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Deploying continuous improvement across the drug discovery value chain

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In addressing the challenges facing pharmaceutical R&D one question is frequently asked: how can continuous improvement (CI), delivered through a Lean Sigma approach, be applied in a research environment to deliver overall benefit? We show that taking a value chain approach to improvement projects in a discovery research organization, initially focusing on the drug discovery project delivery level (i.e. middle layer of the value chain), provides the foundation for an effective CI programme. The adaptation of Lean Sigma principles and methodology, combined with the tenacity and creativity of scientists, enabled the delivery of significant improvements in challenging areas, including target selection, project decision making and the compound design-make-test-analyse (DMTA) cycle.

Introduction

The pharmaceutical industry currently faces several unprecedented and widely reported challenges. In particular, rising investment in R&D has not translated into an increase in number of new drugs to market [1,2]. The resultant reduced return on investment suggests a bleak outlook for pharmaceutical R&D. To mitigate the risk, many companies are employing a range of approaches including mergers and acquisitions, novel organizational models, embracing externalization and collaborations [3,4], and the deployment of continuous improvement (CI). The latter approach, with a focus on incremental and transformational improvement in product quality, delivery time and cost, frequently utilizes Lean Sigma methodology. The methodology has its roots in manufacturing; so, can Lean Sigma be applied successfully in a pharmaceutical research environment? Several global pharmaceutical companies have taken on the challenge of utilizing Lean Sigma to deliver CI in drug discovery [5–10]. In this article we aim to share our successes and learnings in deploying Lean Sigma to deliver a CI programme across the drug discovery value chain to increase clinical proof-of-concept (PoC) success (Fig. 1).

Deployment approach: selecting the right people

A decision was made by the AZ (Oncology Europe senior leadership team) to initiate a CI programme to help address the oncology portfolio challenges of increasing clinical PoC success and the speed of candidate drug (CD) delivery. The agreed scope for the programme covered oncology drug discovery (i.e. target selection to CD decision) encompassing three European research sites. Internal experience and external review suggested Lean Sigma as an effective approach to deliver significant improvement in primary and secondary drug discovery processes (e.g. HTS and compound supply), and importantly involved people working in the process, which can empower scientists to deliver change [5–7,9,10]. Several challenges were evident from the start, including identifying the right projects and the right people to deliver the programme.

The right people included those who could support the delivery of the programme. We thus established a CI team who would be able to:

- manage the identification and delivery of CI projects;
- provide Lean Sigma expertise to the programme and projects;
- communicate progress and benefits to all levels of the organization;
- obtain decisions for project recommendations from sponsors and leaders.

The team consisted of a senior leadership team member, a Lean Sigma expert with pharmaceutical experience, and two respected drug discovery scientists trained in Lean Sigma. As the programme developed, they successfully

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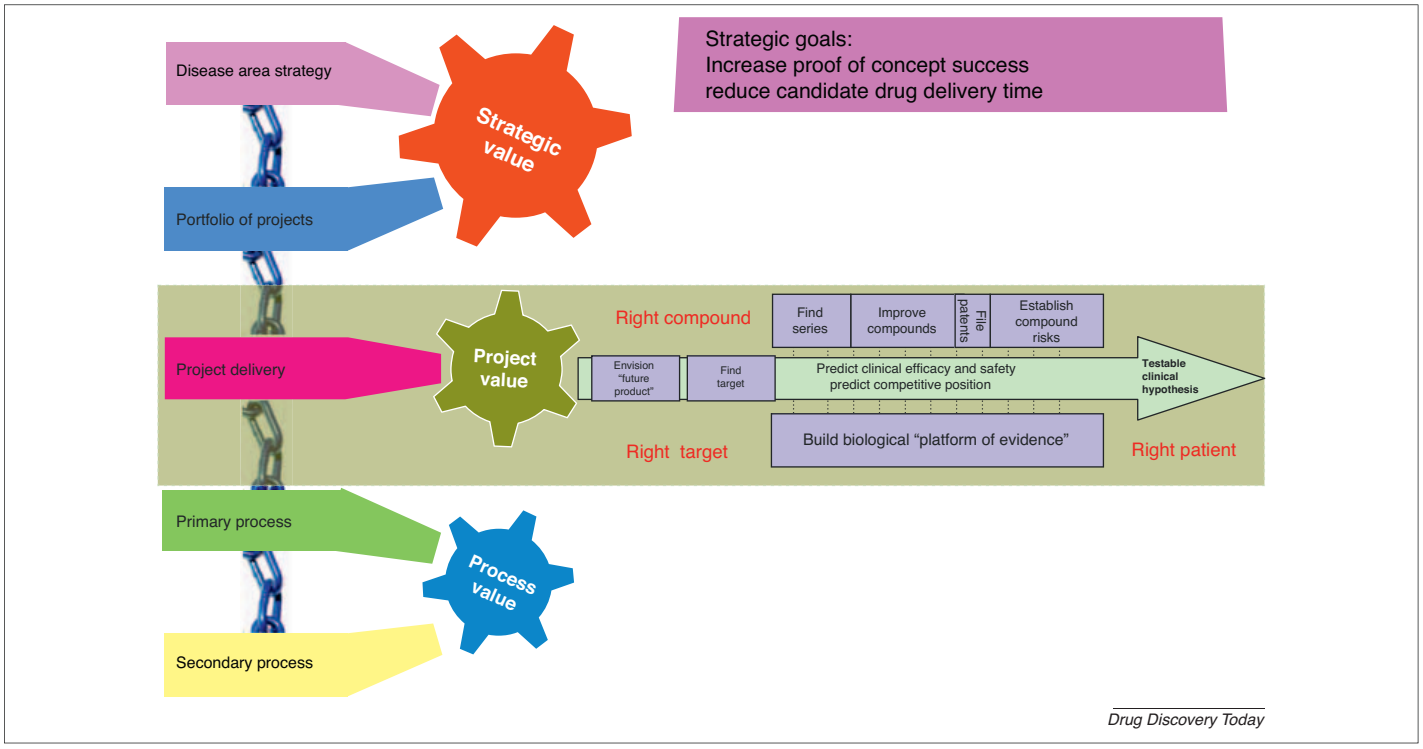

FIGURE 1

Drug discovery value chain and value elements. The drug discovery value chain can be defined as the sequence of activities undertaken to create value-adding candidate drugs for AZ clinical development partners and ultimately the patient. The levels of the value chain relate to the value elements: process, project and strategic, with the middle project level providing an appropriate starting point to identify improvement projects.

blended R&D expertise with Lean Sigma experience, establishing a credible and effective CI team. Utilizing respected internal scientists, who are familiar with the company culture, to support the delivery of change proved highly beneficial in obtaining active support from all levels of the organization.

The senior leadership team member had a key role in providing direct access to the oncology leadership team, ensuring engagement, a mechanism to obtain decisions and sending a message to the whole organization regarding the importance of the programme. In addition, they provided an interface with the value chain network, a cross-research area CI leadership team that used learnings and experience to develop CI across R&D.

Deployment approach: selecting the right projects

In identifying suitable initial projects AZ chose to utilize a value chain approach, considering the whole drug discovery system. As demonstrated in Fig. 1, the drug discovery value chain is made up of several levels that directly translate to the types of value that can be delivered (i.e. process, project and strategic). Projects can be selected at any one of these levels with differing potential benefits and challenges. In this CI programme we initially decided to take a middle-out approach in terms of the level of the value chain (i.e. the discovery project delivery level) and the organizational level of the people who contributed to the projects. However, organizational level was not a criterion for team membership and we purposely expanded the organizational representation in the project delivery teams to ensure the right inputs were utilized.

A cross-functional team obtained customer and performance data, and mapped the drug discovery process at the project delivery level. Using customer survey data (e.g. expectations for CDs) and project performance metrics (e.g. project timelines, attrition rates) the team captured the speed and quality constraints for successful drug discovery project progression. The problem areas were prioritized based on effort versus potential impact and alignment with the strategic goals of increasing PoC success and reducing CD delivery time. The resulting priority problem areas – target selection, project decision making, discovery – development interactions and the compound design-make-test-analyse (DMTA) cycle – provided a spread across the value chain and received backing from the senior leadership team (Fig. 2).

The benefits of the middle-out approach are that projects are identified across the entire process and that you utilize and engage with people across organizational boundaries. It also enables engagement and influence above and below the middle organizational level, providing a key foundation for subsequent CI activities. For example, providing benefits to drug discovery projects in turn helps obtain active senior level support for improvement projects at the top level of the value chain to deliver strategic value (e.g. increased PoC success). The challenges with the middle-out approach are that the resulting projects are often cross-functional and complex. A frequently used starting point is the bottom-up approach [6], working at the secondary process level (e.g. assay development and bulk cell supply), focusing on process excellence, engaging directly with lab-based scientists and rapidly delivering a significant number of projects. Because problems are dealt with in isolation it is unclear if the right project areas are being tackled and unlikely that the benefits will impact the strategic goals. An alternative top-down approach has the benefits of clear direction from senior leadership and will deliver strategic value, but this is challenging in terms of obtaining active senior level support, identifying projects with a manageable scope and engaging with all layers of the organization, particularly lab-based scientists. Not surprisingly, this was

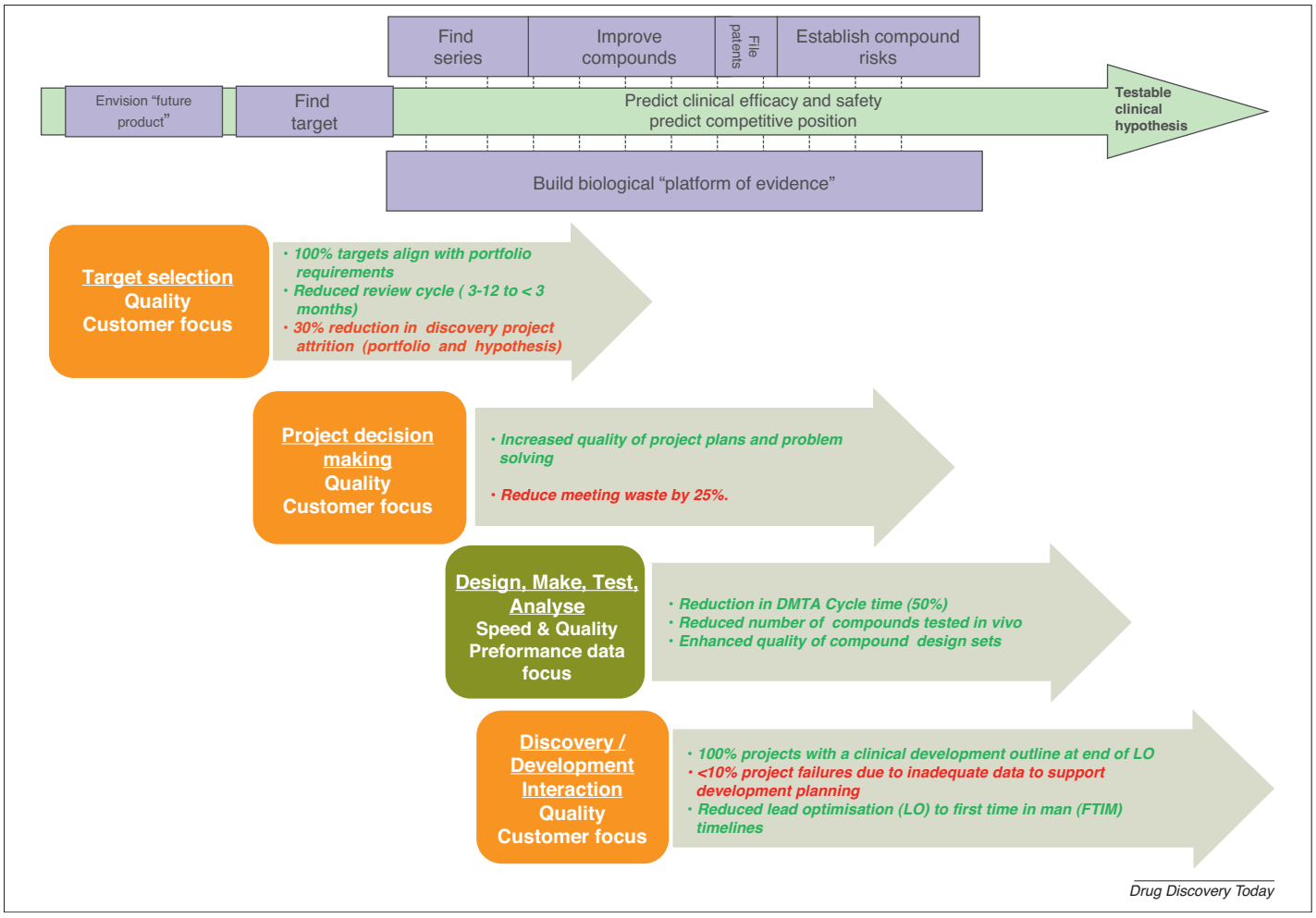

FIGURE 2

Improvement projects summary. Prioritized projects spanned the drug discovery process and either a customer or performance data focus was used to deliver improvements. Quality and/or speed benefits are summarized within the arrows (green: delivered benefits; red: forecasted benefits).

initially the preferred approach for the oncology senior leadership team with a clear message that lead optimization should be the focus; however, this view changed after highlighting the benefits of the middle-out approach, which would enable a joined-up deployment of improvements across drug discovery.

Using the right approach

Several articles highlight the challenges of using Lean Sigma to deliver CI in a research environment and they conclude that the approach should be modified for such innovation-driven organizations [7,8,11]. As Reinersten and Shaeffer report [11], the requirements for CI in R&D and manufacturing have substantial differences. For example, in manufacturing a reduction in variability will deliver process benefits but in R&D we need to distinguish 'desirable' and 'undesirable' variability because elimination of all variability will remove all value. In the DMTA cycle, for instance, it is desirable to have variation in compound design but undesirable if there is variation in the performance of screening assays (e.g. *in vitro* ADME panel). Therefore, to ensure a successful programme, we developed a strategy of focusing on selected Lean Sigma principles rather than adhering fully to Lean Sigma methodology:

i. specify value in the eyes of the customer
   - for example, target selection – what are the important properties of a drug target for clinical development as a drug discovery customer?

ii. identify the value stream and eliminate non-value-adding activities and 'undesirable' variation.
   - for example, project decision making – draw a process map for the project review process and capture where review meetings are not providing any clear benefit to project decision making or where there is duplication;

iii. use customer and performance data to validate problems and root causes
   - for example, target selection – customer and process data collected to prioritize the real problems with how cancer targets are being selected;

iv. make value flow at the pull of the customer
   - for example, project decision making – medicinal chemistry conducts a review of a lead series at the request of the project team;

v. involve, align and empower employees
   - for example, DMTA – empower a team of multidisciplinary scientists who are involved in the DMTA cycle to identify and implement improvements;

vi. continuously improve knowledge in the pursuit of perfection
   - for example, DMTA – capture and monitor data on the DMTA cycle to identify further improvements.

Delivering change

Focusing on these Lean Sigma principles enabled AZ to develop an approach to non-typical Lean Sigma projects. For the projects with a primary quality driver (e.g. target selection),

which in all cases had very few performance data, we took a customer-focused approach (Fig. 2). Following the generation of a process map that highlighted the key customers, we gathered customer data to clarify their priority requirements and obtain a view on how well these were being delivered. Using a cross-functional team, including providers and customers, the root causes for the gaps in delivering customer requirements were identified and solutions generated. For the target selection project this resulted in the design and implementation of a new, simplified process using criteria aligned to priority customer requirements. Thus, to ensure alignment between the selected drug targets and the requirements of the oncology strategy and portfolio, target selection objectives were generated and made visible to all scientists, who could then focus their searches on targets that would fulfill the objectives and probably be accepted into the oncology portfolio. This customer-focused approach was in contrast to the historical process where scientists generated target proposals based on 'good ideas' that were reviewed on multiple occasions, with protracted decision making. To date, the new system has reduced the review process from 3–12 months to <3 months, with a 100% alignment between target proposals and portfolio requirements (Fig. 2).

In the case of the DMTA project, with a primary driver of reducing cycle time, a performance data driven approach was used. Although this could be considered a more typical Lean Sigma project, the challenge was in the scale of the project, involving three research sites and encompassing compound design, compound synthesis and *in vitro* testing (efficacy and non-efficacy). It was approached as three sub-projects executed in parallel with cross-functional team members recruited from all impacted sites. The teams benefited from the solutions and learnings from previous projects, albeit at reduced customer demand levels [12,13]. For example, the establishment of a panel of efficacy and non-efficacy tests run in parallel through a regular cycle to provide data for a chemical design day contributed a 50% reduction in the DMTA cycle time (Fig. 2). Where solutions are available from related projects there is a case for fully adopting the solution. However, as with the DMTA project, the solution often requires modification to resolve the issues that the team have validated with data, to ensure root causes are addressed and benefits realized.

Although challenging in scope, the four major projects were progressed in parallel, which enabled us to track interdependences, avoid overlap and, importantly, ensure the solutions for each project resulted in an overall benefit rather than creating a constraint in another area. For example, portfolio entry for drug targets was successfully resolved by representatives from the target selection and project decision making teams. Owing to the drug discovery cycle there has been insufficient time to realize all potential long-term benefits (e.g. reduction in project attrition) or the impact on the strategic goals (Fig. 2), but the projects have highlighted to many scientists that CI using a Lean Sigma approach provides significant benefits as exemplified by the subsequent customer 'pull' for further improvement projects at multiple levels of the value chain. For example, we are currently using Lean Sigma principles to design

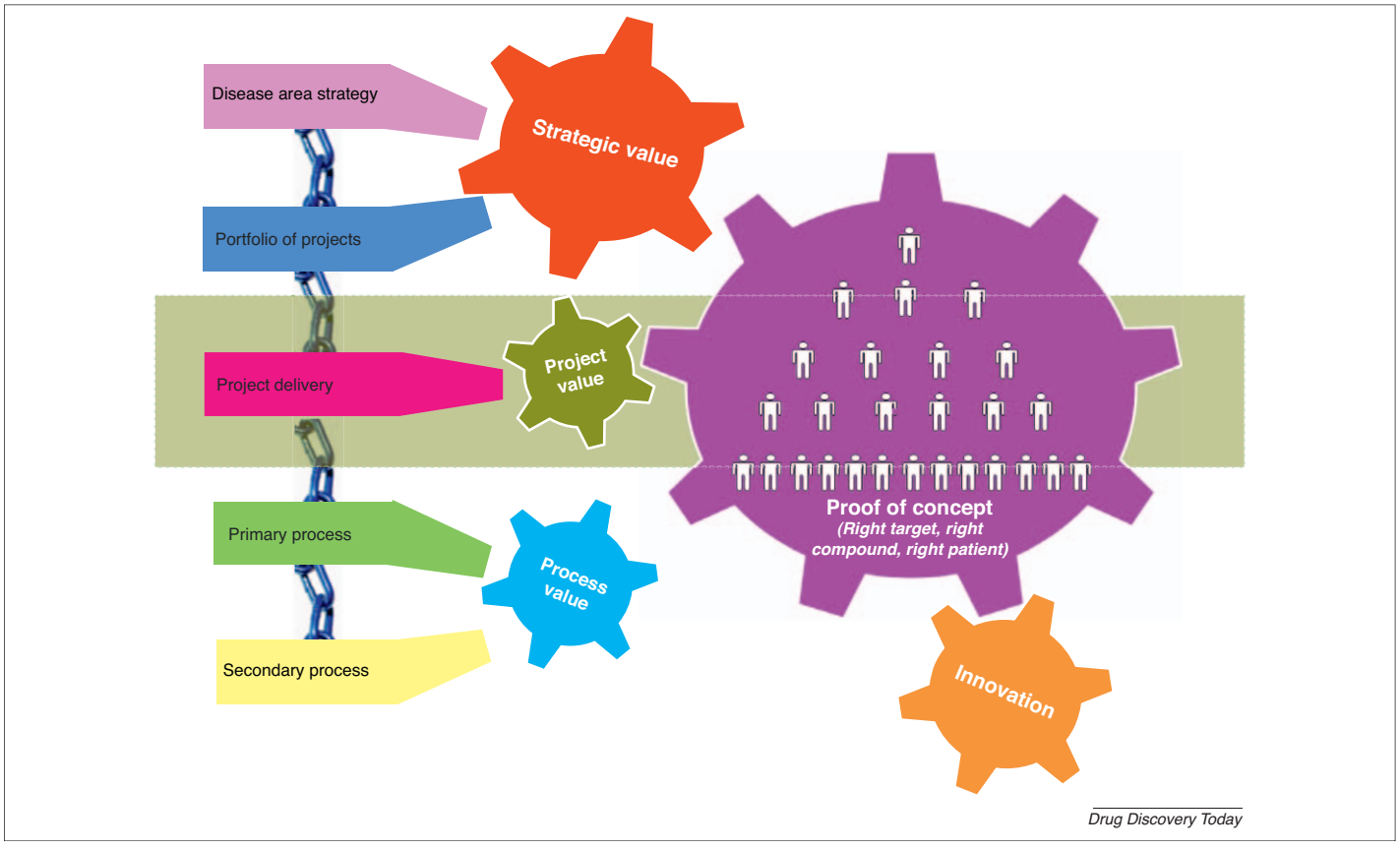

FIGURE 3

Value elements delivering transformational change. The goal of increased proof-of-concept success requires the combined delivery of all value elements (project, process and strategic) and innovation to deliver transformational change. Focusing initially at the middle layer of the value chain provides the continuous improvement foundation, which can then evolve to encompass all levels of the value chain and organization. Delivery of strategic value is a highly significant factor in delivering transformational change but can only be achieved once a CI foundation has been established. *NB*: The size of the cogs reflects the significance of overall contribution.

an operating model to deliver drug discovery projects in a new combined R&D organization, but in parallel working with bench scientists to increase delivery for large-scale CD synthesis for toxicology studies.

Concluding remarks

The middle-out approach provided a powerful method for establishing the foundations for a successful CI programme. The range of improvement projects demonstrated that Lean Sigma principles can be successfully applied to any elements of drug discovery aligned to the goals of increasing PoC speed and success through identifying the right target, right compound and patient. Central to success were the scientists who rose to the challenge of utilizing their R&D experience and creativity to tackle the key problems and deliver sustainable innovative improvements. However, to achieve active engagement with all scientists we believe there is a need to educate through active participation in further improvement projects, or to provide relevant drug discovery Lean Sigma training that enables scientists to apply the key principles in their core role. In addition, it is important that CI delivery by teams or individuals is visibly recognized and rewarded to send a clear message from the business.

In our view, once the middle-out approach is established it is crucial to tackle all levels of the value chain to establish a culture of CI throughout the organization and avoid a plateau of potential benefits. These levels directly translate to the types of potential value that can be delivered in that given level (Fig. 3). Delivering projects at the primary and secondary process levels will engage the majority of lab-based scientists, but is only likely to deliver incremental improvements to drug discovery. Alternatively, focusing solely on strategic value is still only likely to deliver incremental change, albeit at a more significant level. However, as highlighted in Fig. 3, the ability of a drug discovery organization to achieve its full potential is dependent upon working at all levels of the value chain, connecting process, project and strategic value with innovation to achieve transformational change through the efforts of all staff. As the industry strives to increase the level of innovation it is important to recognize that successful CI provides a foundation for innovative drug discovery and that Lean Sigma principles are beneficial in supporting innovation. For example, in the DMTA project, improvements facilitated innovation in compound design by providing robust compound data at the right time. This is a view supported by other CI leaders, but not all industry leaders [8,14].

Considering the challenges the pharmaceutical industry faces, transformational change (e.g. PoC success rate) is ultimately required and deploying CI in a phased approach has the potential to make a significant contribution to addressing the challenge of securing a competitive and innovative drug discovery capability. The reward of increased PoC success is an enticing incentive but will only come to fruition for organizations with the necessary patience, innovation and tenacity.

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