or strongly agreed to Stringent Financial

Penalties, indicating strong support for financial penalties as a form of penalization. For Debarment, the responses were mixed, with a significant number of neutral and disagree responses, suggesting some hesitance or opposition. Many agreed, but the presence of strong disagreement indicates a divided opinion on Review Delays of Subsequent Trials as a penalization strategy. For Issuance of 483s, similar to financial penalties, there is a general agreement, but with more neutral responses. Upon performing Chi-square test for understanding the association between variables, it was found out that the significant associations between responses to different penalization variables suggest that respondents who agree with one form of penalization are likely to agree with others. The strongest associations were observed between "Review Delays of Subsequent Trials" and "Issuance of 483s." It was broadly observed that respondents generally favored some form of penalization, particularly stringent financial penalties and issuance of 483s. There was a significant relationship between the different penalization strategies, indicating a consistency in respondents' attitudes towards penalization.

Sub-questions with open-ended response options:

- On the question of recommendations for more incentivization options, respondents suggested that providing priority in reviews could be a strong motivator for sponsors. If sponsors conduct their trials on time, USFDA could fast-track their future studies for approval. Additionally, granting exclusivity rights to sponsors could incentivize them to complete trials quickly. This exclusivity could be in the form of market advantages, ensuring that sponsors who meet deadlines have a competitive edge. Key

themes that were identified were - prioritizing the review process for future trials, granting market exclusivity for future studies, enhancing the sponsor's credibility by providing clinical provisions for future opportunities. A recurring theme was the idea of accelerated approvals. Respondents believed that if sponsors conduct their clinical trials efficiently, they should benefit from quicker regulatory approvals. In addition, sponsors should be encouraged to work faster by improving their data submission processes. The respondents noted that streamlining clinical trials and data collection would not only help sponsors meet deadlines but also boost their chances of receiving quicker approvals from regulatory bodies. Key themes that were identified were - accelerated approval processes for timely trials, faster clinical trial timelines, streamlined and quicker data submissions. The final incentive-based theme revolves around recognition and market advantages. Participants suggested that sponsors who complete their trials on time should be recognized for their efforts. This could take the form of priority vouchers or public acknowledgment in the market. Moreover, respondents mentioned the importance of a speedy review process for future submissions, which would reward sponsors who consistently meet their timelines. Key themes identified were - recognizing sponsors with priority vouchers or other forms of acknowledgment, market recognition for timely submissions, speedy review processes for future submissions.

- On the question of recommendations for penalization of Sponsors, a significant theme identified by respondents was that sponsors who delay their clinical trials should face severe consequences, such as the

withdrawal of their approval. USFDA should ensure that there is a system in place to review trial results and enforce penalties if deadlines are not met. Respondents emphasized the importance of clinical requirements being followed, with penalties being imposed if these are not met within the stipulated time. Key themes identified were - delayed trials should result in penalties, withdrawal of approval for failing to meet clinical trial deadlines and thorough review of results to ensure compliance with clinical requirements. Participants indicated that there should be strong involvement from the FDA when sponsors fail to conduct trials on time. This could include holding approvals for future submissions or even debarment from future trials. Respondents also mentioned the withdrawal of a sponsor's rights, ensuring that sponsors face consequences if they do not uphold their responsibilities in a timely manner. Key themes identified were - strong FDA involvement to ensure compliance, holding or withdrawing approvals for future studies and debarment from future trials due to non-compliance. The final penalty-related theme focused on financial consequences and product recalls. Respondents recommended that sponsors who fail to conduct their trials within the required timelines should face financial penalties. This could include fines or even the recall of products that have not undergone proper clinical testing. In addition, there should be strict enforcement actions to ensure that sponsors understand the gravity of delaying trials. Key themes identified were - financial penalties for delayed trials, product recalls due to non-compliance with timelines and enforcement actions to ensure timely completion of clinical trials.

Research Question Three: Drug Product Label Modifications

Sub-questions with close-ended response options:

- In first question, an opinion was sought around having a differentiated label/ prescribing infomration for drug products having approval through Accelerated Approval Pathway and, in the second question, opinion was sought whether key details pertaining to accelerated approval should appear distinctly on a drug product label/ prescribing information. In responses for both the questions, majority of respondents affirmed with either agreeing or strongly agreeing to these statements, indicating strong agreement with the statements in both questions. A smaller number of respondents selected ratings of Disagree, Strongly Disagree or Neutral, showing less disagreement or neutrality. There is a strong positive correlation (0.74) between the responses to the two questions. This suggests that respondents who agree with one statement are likely to agree with the other and respondents opinions on these questions are closely aligned. Upon conducting a paired sample T-test to determine if the mean responses differ significantly between the two questions, the T-statistic came out to be 0.172 and p-value came out to be 0.864. The p-value is much higher than the typical significance level of 0.05, indicating that there is no significant difference between the mean responses to the two questions. This suggests that respondents have similar levels of agreement with both statements.
- This next question was a categorical question in which responses were sought for some of the identified variables, viz. Approval Pathway,

Surrogate Marker Details, Clinical Study Timeline, Approval in Other Countries and Post-Approval Commitments that could be displayed on the label/ prescribing information of a drug product that has been granted accelerated approval. For Approval pathway, there seemed to be a very strong agreement towards inclusion of it on the labels/ prescribing information. A similar response was obtained from respondents in the form of strong agreement, at large, and neutrality as well for Surrogate Marker Details. For Clinical Study Timeline as one of the variable, there was again a strong inclination of respondents towards agreement and neutrality, but there was a slight push back in the form of disagreement as well. Approval in Other Countries was voted for positively by a great deal of respondents, but there was some degree of neutrality and some negative connotation as well. A similar case was there for Post-approval Commitments as that of Approval in Other Countries, as there was a positive environment for it, but with some neutrality and bit of disagreement. A Chi-square test was also performed which indicated there were significant associations between almost all pairs of questions, as indicated by the low p-values (all below 0.05). This suggested that respondents' opinions on one aspect (e.g., "Approval Pathway") are strongly linked to their opinions on other aspects (e.g., "Surrogate Marker Details"). The strongest associations (very low p-values) are observed between "Approval Pathway" and "Clinical Study Timeline" (p-value ≈ 1.2e-08) and "Clinical Study Timeline" and "Post-Approval Commitments" (p-value ≈ 2.5e-07). Even there were also least significant associations (still below 0.05) observed such as between "Approval

Pathway" and "Approval in Other Countries" (p-value ≈ 0.0093), which indicated non-independence, meaning opinions on these aspects are not formed in isolation.

Sub-questions with open-ended response options:

- This open-ended question sought and analyzed responses from individuals who provided suggestions for additional variables that could be included on the label or prescription information of a drug product that has been granted approval through the accelerated approval pathway. Using topic modeling (LDA) and word cloud visualizations, key themes and patterns were identified in their suggestions. There were five key themes identified. The first theme was **Approval Process and Criteria**. The keywords cited in the responses for this theme were - approval, pathway, product, date, criteria. In their respones, respondents emphasized the importance of transparency in the approval process, particularly for drugs that have gone through the accelerated approval pathway. They suggested that the drug label should clearly include information about the specific approval criteria, the date of approval, and the pathway followed for approval. Suggested variables from these responses were - Criteria used for approval, Details on whether the drug followed an accelerated approval process and Specific dates related to approval. The second theme identified was **Risks and Side Effects**. The keywords cited in the responses for this theme were - risk, effects, possible, add, black-box. This theme highlighted a significant concern about potential risks and side effects associated with the drugs. Respondents recommended that the

labels should provide detailed information on all possible side effects, as well as the risks involved in taking the drug. Some also suggested that certain drugs should include black-box warnings to alert prescribers and patients to severe risks. Suggested variables from these responses were - Detailed descriptions of potential side effects, Clear risk factors related to the drug and Black-box warnings for high-risk drugs. The third theme identified was **Benefits and Efficacy**. The keywords cited in the responses for this theme were - benefit, drug, accelerated, effective. Respondents suggested that drug labels should clearly communicate the benefits of the drug, especially in cases where the drug has been granted accelerated approval. They want to know how the drug helps patients and how effective it is, particularly when the approval process may have been expedited. Suggested variables from these responses were - Clear benefits of taking the drug, Information about how effective the drug is in patients and Justification for why the drug was approved under the accelerated process. The fourth theme identified was **Study Outcomes and Efficacy Measures**. The keywords cited in the responses for this theme were - outcome, efficacy, results, data. Another common suggestion was to include detailed information about the outcomes of clinical studies. Respondents felt that drug labels should show how efficacy was measured, as well as the results from any clinical trials or studies that led to the drug's approval. Suggested variables from these responses were - Outcome measures from clinical trials, Data on how efficacy was determined and Comparison of results to alternative treatments. The fifth theme identified was **Patient Information and Eligibility**. The keywords cited in the

responses for this theme were - patients, eligibility, label, approval. The final theme focused on patient-specific information. Respondents suggested that labels should include clear guidance on which patient groups are eligible for the drug, as well as any restrictions on who can use the drug safely. This includes information about how the drug affects different groups of patients. Suggested variables from these responses were - Eligibility criteria for specific patient groups, Information on which populations should avoid the drug and Guidance on how approval affects specific patient categories.

Research Question Four: Checks and Balances of Drug Product Costs

Sub-questions with close-ended response options:

- The first question was directed towards seeking the views of respondents if there was a need to rationalize the cost of drug products that have been granted accelerated approvals. A significant portion of respondents (nearly 60%) chose either Agree or Strongly Agree as the options, indicating that most respondents endorsed the idea of rationalizing the costs of drug products that have been granted accelerated approvals. The mean response was 3.63, reinforcing the trend towards agreement. The median response was 4, suggesting that the central tendency among participants was towards agreement rather than neutrality or disagreement. About 23.53% of the respondents chose Neutral, which indicated a moderate level of agreement or neutrality. This showed that while there was strong support for rationalizing drug costs, there was also a notable segment that might be more cautious or undecided. Only 7.84% and 9.80% of participants chose

Strongly Disagree and Disagree, respectively. This indicated that very few respondents disagree with the need for cost rationalization. The mode of the responses was 4, meaning that the most common sentiment among participants was one of agreement with the statement. This supported the overall finding that there was a strong inclination towards rationalizing drug costs among the respondents.

- The second question was directed towards seeking a consensus on the identified variables that could be drivers of cost decisions of drug products that have been granted accelerated approval. The identified variables were - Therapeutic Area, Indication of Use, Disease Condition, Patient Population and Development costs. Chi-square test and Cramer's V test were performed on the responses so obtained to understand the association between the variables and the strength of this association respectively. All tested pairs of variables showed significant associations, as indicated by p-values well below 0.05. This meant that these variables were not independent of each other and had meaningful relationships. Cramer's V values indicated that there was a strong association between Therapeutic Area vs Indication of Use, Therapeutic Area vs Disease Condition, Indication of Use vs Disease Condition, while there was a moderate association between Therapeutic Area vs Patient Population, Therapeutic Area vs Development Costs, Indication of Use vs Patient Population, Indication of Use vs Development Costs, Disease Condition vs Patient Population, Disease Condition vs Development Costs and Patient Population vs Development Costs.

Sub-questions with open-ended response options:

- The third question was an open-ended question and was asking for recommendations around variables that could impact the costs of drugs that have been approved through Accelerated Approval Pathway. Responses obtained were analyzed using NLP technique - Topic Modeling (by using LDA). Respondents identified a range of variables that significantly impact the cost of drug products. These variables included both internal factors (such as manufacturing and development costs) and external factors (like market demand and patient economic status). From the responses, first such identified variable was **Drug Development Costs**. It was put forth as a variable as part of this question and has been reinforced by the respondents as well in their responses. The most frequently mentioned variable was the cost of drug development. Respondents pointed out that the research and development (R&D) process, especially for innovative treatments like gene therapies and personalized medicine, was both lengthy and expensive. The accelerated approval pathway often allows drugs to enter the market before full clinical trials are completed, which can expedite patient access but also means that the upfront costs of development need to be recovered faster. This pressure results in higher drug prices. Another crucial variable highlighted by respondents was the **Manufacturing Cost**. This includes the costs related to the production process, raw material procurement, and maintaining stringent manufacturing conditions (such as temperature control and stability testing). Drugs that require complex production processes, such as biologics, are naturally more expensive to manufacture,

contributing to higher overall costs. Additionally, the cost of ensuring that drugs meet regulatory standards during manufacturing adds to the final price. Several respondents mentioned the **Costs of Raw Materials** as a key variable. The availability, quality, and cost of these materials directly influence the overall cost of producing a drug. The global supply chain, especially during crises like the COVID-19 pandemic, can significantly affect the cost of raw materials. When certain materials become scarce, prices rise, which leads to an increase in drug prices. Also, there are raw materials which are specialized and noble components, that add to the costs of drugs. **Disease and Patient Demographics** were yet other variables pointed out by the respondents. A more nuanced approach suggested by some respondents was to tie the cost of a drug to the type of disease and the economic status of the patient population. Drugs that treat life-saving conditions, such as cancer or genetic diseases, are often priced much higher than those for lifestyle conditions. Respondents suggested that the pricing model should be adjusted based on the critical nature of the disease and the ability of the patient to afford the treatment. Finally, **Distribution Costs** were mentioned as another important factor. This includes logistics, transportation, and storage, especially for drugs that require cold storage or other special handling. Distribution adds another layer of expense to the overall cost of a drug. Respondents noted that ensuring equitable access to drugs across various regions increases costs, particularly for drugs that require careful handling during transit.

- The fourth question revolves around seeking recommendations on possible measures by USFDA to contain inflated cost of drug products that have

been approved through accelerated approval pathway. It was also analysed using NLP technique - Topic Modeling (by using LDA). As highlighted above in the “Results” section of this question, USFDA is not a direct stakeholder to control the costs of drug products. The Sponsors, manufacturers, payers and insurance agencies are the ones to decide and agree on the costs of drug products. There are other agencies, like, Centre for Medicare and Medicaid Services (CMS) and Federal Trade Commission (FTC) who are involved in monitoring and compliance of justified and fair pricing of drug products. The USFDA; however, could indirectly help in rationalizing the costs by exercising some initiatives in its own jurisdiction, viz. related to drug development, compliance and so on. This question focused on the respondents' suggestions for how the USFDA could facilitate control the rising costs of drug products. Several potential measures were identified, ranging from price regulation strategies to more stringent post-approval monitoring. From the responses, the first key measure identified was **Differential Pricing Based on Economic Status**. This key suggestion was of differential pricing based on the economic status of patients. This approach allowed for more flexible pricing that adjusted to the patient's financial capacity, ensuring broader access to essential drugs. The idea was to create a pricing structure that makes expensive treatments like gene therapy more accessible to low-income patients without discouraging innovation or investment in drug development. Second such measure identified was **Disease-Based Pricing**. Respondents suggested that the agencies should consider disease-based pricing, where the price of a drug is based on the

critical nature of the condition it treats. Life-saving drugs should be priced differently than drugs that treat lifestyle conditions. This would allow patients who need urgent treatment to access it at a more reasonable cost while allowing other drugs to be priced according to their demand and urgency. The third option suggested was to have a **Competitive/ Reference Pricing**. This suggested measure was for the implementation of competitive pricing based on reference prices from similar treatments. This would ensure that drug prices remain competitive and fair across the market. By comparing the prices of newly approved drugs to those of existing treatments, the agencies could set a benchmark that prevents inflated pricing. This approach encourages competition among pharmaceutical companies and can drive down prices. The fourth suggestion emerged out of the responses was **Adjusted Pricing During Accelerated Approval**. Respondents also emphasized the need for adjusted pricing during the accelerated approval process. Prices should be set in a way that ensures patients can access drugs without pharmaceutical companies benefiting excessively before confirmatory evidence is established. The accelerated approval pathway allows drugs to be sold before all clinical trials are completed. While this speeds up access, it also poses the risk of high prices without full proof of efficacy. Adjusting prices during this period could balance access with fair pricing. The fifth suggestion evolved out of the responses was **Technology-Based Pricing Adjustments**. With advancements in Artificial Intelligence and Machine Learning, respondents suggested that the agencies should encourage pricing adjustments that reflect the reduced costs associated with these

technologies. Along with other relevant agencies, the USFDA should also try to best leverage these technological advancements in drug research and development approaches, manufacturing, regulatory submissions and maintaining compliance throughout the lifecycle of drug products. If a pharmaceutical company has successfully reduced its development costs through technology, these savings should be passed on to the patient. This would incentivize innovation while also ensuring that patients benefit from reduced prices.

4.4 Conclusion

It can be implied that the results and the analysis of all the four research questions have been able to successfully aligned with the expectations that were envisaged while jotting down this research proposal.

Research Question 1 – Timeboxing of Confirmatory Clinical Trials:

It can be quite well understood through the responses received and the analysis performed that timeboxing holds the key in good conductance of clinical trials and prove be an important torchbearer for early patient access of drugs with utmost safety, efficacy and quality profiles. The recommendations so received are optimistic and forward-looking. This sentiment analysis revealed that the majority of participant responses to time-boxing in clinical studies were neutral, with a substantial portion expressing positive sentiment. The few negative responses highlighted concerns related to time management and industry practices. Positive sentiment was closely associated with the impact of time-boxing, sponsor involvement, and disease management, suggesting that participants recognized the value of structured time management in clinical trials. Neutral responses were more focused on the technical and procedural aspects of clinical studies, while

negative responses brought attention to the challenges and pressures involved in adhering to strict timelines.

Overall, the findings of this sentiment analysis provide valuable insights into how participants perceive the process of time-boxing in clinical studies. The largely neutral and positive sentiment indicates that time-boxing is seen as an effective strategy for managing clinical trials, although some concerns remain, particularly around time constraints and industry demands.

Research Question 2 – Incentivization and Penalization of Sponsors:

The findings from this analysis suggest that respondents believe both incentives and penalties play a crucial role in ensuring that sponsors conduct their clinical trials on time. By offering prioritization in review processes, market exclusivity, and public recognition, sponsors are motivated to complete their trials efficiently. On the other hand, financial penalties, FDA involvement, and the withdrawal of approvals serve as strong deterrents for sponsors who fail to meet their obligations. This results highlighted the key factors that could help improve the timeliness of clinical trials, ensuring that sponsors are held accountable for their responsibilities while also being rewarded for their efficiency. The insights provided here can help regulatory bodies and sponsors alike in fostering a more effective and compliant clinical trial process.

Research Question 3 – Drug Product Label Modifications:

Overall, the responses received from the respondents are indicative of a positive perception of modifications proposed on the labels/ prescribing informations. The suggestions provided by respondents reflect a deep concern for safety, transparency, and effectiveness when it comes to drug labeling. People want to see clear, evidence-based information on risks, benefits, and outcomes, as well as specific guidance for patients. These insights can guide improvements in drug labeling to better inform both patients

and healthcare providers, ensuring safer and more effective use of drugs that have been granted accelerated approval.

Research Question 4 – Checks and Balances of Drug Product Costs:

Costs of drug products always hold the key in better patient access. This becomes all the way important when the drug products are of the stature where their full safety, efficacy and quality profiles are yet being subjected to evaluation and these drug products in commercial value chain are the result of their interim analysis. This analysis reveals that respondents identified a wide range of variables and measures that could help regulate drug prices. From the cost of drug development and manufacturing to innovative pricing models, there are several opportunities for the USFDA, other agencies and policymakers to intervene and help contain the costs of life-saving treatments. The insights gathered here point toward flexible pricing models, better regulation during the accelerated approval process, and the potential for technology-driven cost reductions as essential strategies for the future. By focusing on these core suggestions and addressing the key cost drivers, there is significant potential to create a more equitable and sustainable pricing environment for both patients and pharmaceutical companies.

CHAPTER V:

DISCUSSION

5.1 Discussion of Results

The results obtained from this research reflect an optimism on the identified research questions and help laying down a landscape and setting up a basic framework for implementation of recommendations. The pointers highlighted in the outcomes of each of the research question are being discussed in a bit of details, as under.

5.2 Discussion of Research Question One: Timeboxing of Confirmatory Clinical Trials

Timeboxing of confirmatory clinical trials has been considered as a first step in help realizing the ultimate objective of Accelerated Approval Pathway, i.e. early, safe, efficacious and quality patient access of new Oncology treatment modalities. Though, there are existing regulations around timeboxing of clinical trials and declaration of duration in which a confirmatory clinical would take place, post grant of an accelerated approval, but these seem to be circumvented many a times. Hence, a reinforcement of it is the need of the hour.

A blanket timeboxing duration has not been so well accepted by majority of the respondents. They seem to be a bit more cautious in placing a blanket timeboxing duration on cards. This may be due to the reason that every clinical trial has its own dynamics, with respect to disease area or therapeutic area, availability of patient population, demographics of patient population, scale of clinical trial, phase of clinical trial, etc., and these dynamics make every clinical trial to be assessed through a fresh pair of eyes. Hence, it may not be prudent to confine every clinical trial under the same timeboxing criteria.

For different identified variables, viz., Therapeutic Area, Disease Area, Patient Population and Patient Enrolment, there seems to be a healthy agreement and consensus

on having different timeboxing for different variables. This does make a perfect sense as well, as these are the important dynamics of clinical trials and these play a crucial role in smooth conductance and timely completion of a clinical trial.

Overall, for all the identfied variables, a generic timeboxing range of 3 to 5 years for all clinical trials is an acceptable timeframe for most of the respondents. It is also a reasonable timeframe as well, since on an average, most of the clinical trials, irrespective of their disease area or therapeutic area, availability of patient population, demographics of patient population, scale of clinical trial, phase of clinical trial, etc., trials could be rendered complete.

There are some other pertinent variables that have been put forth by the respondents that may have an impact on timeboxing of confirmatory clinical trials. Some of them are – Geography and demograhic conditions, Patient drop out, Design issues, Collaborative research, M&A scenarios, Finding suitable investigator and eligible sites, utilizing Real World Evidence (RWE), Emerging alternative therapeutic options, Emerging technologies, like, Cell and Gene Therapy and utilization of AI and ML techniques and Market dynamics.

In addtion to it, there are some interesting responses that have been put forth by some of the respondents that provide a forward-looking viewpoint in conductance of clincal trials. Some of them are:

- *"I believe that the variables depend entirely on the type of uncertainty that needs to be addressed in confirmatory trials. In fact, this applies to my answers in items 3 and 4 as well - there is no multiple choice answer. Biology should lead the way."*
- *"Prevalence of Disease (higher burden should mandate timeboxing), CD and NCD (non-Communicable Disease) because not enough research is*

happening in NCD space (e.g. AMR) so some laxity to encourage sponsor maybe required, Emerging Technologies (Cell & Gene, AI,ML)."

- *"This must be based on practical time bound approach with some extra time to allow industry some flexibility and ensure that the timeline is not too tight that will make things fail. Also the Industry should be allowed to request some extra time which is not more than 6 months."*
- *"Confirmatory clinical studies' protocol should be integrated with the protocol for clinical studies that form the basis of approval. Alternatively, RWE based protocols should be integrated at the time of approval and findings should be filed annually."*

5.3 Discussion of Research Question Two: Incentivization or Penalization of Sponsors

Incentivization or penalization of Sponsors for diligently completing or not diligently completing confirmatory clinical studies, post granting of accelerated approval, respectively seem to have been agreed upon as viable options to realize the benefits of Accelerated Approval Pathway. While, there have been not many visible and documented efforts by health agencies in the US for incentivizing diligent Sponsors, but they have been pulling up Sponsors for not being able to meet the deadlines of confirmatory clinical trials. There are incremental regulations that have been put in place, as to seek a confirmation from Sponsors in their trial protocols about time limits of confirmatory clinical studies. Sometimes the Sponsors tend to abide by these timelines and many a times not. This is the area to ponder on to make AAP a continued success.

Incentivization as a forward-looking approach has been quite well aceepted by majority of respondents, as most of them have provided an agreement to the provided variables of Exclusivity Provisions, Pricing Preferences, Review Acceleration and Speedy Reimbursement Options. Amongst all of them, Review Acceleration tops the

chart with Exclusivity Provisions and Speedy Reimbursement Options to follow. Such responses could be due to the thought that Sponsors, if incentivized, would be motivated to diligently and steadfastedly complete the confirmatory clinical trials for the drugs approved through Accelerated Approval Pathway.

From the responses, Penalization as a stick for Sponsors could be construed as a mixed bag of reactions for the identified variables of Stringent Financial Penalties, Debarment, Review Delays of Subsequent Trials and Issuance of 483s. While there has not been a straighforward agreement towards penalization as an option, there seem to be quite big degree of endorsements for Review Delays of Subsequent Trials, Issuance of 483s and Stringent Financial Penalties. It is also interesting to see Neutrality as a big choice for all the variable options. Such respondents could be considered as a population who takes informed decision and could make a shift on either of the sides, per their situational wisdom.

For incentivization, there are some additional variables that have been discussed by the respondents. These are – FDA Priority Voucher Program, Public recognition by USFDA, Exclusivity extension, Introduction of safety logo on Labels of drugs which swiftly complete the confirmatory clinical studies, Expediting clinical protocol reviews, New tax credit or repurposing a part of the existing research-and-development tax credit, Extending patient recruitment assistance and Prioritize FDA meeting with Sponsor.

For incentivization, there are some interesting statements that have appeared in the responses, which may pave further way for incentivization. Some of them are, as under:

- *"Depending on the classification of a new drug i.e. Orphan status or advanced therapy, the Sponsor may be incentivized with FDA priority voucher program. Generally this incentive encourages the Sponsor to*

further develop new drugs in a given Therapeutic/ disease areas of their expertise. I am in favor of non-financial incentives granted by FDA that may benefit the Sponsor to bring their drug early to the market and expand patient reach than setting exorbitant prices that are generally out of reach for many patients."

- *"No incentivization other than allowing practical time bound approach + provision to request an extra upto 6 months grace period. The sponsor is already incentivized due to the accelerated approval and having some risk for the patients."*
- *"Financial penalties and acceleration of reviews are strong stick and carrots to enable the completion of studies. The financial penalty should not be one time and should be significant if the sponsor continues to delay trial for unspecified and/oir unwarranted reasons."*
- *"Accelerated approval pathway is a good way to incentivize the sponsor. Agencies should maintain a safety Logo and allow sponsors to print it on their labels which will make their reputation among healthcare providers and patients this will help to sell the most safe drugs and will motivate another sponsors to try to get it by performing clinical studies."*
- *"Overall approach to accelerated approvals should be updated to ensure that confirmatory clinical studies or RWE protocols are integrated with original clinical protocols. This way, status of these studies should be published on public platforms to bring more transparency to the prescribers and patients."*

For Penalization, there are additional inputs shared by the respondents that may serve as variables to penalize the Sponsors who do not comply to the confirmatory

clinical trial timelines. These are – Legal action, Enforce product recalls, Fee hike for next reviews, Increase tax liability and Reduce R&D incentives,

For penalization as well, there were some great ideas that have been put in place by the respondents which could lead to further future deliberations. Some of these are:

- *"FDA may consider Legal action i.e. imposing debarment combined with monetary penalties that prevent the Sponsor to market the drug until the fulfillment of Sponsor's commitments in a timely manner. FDA should be given legal authority to regulate prices (currently not the case) and if the Sponsor fails to the time-bound commitments, FDA should also have the authority to penalize the Sponsor by cutting drug prices of the drug in market."*
- *"Medicare and Medicaid should not be allowed to pay more than a fixed amount for such products if they fail to meet their timelines as a result of poor diligence or deliberate delays. This amount could be set by Congress and be just enough to cover costs but not enough to offer substantial return."*
- *"Publish the sponsor details on the website and ensure the repeated offenders get impacted with the affiliation."*
- *"Sponsor should provide explanation why he is not abiding and if reason is not acceptable, some kind of non-compliance certificate (not equivalent to 483), which can be displayed on Regulatory agency's website. In addition, sponsor should give timelines in agreement with Regulatory to complete the confirmatory clinical trials."*

- *"Reduce R&D incentives, including strict construal clauses in agreement for non-compliance, enabling public disclosure for failure to conclude confirmatory trials"*

5.4 Discussion of Research Question Three: Drug Product Label Modifications

The option of Differentiated label/ prescribing information for products granted an accelerated approval has been overwhelmingly welcomed by the respondents.

Similarly, the idea of having a highlighted drug product label/ prescribing information for drug products with accelerated approvals has been very well accepted by the respondents, as a big chunk of them agree to it.

At this point in time, the labels/ prescribing informations of such products are treated as routine artefacts, with a minimal information appearing about the accelerated status of the product on them. In order for a better stakeholder visibility and transparency, at large, there should be a preferential labeling of such products so that patients and healthcare providers would be able to conspicously make out for such products and take much better informed decisions.

When it comes to the display of identified discrete variables out of Approval Pathway (Traditional or Accelerated), Surrogate Marker details, Tentative Confirmatory Clinical Study Timeline, Approval in other countries and Post-approval Commitments on the label/ precribing information of drug products that have been granted accelerated approvals, there is largely a positive consnesus in the responses to have them. Respondents agree to have all of them on the labels/ prescribing informations. Currently, information pertaining to approval pathway and surrogate markers tend to make it to the labels/ prscribing information, but that too not in a conspicuous or highlighted manner. The other artefacts do not make it to the labels. This positive sentiment may be due to the

fact that respondents do intend to see more transparent information dissemination, which would help making the patients and healthcare provider better informed decisions.

Per the respondents, the other variables that may be important to appear on the labels/ prescribing informations could be – Potential risks and uncertainties associated with the use of the drug, Disclaimers like especially for X population, Information regarding other similar approved drugs for this unmet need, A Safety Logo as to what is the safety rating of the drug, QR Code which takes to an easy explainable video for the layman and Enrollment information for ongoing trials so that eligible patients can participate/enrol.

In addition to above, there are some suggestions/ statements that have been made by the respondents which could act as futuristic pathbreakers.

- *"FDA already mandates a black-box warning warranting the Sponsor to clearly mention any safety concerns associated with drug. The label should also include the approval pathway (accelerated approval conditions and limitations) for transparency to both the Prescribers and users clearly mentioning the limited clinical experience of the drug and caution the prescribers to carefully assess the data presented in the label and advice their patients objectively the benefits and risks associated with the drug."*
- *"Potential risks and uncertainties associated with the use of the drug that are specifically called out due to AAP approach."*
- *"It should include clear language understandable to lay persons that drugs under accelerated approval have not yet shown a clinically meaningful benefit, that the approval is entirely based on the expectation that they will provide such a benefit, and that approval may be withdrawn*

if no benefit is demonstrated. It should also describe potential risks of the product not delivering on the expected clinical benefit."

- *"Few disclaimers like especially for X population"*
- *"Category to include previously approved drug compounds in similar class of mechanism of action, as the drug being submitted for accelerated approval."*
- *"As proposed a safety (or similar) Logo should be assigned and Publich should be aware that medicines containing these label are safest."*
- *"QR Code which takes to an easy explainable video for the layman."*
- *"Enrollment information for ongoing trials so that eligible patients can participate/ enrol."*

5.5 Discussion of Research Question Four: Checks and Balances of Drug Product Costs

Question on need for rationalization of costs of drug products that have been approved through accelerated approvals has been largely affirmatively responded by the respondents. There is some degree of Neutrality in the response, which indicates that there are some respondents who prefer to sit at the sidelines and would take an informed call, based on the current outcomes. There are very few responses who are not aligned with this thought.

Out of the suggested variables of Therapeutic Area, Indication of Use, Disease Condition, Patient Population and Development Costs, which could be important in deciding about the costs of such products, largely a consensus is there in the responses for all of them to be decisive factors for costs. Development Costs is the leading factor that seem to have most impact on the costs of drug products. Next in the fray are Disease Condition and Indication of Use. For sure, research and development costs would have a greatest impact on the overall costs of the drug products – this will be all the way

important for products which have seen the light of the day through Accelerated Approval Pathway. The Sponsors would spend a big buck on bringing such drugs to the market and they would like to reap in the money spent as soon as possible. Hence, the costs of such drugs would always remain high owing to the high R&D costs.

Based upon the responses received, below have been pitted as the most favorable variables that would impact the costs of drug products that have been granted accelerated approvals – Geriatric and pediatric populations, Differential pricing based on patient economic status, Manufacturing costs, Complex manufacturing processes, Prices of alternative treatment options/ Competition or reference pricing, Leveraging emerging technologies, like, AI, ML, NLP, etc., Other third party or gevernment reimbursements, Combination therapy and Health Economic/ Technology Assessments of disease areas.

Below are certain conspicuous statements made in the responses by the respondents that might serve as food for thought for next level work in this area.

- *"Disease prevalence and economic status of the patient population. Many life-saving drugs that have emerged in the recent past are highly specialized (cell and gene therapy, personalized medicine etc.) that are priced exorbitantly. This discourages the patients who are unable to afford such costly medicines. A differential pricing based on the economic status of patients may be a good option for cost-containment. Another factor is the type of disease i.e. life-saving vs. lifestyle improvement. As an example many of the Oncology products if not all are life-saving whereas, chronic weight management (obesity), smoking, alcohol, substance addiction, stress etc. are life-style disorders. A differential pricing of drugs distinguishing between the type of diseases is another way to keeping a check on inflated prices of drug products."*

- *"Manufacturing costs (Challenges in raw material procurement, complex manufacturing process, stringent storage conditions, stability issues)"*
- *"Emerging technologies like AI, ML, NLP holds promise to bring down the timeline and cost of drug development. So Regulatory Authority should evaluate if these gains have been achieved by the Sponsor, then it should reflect in the pricing so that the benefits are passed on to the patient and patient family."*
- *"Combination therapy including other approved drug from different mechanism of action as the currently evaluated monotherapy."*
- *"Other treatment choices available, health economics assessment of disease areas, country wise affordability standards"*

In the US, currently, the USFDA itself does not have the jurisdiction to regulate the prices of the drug products. These are prerogatives of other bodies/ agencies, viz. Centre for Medicare and Medicaid Services (CMS) and Federal Trade Commission (FTC). The respondents have highlighted these limitations and tried to put forth some measures that USFDA could directly or indirectly exercise to help contain costs of drug products. Some of them are – Grouping of products on the basis of indications or type of drug applications, Government grants or subsidies, Strong post-approval monitoring, Value-based pricing agreement for payers, Enhanced promulgation of Patient Support Programs, Narrowing the use of drugs to only areas that evidence to support it exists and withdraw approval if no evidence is forthcoming, Promote adoption of emerging technologies such as AI, ML, NLP, Digital innovation and HA's pathway to accept these tools, Collaboration of USFDA and Industry to rationalize the costs, Having a public list of costs of drugs available for similar disease or indication to have a healthy comparison, Price approval along with the initial approval of application and Outcomes based pricing.

Some of the respondents have made some interesting recommendations for USFDA and other agencies involved to contain the prices of drugs. Some of these are:

- *"Grouping by seeing the commonalities like indications, type of drug product application (like Orphan drug/ Gene therapy etc.)"*
- *"Strong post-approval monitoring of drug products approved through the accelerated approval pathway to ensure that manufacturers adhere to pricing commitments, also through promoting value based pricing agreements for payers."*
- *"Currently, FDA has no legal authority to investigate or control the prices set by manufacturers, distributors and retailers. When the Sponsor is incentivized by FDA with direct and indirect financial benefits, the Sponsor has the moral responsibility to position the drug in market at a reasonable price. This will encourage the Pharmacy Business Management (PBM) companies in collaboration with Health Insurance companies who offer Prescription plans to subsidize the cost passed on to the patients. Additionally, if USFDA encourages multiple innovative therapies for a particular disease, the market competition between the manufacturers will contain inflated drug prices to a certain extent. Furthermore, patients should be offered 'patient-support programs' by the Sponsor to take advantage of using their drug on a continuous basis depending on duration of therapy. i.e. Sponsors to build user loyalty of their brand that may guarantee steady-stream revenue and curtail higher prices."*
- *"FDA does not have a mandate to consider costs. They do have a mandate to ensure that confirmatory evidence is generated in a timely manner and*

according to the same standard as traditionally approved drugs. When drugs do not meet that standard, FDA should consider narrowing their use to only areas that evidence to support it exists and withdraw approval if no evidence is forthcoming."

- *"Nudge adoption of emerging technologies such as AI, ML, NLP so that Sponsors can radically transform the traditional drug development model to bring in efficiencies around timeline and cost."*
- *"Reduce the application fee"*
- *"I think the only way to bring down the cost of drugs is through use of innovative approaches and bring down of cost of development and approval. To enable that, lot of work needs to be done on digital innovation and HA's pathway to accept these tools."*
- *"Price point is critical to make the drug available to most needy patient waiting for new drug. Pharma and regulatory authority have to collaborate to rationalize the cost with best interest of the patient in mind."*
- *"Making public list of company prices offered after approval for similar drugs, showing dynamic variables that determine the market penetration and patient benenfit from the brand since approval e.g. no. patients treated, patient populations, countries in which compound was provided approval etc."*
- *"USFDA should motivate sponsors to develop the drugs in countries where more resources are available rater than in US where cost of everything is highest. FDA should sposor developing countries to develop*

the drugs those are most required and incentivize them to reduce the drug cost."

- *"USFDA can make a request to the federal government to amend the inflation reduction act to make it more meaningful so that law provide financial relief by lowering drug costs and strengthening medicine for the future."*
- *"Outcomes based pricing models"*

CHAPTER VI:

SUMMARY, IMPLICATIONS, AND RECOMMENDATIONS

6.1 Summary

This study was designed to get insights from prospective respondents on the identified four gap areas in Accelerated Approval Mechanism, viz., timeboxing of confirmatory clinical studies, incentivization/ penalization of Sponsors for diligently conducting or not diligently conducting and delaying the confirmatory clinical studies respectively, introducing drug label/ prescribing information modifications to drug products approved under Accelerated Approval Pathway and keeping checks and balances on the costs of drug products approved under this pathway. Overall, the study was able to meet its objectives and its outcomes indicated towards holding these gaps good and suggested recommendations that might help addressing these gaps to elevate productivity of this study.

6.2 Implications

The outcomes of this study has multi-faceted implications.

The idea of timeboxing has a good bearing for patients who are part of the clinical trials and are being treated with drugs which have ‘half-baked’ safety, efficacy and quality profiles. It will also put the USFDA at a bit of ease, as there would be a time-capping on the confirmatory clincal studies which would reduce the burden that USFDA would have from constant monitoring and ensuring compliance. It would also help the physicians in making informed decisions for their patients about the availability of treatment modality as a “full-fledged” drug product withstanding all testing and compliance requirements. For Sponsors, it would help them having a clear visibility on the research and development pipelines and steering and allocating fundings, per the product needs.

Incentivization or penalization of Sponsors will indirectly help patients in receiving the treatment modalities which would have a strong backing from the Sponsors themselves; as, if they complete the confirmatory studies diligently, they would be motivated to bring the drugs in market more swiftly and willingly and, if they do not do so, they would have the whip struck on them, which may push them hard to complete the trials in time or pull them back. Health Authority and Physicians, both, will have products with complete safety, efficacy and quality profiles and it would make their lives easier to push 'wholesome' products to market and patients, respectively. For Sponsors, incentivization would be a win-win that they would be motivated to meet the timelines and bring the products on market swiftly to reap in the benefits early. It will also help raising their image and strong credibility in the market. Penalization would help them staying alert and get going to meet the timelines to reach the compliance goals as early as possible.

Drug label modifications will help patients by getting to understand the 'behind the curtain' facts of the drug products and taking an informed decision to go or no-go for a particular trial of a drug product. The health agency will remain at ease, as there would be a great degree of transparency which would lead to less back-and-forth from various stakeholders about the peculiarities of drug products. Physicians will also be happy to have things so clear about drug products and taking direct decisions about their patients. The Sponsors will also be placed comfortably and there would be less questions raised by various stakeholders and they would be perceived as transparent organizations.

Costs rationalization will have a direct bearing on the patients, as they would get the drug products at affordable prices and their pockets will be at ease. The health agency would also be perceived as 'patient-pro' and their image would get enhanced. The Physicians will be able to choose the right-most and most economic treatment modality

for their patients and would also have more choices to compare and decide. The Sponsors may not get the pat from shareholders, but they would be more happy to make out for the lost numbers from better economies of scale and volumes.

Overall, addressal of these four gaps would have the Science win, ultimately.

6.3 Recommendations for Future Research

Basis the analysis of responses received, there may be below-mentioned areas where there could be an opportunity to dive more in and perform research from a futuristic perspective.

- **Application of Real World Data (RWD) and Real World Evidence (RWE):** Study of application of RWD and RWE in facilitating the clinical trials and their impact on drug products' availability through Accelerated Approval Pathway could be one of the potential topics where research efforts can be directed. Impact of these approaches could be studied on safety signals and label updates of drugs approved through AAP. Impact of RWE-based clinical trial protocol integration with the protocols of studies that form the basis of approval could also be studied.
- **Emerging technologies like AI/ ML/NLP and their adoption in clinical trials:** Studies can also be directed towards adoption of digital technologies like AI/ ML/ NLP in conductance of clinical trials and how these could impact the drugs which are approved through AAP.
- **Emerging treatment modalities, like, gene therapy, personalized medicines, etc.:** Studies can also be performed to see what impact emerging treatment modalities like, gene therapy or personalized medicines have if those drug products are approved through AAP. It would be interesting to see if there is an impact on overall timeline of

approval, time duration of conductance of clinical trials, clinical trial protocols designs, etc.

- **Inflation Reduction Act (IRA):** It would be interesting to see whatbenefits IRA has brought for the drug products and patients, post its introduction, for drug products approved through AAP. In what manner, it has impacted the costs of such drug products.

6.4 Conclusion

Overall, by screening the responses received to the main research questions and sub-questions entailed in them, and the analysis so performed, it can be very well inferred that these four main research questions hold their sanctity. Outcomes of the analysis around those questions and recommendations so received, if followed, could prove to be beneficial for all the stakeholders involved in the value chain of clinical trials, i.e. the patients, the physicians, the health authorities, the health technology assessments and the Sponsors.

On the basis of outcomes of this research, there could be below proposals for health agencies that could be taken up for further benefitting the overall ecosystem of the Accelerated Approval Pathway.

- Reputation rating of Sponsors basis their performance in diligently following AAP principles
- Introduction of allowance of up to 6 months without any penalization in case a Sponsor is slipping on the confirmatory clinical study timelines
- RWE-based protocols for confirmatory clinical studies should be integrated at the time of initial approval and findings should be filed annually

- Preferential review of future submissions for those Sponsors who comply to the AAP principles
- Introduction of a Safety Logo on Labels/ Prescribing information for products which have been approved through AAP
- Possibility of legal action on Sponsors who are in non-compliance to AAP principles
- Issuance of a non-compliance certificate (on the tunes of FDA Form 483) to Sponsors who are in non-compliance to AAP principles
- Possibility of CMS to fix a capped amount for such products which fail to meet their timelines as a result of poor diligence or deliberate delays
- Possibility of reducing R&D incentives, including strict construal clauses in agreement for non compliance, enabling public disclosure for failure to conclude confirmatory trials
- Possibily of fee hike for next reviews for Sponsors who are in non-compliance to AAP principles
- Possibility of introduction of QR codes on labels that would take to an easy explainable video for the layman about the nuances of the drug product approved under AAP
- Possibility of introduction of inclusion of enrolment information for ongoing trials so that eligible patients can participate/enrol
- Possibility of USFDA in being a key stakeholder for devising different pricing models and taking price decisions of products approved under AAP
- Possibility of having a public list of company prices offered after approval for similar drugs, showing dynamic variables that determine the market

penetration and patient benenfit from the brand since approval e.g. no. patients treated, patient populations, countries in which compound was provided approval etc.

APPENDIX A

SURVEY COVER LETTER

Rajneesh Vats

Doctorate Student, Swiss School of Business Management (SSBM), Geneva, Switzerland

Email: vats.rajneesh@gmail.com ; Cell Phone: +91 844 738 4441

Subject: Rajneesh Vats: Kind request to fill out the Questionnaire to support my Doctorate Program Research

Dear Prospective Respondent,

I am pursuing a Doctorate Program from Swiss School of Business Management, Geneva, Switzerland. Could you kindly fill out this questionnaire to facilitate me with fulfilment of my research and return it back in two-weeks from the receipt of it?

I consider you as one of the key authorities in Pharmaceutical Industry, who has not only closely witnessed evolution of Accelerated Approval Program of USFDA but also continuously contributed to confine it to its desired objectives. I am sure you would be able to do justice to these questions by virtue of your acquired knowledge, experience and wisdom and your responses and guidance would help paving the righteous path to my research.

USFDA's Accelerated Approval Pathway – Progressive journey and opportunities for a balancing act for Oncology Drugs

This questionnaire is being presented to you as part of my doctoral program research, titled - "USFDA's Accelerated Approval Pathway – Progressive journey and opportunities for a balancing act for Oncology Drugs."

Accelerated Approval Pathway (AAP) is one of the instrument that is exercised by USFDA to grant approvals to drug product in an expedited manner, relying on the demonstration of the effect of a drug on its surrogate endpoint or on an intermediate clinical end-point that is reasonably likely to predict a clinical benefit to approve drugs, instead of direct clinical benefit generated by that particular drug or its benefit upon a validated surrogate endpoint.

Though; USFDA grants approvals to drug products on the basis of predicted clinical benefit, yet it mandates the Sponsors to complete the confirmatory clinical studies in a committed and reasonable timeframe proving the clinical benefit. There are some challenges noticed with this Pathway. It has been observed that there are occasions when these confirmatory clinical studies are not completed, as committed and there is no 'time-boxing' around them. This may be attributed to not enough incentives available for Sponsors for completing these studies. On the other hand, laxity has also been seen, at times, by the USFDA that they do not penalise such Sponsors adequately for not conducting these confirmatory studies. It has also been observed that Labels/ Prescribing Informations (PIs) of such drug products, which have been granted Accelerated Approvals by USFDA, do not contain adequate information to distinguish them from conventional product Labels/ PIs. Another challenge with such drug products that have been granted Accelerated Approvals is the cost of such products, which have been observed to be exorbitantly high at times, and the USFDA does not have much of modalities to regulate them.

Through this research, I am trying to delve more into above areas and attempting to figure out possible suggestions/ recommendations to address them.

Could you kindly take 20 minutes out of your valuable time and help me by responding to below questions?

It will pave me with a recipe to address these challenges and put them forward to Sponsors and USFDA so that this Approval Pathway does not lose its sheen and continue to remain an important instrument for swifter patient access of treatment modalities for unmet needs.

Kindly note that your participation in responding to this questionniare is completely voluntary. All your responses to this questionnaire will be kept anonymous and confidential and data so gathered will solely be used for this research purpose only. Your personal information will be processed in accordance with the apt GDPR and Data Privacy regulations and it will not be shared with any one else.

Thank you so much in advance.

Kind regards,
Rajneesh

APPENDIX B

INFORMED CONSENT

Rajneesh Vats

Doctorate Student, Swiss School of Business Management (SSBM), Geneva, Switzerland

Email: vats.rajneesh@gmail.com ; Cell Phone: +91 844 738 4441

Subject: Rajneesh Vats: Informed Consent to fill out the Questionnaire to support my Doctorate Program Research

Dear Prospective Respondent,

I am pursuing a Doctorate Program from Swiss School of Business Management, Geneva, Switzerland. Could you kindly provide consent to my filled out questionnaire to facilitate me with fulfilment of my research?

As informed, this study is being conducted to delve deep into the challenges associated with USFDA's Accelerated Approval Pathway, gather data and, in turn, wisdom through your responses to attempt to figure out possible suggestions/ recommendations to address those challenges, especially in context to timeboxing of confirmatory clinical studies, incentivization and penalization of Sponsors for diligently and timely conducting and not conducting confirmatory clinical studies respectively, around possible drug product label modifications and exercising checks and balances around the cost of products that have been approved through Accelerated Approval Pathway.

Kindly note that your participation in responding to this questionnaire is completely voluntary and you have all the rights to refuse to participate in this study or withdraw at any point in time. All your responses to this questionnaire will be kept anonymous and confidential and data so gathered will solely be used for this research purpose only. Your personal information will be processed in accordance with the apt GDPR and Data Privacy regulations and it will not be shared with any one else. Kindly also be aware that this study does not pose any risk and is not expected to cause any harm to any of its participants in any tangible or intangible form.

Should you have any questions, clarifications or concerns about this study, its approach or the questionnaire, kindly feel free to connect with me at any point of time.

In case, I fail to get your formal response to this request of mine due to your occupancy or any other reason, your response to the questionnaire would be treated as a formal and voluntary consent to participate in this study.

Thank you so much in advance.

Kind regards,
Rajneesh

APPENDIX C

INTERVIEW GUIDE

Rajneesh Vats

Doctorate Student, Swiss School of Business Management (SSBM), Geneva, Switzerland

Email: vats.rajneesh@gmail.com ; Cell Phone: +91 844 738 4441

Interview Guide: USFDA's Accelerated Approval Pathway – Progressive journey and opportunities for a balancing act for Oncology Drugs

Background: I am Rajneesh and I am pursuing a Doctorate Program from Swiss School of Business Management, Geneva, Switzerland. This study is being conducted to delve deep into the identified challenges associated with USFDA's Accelerated Approval Pathway.

Kindly note that your participation in responding to this questionniare is completely voluntary and you have all the rights to refuse to participate in this study or withdraw at any point in time. All your responses to this questionnaire will be kept anonymous and confidential and data so gathered will solely be used for this research purpose only. Your personal information will be processed in accordance with the apt GDPR and Data Privacy regulations and it will not be shared with any one else. Kindly also be aware that this study does not pose any risk and is not expected to cause any harm to any of its participants in any tangible or non-tangible form.

Before we proceed, I would request your formal consent to record your responses to my questions to enable analysis.

There are primarily four areas identified where there are still some challenges and gaps in Accelerated Approval pathway, which need addressal. These are - timeboxing of confirmatory clinical studies, incentivization and penalization of Sponsors for diligently and timely conducting and not conducting confirmatory clinical studies respectively, around possible drug product label modifications and exercising checks and balances around the cost of products that have been approved through Accelerated Approval Pathway. There are five questions associated with timeboxing of confirmatory clinical studies, out of them four are close-ended and one is open-ended. For Incentivization and penalization of Sponsors, there are a total of five questions again, out of them three are close-ended and two are open-ended. For the topic of drug product label modifications, there are a total of four questions, out of which three are close-ended and one is open-ended. For the topic of checks and balances of drug produt costs, there are a total of four questions, out of two are close-ended and two are open-ended.

Should you have any questions, clarifications or concerns about this study, its approach or the questionnaire, kindly feel free to connect with me at any point of time.

Thank you so much in advance.

Kind regards,
Rajneesh

APPENDIX D

QUESTIONNAIRE FOR INDUSTRY

USFDA's Accelerated Approval Pathway – Progressive journey and opportunities for a balancing act for Oncology Drugs

This questionnaire is being presented to you as part of my doctoral program research, titled - "USFDA's Accelerated Approval Pathway – Progressive journey and opportunities for a balancing act for Oncology Drugs."

Accelerated Approval Pathway (AAP) is one of the instrument that is exercised by USFDA to grant approvals to drug product in an expedited manner, relying on the demonstration of the effect of a drug on its surrogate endpoint or on an intermediate clinical end-point that is reasonably likely to predict a clinical benefit to approve drugs, instead of direct clinical benefit generated by that particular drug or its benefit upon a validated surrogate endpoint.

Though; USFDA grants approvals to drug products on the basis of predicted clinical benefit, yet it mandates the Sponsors to complete the confirmatory clinical studies in a committed and reasonable timeframe proving the clinical benefit. There are some challenges noticed with this Pathway. It has been observed that there are occasions when these confirmatory clinical studies are not completed, as committed and there is no 'time-boxing' around them. This may be attributed to not enough incentives available for Sponsors for completing these studies. On the other hand, laxity has also been seen, at times, by the USFDA that they do not penalise such Sponsors adequately for not conducting these confirmatory studies. It has also been observed that Labels/ Prescribing Informations (PIs) of such drug products, which have been granted Accelerated Approvals by USFDA, do not contain adequate information to distinguish them from conventional product Labels/ PIs. Another challenge with such drug products that have been granted Accelerated Approvals is the cost of such products, which have been observed to be exorbitantly high at times, and the USFDA does not have much of modalities to regulate them.

Through this research, I am trying to delve more into above areas and attempting to figure out possible suggestions/ recommendations to address them.

Could you kindly take 20 minutes out of your valuable time and help me by responding to below questions? It will pave me with a recipe to address these challenges and put them forward to Sponsors and USFDA so that this Approval Pathway does not lose its sheen and continue to remain an important instrument for swifter patient access of treatment modalities for unmet needs. Thank you so much.

Email *

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A. Time-boxing (mandatory confining of a time limit) of confirmatory clinical studies:

Description (optional)

1. In your opinion, should time-boxing of confirmatory clinical studies, post grant of an accelerated approval of a drug product for an indication, be made mandated and fixed? *

	1	2	3	4	5	
Strongly Disagree	○	○	○	○	○	Strongly Agree

2. Should there be a blanket time-boxing duration mandated for every confirmatory clinical study? *

	1	2	3	4	5	
Strongly Disagree	○	○	○	○	○	Strongly Agree

3. Should this time-boxing be different for below different possible variables of confirmatory clinical studies? *

	Strongly Disagr...	Disagree	Neutral	Agree	Strongly Agree
Therapeutic Ar...	○	○	○	○	○
Disease Area	○	○	○	○	○
Patient Populat...	○	○	○	○	○
Patient Enrolm...	○	○	○	○	○

4. What should be the time-boxing range for below different possible variables of confirmatory clinical studies? *

	1 to 3 years	3 to 5 years	5 to 6 years	Beyond 6 years
Therapeutic Area	○	○	○	○
Disease Area	○	○	○	○
Patient Population	○	○	○	○
Patient Enrolment	○	○	○	○

5. In your opinion, what could be other possible variables that have a significant impact on time-boxing of confirmatory clinical studies? *

(Kindly write your response in maximum 150 words)

Long answer text

B. Incentivization or penalization of Sponsors:

Description (optional)

1. Should there be an incentivization provided or penalization exercised for timely completion or not able to complete the confirmatory clinical studies, respectively, for Sponsors, post accelerated approvals are granted for their drug products? *

	1	2	3	4	5	
Strongly Disagree	○	○	○	○	○	Strongly Agree

2. Should incentivization be provided to eligible Sponsors in the form of below different possible incentivization variables upon successful and speedy conductance of confirmatory clinical studies? *

	Strongly Disagr...	Disagree	Neutral	Agree	Strongly Agree
Exclusivity Pro...	○	○	○	○	○
Pricing Prefere...	○	○	○	○	○
Review Acceler...	○	○	○	○	○
Speedy Reimb...	○	○	○	○	○

3. Should penalization be exercised on eligible Sponsors in the form of below different possible penalization variables upon delayed conductance or non-conductance of confirmatory clinical studies? *

	Strongly Disagr...	Disagree	Neutral	Agree	Strongly Agree
Stringent Finan...	○	○	○	○	○
Debarment	○	○	○	○	○
Review Delays ...	○	○	○	○	○
Issuance of 48...	○	○	○	○	○

4. In your opinion, what could be other possible variables to incentivize a Sponsor for conducting a confirmatory clinical trials with due diligence? *

(Kindly write your response in maximum 150 words)

Long answer text

5. In your opinion, what could be other possible variables to penalize a Sponsor for not conducting a confirmatory clinical trials with due diligence? *

(Kindly write your response in maximum 150 words)

Long answer text

C. Drug product label modifications:

Description (optional)

1. In your opinion, should there be a differentiated label/ prescribing information of a product that has been granted an accelerated approval than a product that has been approved traditionally? *

	1	2	3	4	5	
Strongly Disagree	○	○	○	○	○	Strongly Agree

2. Should key information highlighting accelerated drug approval be distinctly displayed on the label/ prescribing information; viz. in different colour or as a boxed text? *

	1	2	3	4	5	
Strongly Disagree	○	○	○	○	○	Strongly Agree

3. Information pertaining to which of the below different possible variables should be displayed on the label/ prescribing information (either in a box or in different colour) of a product that has been granted accelerated approval? *

	Strongly Disagr...	Disagree	Neutral	Agree	Strongly Agree
Approval Path...	○	○	○	○	○
Surrogate Mar...	○	○	○	○	○
Tentative Confi...	○	○	○	○	○
Approval in oth...	○	○	○	○	○
Post-approval ...	○	○	○	○	○

4. In your opinion, what could be other possible variables that could be included on the label/ prescribing information of a drug product that has been granted approval through accelerated approval pathway? *

(Kindly write your response in maximum 150 words)

Long answer text

D. Checks and balances of drug product costs:

Description (optional)

1. Do you think there is a need to rationalize the cost of drug products that have been granted accelerated approvals? *

	1	2	3	4	5	
Strongly Disagree	○	○	○	○	○	Strongly Agree

2. Which of the below variables could be the drivers of cost decisions of the drug products that have been granted accelerated approvals? *

	Strongly Disagr...	Disagree	Neutral	Agree	Strongly Agree
Therapeutic Ar...	○	○	○	○	○
Indication of Use	○	○	○	○	○
Disease Condit...	○	○	○	○	○
Patient Populat...	○	○	○	○	○
Development c...	○	○	○	○	○

3. In your opinion, what could be other possible variables to have an impact on cost of drug products that have been approved through accelerated approval pathway? *

(Kindly write your response in maximum 150 words)

Long answer text

4. What could be possible measures by USFDA to contain inflated cost of drug products that have been approved through accelerated approval pathway? *

(Kindly write your response in maximum 150 words)

Long answer text

APPENDIX E

QUESTIONNAIRE FOR HEALTH AUTHORITY

USFDA's Accelerated Approval Pathway – Progressive journey and opportunities for a balancing act for Oncology Drugs

This questionnaire is being presented to you as part of my doctoral program research, titled - "USFDA's Accelerated Approval Pathway – Progressive journey and opportunities for a balancing act for Oncology Drugs."

Accelerated Approval Pathway (AAP) is one of the instrument that is exercised by USFDA to grant approvals to drug product in an expedited manner, relying on the demonstration of the effect of a drug on its surrogate endpoint or on an intermediate clinical end-point that is reasonably likely to predict a clinical benefit to approve drugs, instead of direct clinical benefit generated by that particular drug or its benefit upon a validated surrogate endpoint.

Though; USFDA grants approvals to drug products on the basis of predicted clinical benefit, yet it mandates the Sponsors to complete the confirmatory clinical studies in a committed and reasonable timeframe proving the clinical benefit. There are some challenges noticed with this Pathway. It has been observed that there are occasions when these confirmatory clinical studies are not completed, as committed and there is no 'time-boxing' around them. This may be attributed to not enough incentives available for Sponsors for completing these studies. On the other hand, laxity has also been seen, at times, by the USFDA that they do not penalise such Sponsors adequately for not conducting these confirmatory studies. It has also been observed that Labels/ Prescribing Informations (PIs) of such drug products, which have been granted Accelerated Approvals by USFDA, do not contain adequate information to distinguish them from conventional product Labels/ PIs. Another challenge with such drug products that have been granted Accelerated Approvals is the cost of such products, which have been observed to be exorbitantly high at times, and the USFDA does not have much of modalities to regulate them.

Through this research, I am trying to delve more into above areas and attempting to figure out possible suggestions/ recommendations to address them.

Could you kindly take 15 minutes out of your valuable time and help me by responding to below questions? It will pave me with a recipe to address these challenges and put them forward to stakeholders involved so that this Approval Pathway does not lose its sheen and continue to remain an important instrument for swifter patient access of treatment modalities for unmet needs. Thank you so much.

Email *

Valid email

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A. Time-boxing (mandatory confining of a time limit) of confirmatory clinical studies:

Description (optional)

1. Despite USFDA's Food and Drug Omnibus Reform Act (FDORA) of 2022 and The Consolidated Appropriations Act of 2023 (CAA) being in place, is time-boxing of confirmatory clinical studies, post grant of an accelerated approval of a drug product for an indication, still a challenge? *

	1	2	3	4	5	
Strongly Disagree	○	○	○	○	○	Strongly Agree

2. Are there any other provisions being promulgated by USFDA that could make time-boxing of confirmatory clinical studies further mandated and fixed? If those could be disclosed at this point in time, what are those? *

(Kindly write your response in maximum 150 words)

Long answer text

B. Incentivization or penalization of Sponsors:

Description (optional)

1. Should there be a reasonable incentivization provided or penalization exercised for timely completion or not able to complete the confirmatory clinical studies, respectively, for Sponsors, post accelerated approvals are granted for their drug products? *

	1	2	3	4	5	
Strongly Disagree	○	○	○	○	○	Strongly Agree

2. Under USFDA's current or futuristic regulatory framework, are there any provisions available or envisaged for incentivization or penalization of Sponsors for completing confirmatory studies or not completing them in a genuinely agreed timeframe, respectively, post accelerated approvals are granted to them? *

(Kindly write your response in maximum 150 words)

Long answer text

C. Drug product label modifications:

Description (optional)

1. To benefit the physicians and potential patients at large, should there be a differentiated label/ prescribing information of a product that has been granted an accelerated approval than a product that has been approved traditionally? *

	1	2	3	4	5	
Strongly Disagree	○	○	○	○	○	Strongly Agree

2. Under the current gamut of USFDA regulations, could variables; like, surrogate marker details, tentative confirmatory clinical study timeline, approval in other countries, post-approval commitments, if any, be included on the label/ prescribing information of a drug product that has been granted approval through accelerated approval pathway? *

(Kindly write your response in maximum 150 words)

Long answer text

D. Checks and balances of drug product costs:

Description (optional)

1. Do you think there is a need to rationalize the cost of drug products that have been granted accelerated approvals? *

	1	2	3	4	5	
Strongly Disagree	○	○	○	○	○	Strongly Agree

2. What are various measures currently being exercised by USFDA or from a futuristic perspective to contain inflated cost of drug products that have been approved through accelerated approval pathway? *

(Kindly write your response in maximum 150 words)

Long answer text

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