Optimizing value creation in biopharma is like "the flop" in Texas hold 'em

In a previous blog post, I argued that pharmaceutical Research and Development (R&D) is more like poker than chess given the probabilistic nature of developing new medicines. In this blog, I build out this argument further and introduce a new concept, the Critical Value Creation Period (CVCP). The CVCP is the moment in R&D where the probability of success (PoS) for an investigational medicine becoming a new medicine jumps substantially. For most investigational medicines, this period is in early clinical development. By analogy, early development is like the "flop" in Texas hold 'em poker. Stay with me on this one…hopefully this will become clear by the end of this blog post!

Here, I first build out the CVCP argument, which is modeled after an investment thesis proposed by Bain Capital Life Sciences (see here for a presentation by Dr. Adam Koppel at BCLS). Then, I introduce the poker analogy – with focus on the flop. Next, I discuss practical implication of the CVCP model on decision making in biopharma. Finally, I provide two brief case studies that reinforce these concepts. For those not interested in poker, you can skip the second section and focus on the first, third and fourth sections. Also, you can listen to an AI podcast derived from this post here, which is an interesting synthesis of the concepts and use cases described in this blog post. A link to the blog post in pdf format is here.

Section 1: CVCP investment thesis

Throughout this blog, while I focus on value creation as a financial term, financial value creation follows unmet medical need, and that is our ultimate focus at Bristol Myers Squibb (BMS). Unmet medical need and improving the lives of patients is the most important feature of a health investment thesis.

The investment thesis presented in this blog post is two-fold: healthy biopharma companies should have a balance of **stable products** that will deliver reliable returns based on knowledge of the industry today, with sufficient **mega-blockbuster opportunities** that could deliver outsized returns should new areas of biology emerge (e.g., SARS-CoV2 vaccines for COVID-19, hepatitis C virus cures, immuno-oncology, incretins in obesity). Said another way, if a company focuses only on mega-blockbusters, there is risk of failing to deliver stable growth; and if a company only focuses on markets today, there will be insufficient opportunities for outsized returns. Note that the term "stable products" and "mega-blockbusters" are financial terms. Many important and transformational medicines for patients fall under the stable products category.

To achieve a balanced mix of products, there are three unifying principles:

1. **R&D is at the core of value creation.** A productive and sustainable biopharma company needs an R&D organization to develop a core of stable products while constantly probing for mega-blockbuster opportunities. An important assumption is that the distinction between stable products and mega-blockbusters is nearly

impossible to predict pre-clinically and only becomes apparent upon achieving an ***aspirational product profile in clinical development*** – often at the clinical proof-of-concept (PoC) stage in early development. Accordingly, a healthy biopharma company needs to ensure adequate support for early clinical development to test and achieve aspirational product profiles. Once an aspirational product profile is recognized, a healthy biopharma company needs to move as fast as possible – with concentrated risk in as many indications as possible – to position promising investigational medicines to reach the greatest number of patients if regulatory approval is granted.

2. **It is useful to think of value creation along the Research-Development-Commercial (RDC) continuum.** At an early stage of research, new targets and platforms have little value relative to the final product (a commercially successful medicine). At the other extreme, once a medicine is approved, there is value in the form of revenue to a company, but much less value in terms of return on invested capital (ROIC). There are caveats to these statements, of course. For example, discovery platforms can create substantial value if the output of a platform results in the efficient delivery of approved products, even if those products are in the "stable" financial category. Additionally, effective marketing and positioning of approved medicines can deliver value for commercial products.

3. **The "sweet spot" in the RDC continuum is the point where PoS transitions from <10% (e.g., Research) to >50% (e.g., post-PoC).** This blog post refers to this point as the "**critical value creation period**," or CVCP (Figures 1-2). It is during the CVCP that it is first possible to reliably **differentiate mega-blockbusters from stable products**. It is during and immediately after the CVCP where the **greatest acceleration in clinical development** occurs, including determining the acceptable risk for concurrently developing an asset in multiple indications. It is during CVCP where companies have **differential insights into assets** (internally

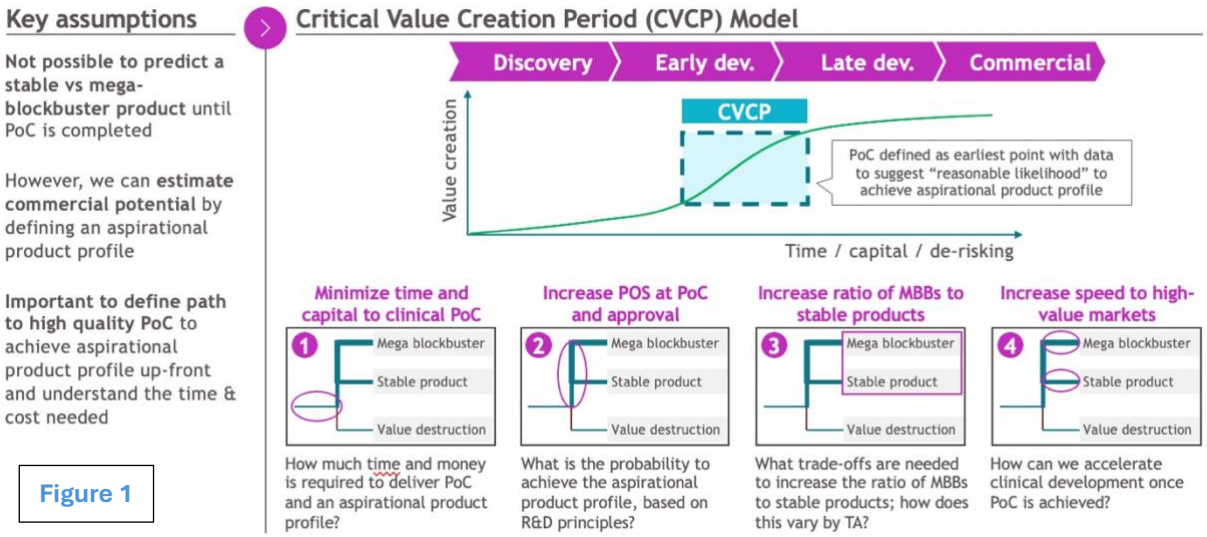

Figure 1

derived or through business development) to position medicines for the greatest ROIC.

Accordingly, a successful biopharma company should (1) minimize the time and capital invested to get to the clinical PoC inflection point (e.g., AI/ML to speed predictive molecule invention); **(2)** increase the PoS of both a positive PoC clinical study and ultimately an approved product (e.g., picking the right targets based on causal human biology, matching therapeutic modality to molecular mechanism of action, translational readouts to facilitate PoC interpretation); **(3)** increase speed to high value markets (e.g., efficient trials, concentrated risk in multiple indications); and **(4)** increase the ratio of mega-blockbusters to stable products through rigorous and disciplined portfolio prioritization. *These concepts are shown graphically in **Figure 1**, with practical examples in Section 3.*

The term "proof of concept" can vary by therapeutic hypothesis and indication, which is why the CVCP period is broadly represented in Figure 1. For example, in oncology, it is often possible to achieve early evidence of monotherapy activity in a small number of patients. In cardiovascular, neurology, and immunology, PoC often – but not always – requires more investment, including Phase 1b/2a studies in a larger number of patients. The exceptions depend on the disease and asset under investigation.

Figure 2 provides hypothetical examples of achieving PoC for investigational medicines with different levels of commercial potential. Hypothetical products "a" and "b" have high mega-blockbuster potential but differ in the time and investment required to achieve an aspirational product profile that firmly establishes that commercial potential. Examples in immunology include the ability to show immune reset in a small number of patients ("early evidence of mega-blockbuster potential," category "a") vs. anti-inflammatory medicines that require testing in many patients and multiple indications before differentiation from standard of care is possible ("long time or high investment required to determine mega-blockbuster potential," category "b"). Hypothetical products "c" and "d" both have lower commercial potential (i.e., stable products) and differ in the

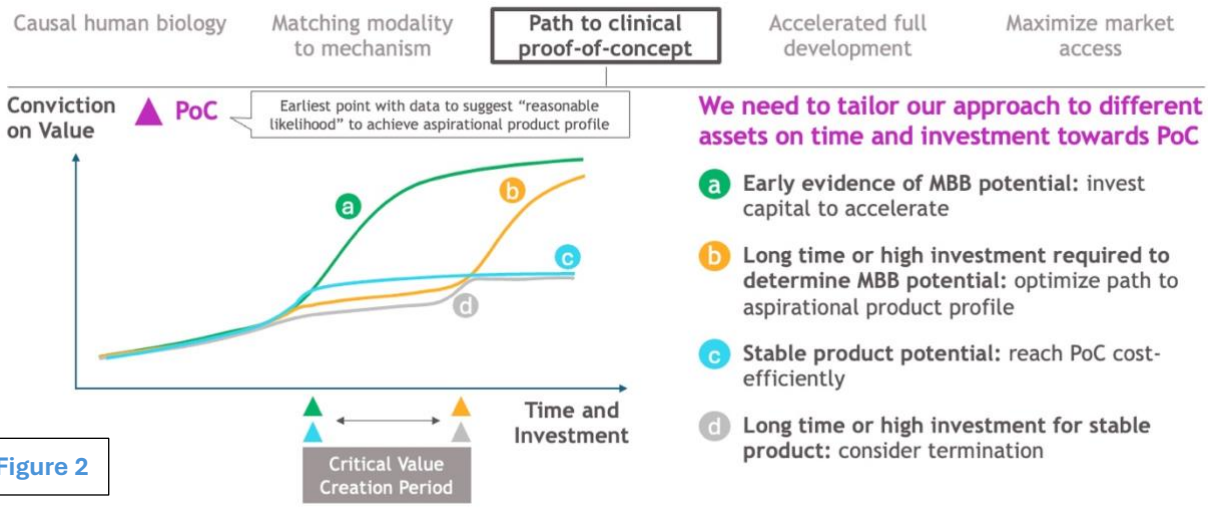

Figure 2

time and investment required to establish commercial potential. Examples in oncology include first-in-class targeted therapies in low prevalent indications with rapid PoC (category "c") vs. best-in-class targeted therapies that require larger PoC studies to demonstrate differentiation from established treatment options (category "d").

Note that a biopharma's decision to invest in a program that falls in one or another CVCP category depends on many factors. While everyone wants something in category "a," the reality is that there are not many of these types of assets. Some companies may decide to invest in category "b" assets (mega-blockbuster potential with large investment to PoC) if it fits with a broader therapeutic area or company strategy, whereas others may decide to forego these investments in favor of earlier de-risking clinical trials. Similarly, some companies may invest in category '"c" assets (stable products with early PoC) whereas others may decide small returns are inconsistent with broader financial ambitions. What should be clear is that expensive and extended PoC assets with only stable product potential (category "d") should be minimized.

There are key questions a biopharma organization should ask as programs advance along the RDC continuum (Figure 1). First, what will it cost (time and money) to deliver an aspirational product profile at PoC? **Second**, once PoC is achieved, how can acceleration be achieved in clinical development? **Third**, what concentrated risk is acceptable to maximize value for an organization? And **fourth**, what trade-offs are needed to maximize the ratio of stable and mega-blockbuster products?

Section 2: Poker analogy

OK – now to poker. Again, for those not interested in poker, go straight to Section 3. First, a brief primer, with help from ChatGPT.

Texas hold 'em is a card game where players compete to have the best combination of cards and win chips or money from other players. The main goal is to make the best five-card hand possible based on two private cards and five community cards. The player with the best hand wins the round and gets the pot (all the chips or money bet during the game). Sometimes, a player can also win by making everyone else fold (quit the round), even if their hand isn't the best.

To start, each player gets two cards they keep secret (called "**hole cards**"). Players place a bet or fold based on these first two private cards. Once betting is complete, the dealer places three community cards face-up and visible to all players. This is called "**the flop**." Players bet, check or fold based on the five -card combination of two private cards and three community cards. Next, the dealer places one more community card face-up for a total of four community cards. This is called "**the turn**." Players bet, check or fold based on the five -card combination of two private cards and four community cards. Finally, the dealer places one more community card face-up. This is called "**the river**." Players bet,

check or fold based on the five -card combination of two private cards and five community cards.

After all the betting rounds are done, players show their cards, and the best five -card hand wins. Hands are ranked based on their strength, with a Royal Flush (the best possible hand) at the top. Four of a kind is better than three of a kind is better than two of a kind is better than a single high card. There are other combinations ("full house" [two of a kind and three of a kind in one hand], "straight" [five sequential cards], and "flush" [five cards of the same suit]) that are better than three of a kind but worse than four of a kind.

What is important to know – and what is relevant for the drug R&D analogy – is that the probability of success fluctuates after each round of betting. A player could have a very strong hand with the first two private cards (e.g., pair of aces) and feel very confident about their chances of winning. However, if the next three community cards ("the flop") are of the same suit, are sequential cards, or are two cards of a lower suit (e.g., pair of tens), then suddenly the odds may change in the favor of another hand. The next two community cards refine odds further – either in favor of or against a winning hand.

The biggest change in odds for a particular hand occurs when the flop is revealed. The flop significantly alters the probability of making a strong hand based on the community cards and drastically changing the odds of winning depending on the initial hole cards and the flop's composition. This is because the flop provides crucial information about potential hand types like pairs, straights, or flushes, allowing for a large shift in perceived hand strength compared to pre-flop estimations. If players remain, then the final card of the five community cards (the river) is the ultimate card which decides who wins and who loses.

How are odds of winning in poker related to odds of a successfully approved drug in biopharma R&D? In drug R&D, programs that start clinical trials have an ~10% chance of becoming an approved drug. Once PoC is achieved, odds increase up to 30-60% of becoming an approved drug, depending on several factors (e.g., strength of the therapeutic hypothesis, quality of PoC achieved). Once an investigational medicine starts Phase 3, there is an ~60-70% chance of becoming an approved drug. Again, the biggest inflection in PoS is from Phase 1 start to PoC achieved (a delta of up to 50%), consistent with the biggest delta in Texas hold 'em occurring with the flop.

Continuing with the analogy, the first two private cards are analogous to discovery research (pre-IND programs), where one card represents the biological target and the other card represents the therapeutic modality that perturbs the target. Using R&D principles I have described previously, these two cards represent "causal human biology" and "matching modality to mechanism." The three community cards, aka the flop, represent early development, when it is possible for the first time to see the effect of perturbing a target in humans. Moreover, if a PoC is designed effectively, a lot of information can be revealed about a therapeutic hypothesis at this stage of R&D. By analogy with poker, early clinical

development represents the biggest change in odds for an R&D program (from ~10% to potentially >50%, depending on the quality of PoC designed and achieved). Phase 2 development is equivalent to the turn, and Phase 3 development is the river. The final card is the card that ultimately determines success or failure in poker, just like Phase 3 is what ultimately determines success of failure of an investigational drug. But the biggest change is odds is the flop not the river.

To summarize:

Hole = first two private cards = discovery research (pre-IND programs)
Flop = next three community cards = Phase 1 early development = *biggest change in odds*
Turn = fourth community card = Phase 2 development
River = fifth community card = Phase 3 development = *ultimately decides who wins / loses*

There is one more relevant analogy to poker: proprietary vs. public information, and how that guides the competitive landscape. For most large biopharma companies, pre-IND portfolios are confidential. That is, the targets and modalities are not publicly disclosed until a clinical trial starts. In the same way, hole cards are private to an individual poker player. In contrast, once a program enters clinical development, the biological target and therapeutic modality are publicly disclosed. By analogy, the flop represents the first set of community cards, which is information available to all poker players. Once targets and modalities are disclosed, a new level of competition emerges among biopharma companies.

I recognize that for many readers, this analogy is too esoteric to be helpful. Hopefully for some, the concepts resonate. Now, back to the CVCP model, and the practical implications of the model.

Section 3: Practical implications of the CVCP model

It is important to create a biopharma organization built around the CVCP investment thesis. This includes a commitment to defining strong therapeutic hypotheses and aspirational product profiles in Research; testing high quality PoC that yield aspirational product profiles in early clinical development; engaging in portfolio prioritization that maximizes opportunities across the full RDC continuum; accelerating clinical development and concentrating risk at the appropriate stage of clinical development; and allowing for unexpected or "black swan" mega-blockbuster opportunities.

More specifically, there are four ways a biopharma company can leverage the CVCP model. I briefly described these four concepts in Section 1, using **Figure 1** as a reference and laying out the "what" of the CVCP model. Below, I explain the "how."

1. **Minimize the time and capital invested to get to the clinical PoC inflection point.**

a. Invest in an **R&D framework** that increases probability of success at PoC and increases probability of delivering mega-blockbusters. In previous blogs I have defined three key areas of Research and Early Development, to which I now add principles in full Development and Commercial:
    i. Causal human biology (CHB)
    ii. Matching modality to mechanism (MMM)
    iii. Path to clinical PoC (P2PoC)
    iv. Accelerated Full Development (AFD)
    v. Maximize Market Access (MMA)
b. As part of the R&D framework, it is important that an organization has connectivity across RDC continuum to *collaboratively* define **aspirational product profiles** that are feasible to test in early development. There needs to be support from Development that the P2PoC is clinically and operationally feasible, and there needs to be support from Commercial that an aspirational profile will deliver either a stable or mega-blockbuster product.
c. Once a path to PoC has been defined, it is important to **empower and reward teams** to deliver on PoC on time and according to plan.
d. Once teams have charted a course to PoC, it is important to **minimize strategic de-prioritization pre-PoC**. This should not be underestimated as a source of inefficiency in large biopharma companies, where there may be a disconnect across the RDC continuum.
e. Companies should invest in **differentiated modality platforms** that compress timelines and decrease investment from new idea to positive PoC (e.g., targeted protein degradation, radiopharmaceuticals, cell therapy). An upside of investment in a differentiated platform is as products emerge, it is more difficult for new entrants to penetrate the moat established with a differentiated platform.
f. Companies should invest in **artificial intelligence (AI) and machine learning (ML)** to efficiently deliver new medicines into clinical development to test clinical PoC. For example, it is now possible to implement AI/ML for predictive molecule invention via multi-parameter optimization of small and large molecules in late discovery. See my recent blog here on AI/ML in Research and a link to a BMS video on predictive molecule invention here.
g. Companies should have a **robust Research BD strategy** to partner externally in areas for which a company does not have internal expertise and/or in areas that have the disruptive potential.

2. **Increase the PoS of a positive PoC clinical study and ultimately PoS of an approved product.** While PoS is largely set by the R&D framework, there are additional considerations in clinical development.
    a. A successful biopharma company needs to be very clear on **what constitutes PoC**. As above, PoC will vary by asset and indication.
    b. Ensure **creative clinical trial designs to test PoC**. While there may be a tendency for a fully baked first-in-human (FIH) start to new molecular entity

(NME) approval plan through all stages of clinical development, such a plan may be cost prohibitive, which in turn may discourage risk-taking and experimentation in early development.

c. Invest in **clinical, biomarker and translational** plans that allow one to determine as early as possible if an aspirational product profile is achievable. A deep understanding of the R&D framework (especially CHB to P2PoC) and a clinical plan that is evaluating probability of achieving the profile can facilitate prioritization decisions.
d. Leverage CVCP insights to identify **external assets** that are underappreciated or misunderstood by competitors (e.g., mechanism of action of a therapeutic modality, models of disruption for mega-blockbuster opportunities). While this includes differential access to BD deals through creative deal structures in Research focused on platforms, modalities, and high-risk programs, the focus here is bringing in clinical assets at an early stage of development. Note that while late-stage acquisitions almost always have high PoS, because late-stage assets fall outside of the CVCP, there is much less value returned (see below).
e. As in Research, companies should invest in **artificial intelligence (AI) and machine learning (ML)** to efficiently execute clinical trial plans (e.g., site selection, document writing, data interpretation). As part of the AI/ML investment, companies need to pressure the organization to compress timelines and constrain costs while always focusing on quality.

3. **Increase speed to high value markets (e.g., number of indications and patients with favorable pricing).**
    a. Establish a **decision-making and prioritization framework** that understands the CVCP dynamics, with the ability to recognize the most promising mega-blockbuster opportunities to invest behind. As above, it is important to minimize strategic de-prioritizations pre-PoC, assuming there is alignment across the organization on the path to PoC and the potential of an aspirational product profile. At the same time, portfolio prioritization is critical to resource the most promising programs – and stop those that are less promising. Once a program is identified as a high priority, it is important to move as quickly as possible to registrational trials.
    b. It is important that a biopharma company has a **clinical trial infrastructure** that is equally positioned to testing clinical PoC in early development and accelerating registrational trials. That is, clinical development speed comes in two flavors: speed to PoC and speed from PoC to the commercial market.
        i. If an aspirational profile is recognized in late discovery, then speed through *all stages* of clinical development is warranted. This is the exception rather than the rule.
        ii. For most medicines, the aspirational profile is not recognized until clinical development, and appropriate patience through early development may be required until PoC is adequately tested.

4. **Increase the ratio of mega-blockbuster to stable products.**
    a. As above, an organization should continuously evaluate whether a program has an opportunity to become a mega-blockbuster product (i.e., "hunt for mega-blockbusters"). This will require **portfolio prioritization** and difficult trade-off decisions along the RDC continuum.
    b. Establish a culture where a portion of the portfolio (10-20%) is directed at **new opportunities** that may fall outside of a company's commercial strategy (aka, "black swan" events), assuming such new ideas are consistent with the R&D Framework and can be tested in a capital-sparing manner. This will allow a biopharma company to deliver unexpected mega-blockbusters.
    c. Ensure robust **engagement with the external BD community** to continuously source and identify mega-blockbuster opportunities. Many of these partnerships will be within Research, with the ability to bring programs into early development to test PoC.

Section 4: Case studies of CVCP in action

Cystic fibrosis (CF). Aurora Biosciences was a small company developing small molecule chaperones in cystic fibrosis. In 2000 Aurora struck a deal with the Cystic Fibrosis Foundation (CFF) to advance these programs. In 2001, Aurora was acquired by Vertex for access to a discovery platform – *not* the CF discovery assets. Vertex agreed to continue the CF discovery programs via funding from the CFF. Consistent with the CVCP model, Vertex advanced the lead molecule, ivacaftor, into a PoC study in a small subset of CF patients (G551D mutation carriers, which represents ~5% of the overall CF patient population). The aspirational profile was achieved in a 39 patient, 28-day PoC study (link to the 2010 NEJM publication here). This observation encouraged the development of next-generation molecules. Today, the CF portfolio delivers >$10B in annual revenue for Vertex (link here). For more on this case study, see this blog from David Shaywitz, which also goes into depth on other features related to the R&D principles described above.

Hypertrophic cardiomyopathy (HCM). MyoKardia was launched in 2012 by academic investigators steeped in the molecular understanding of HCM. The company leveraged several decades of genetic and biochemical research in HCM (short summary slide deck here). In 1990, the first genetic mutations in the sarcomeric protein, *MYH7* (R403Q), were identified in the laboratories of Kricket and Jon Seidman at Harvard Medical School (here). Since that initial discovery, >100 genetic variants have been described in *MYH7*, which cluster in the myosin head and are enriched in HCM cases (14%) vs. controls (1%) (here). Structural, biochemical and molecular analyses in engineered human cells, reconstituted human protein systems, and *in vivo* animal models demonstrated that *MYH7* mutations dysregulate actin-myosin cross-bridges, leading to enhanced contraction, impaired relaxation, and a persistent energetic burden. These genetic and molecular observations led to the development of a biochemical assay where ATPase rate served as a proxy for the number of actin-myosin cross-bridges that form during a completed power cycle (here). From this biochemical screen a small molecule myosin inhibitor was identified. In a small,

open-label clinical trial of 21 symptomatic patients with obstructive HCM (oHCM), mavacamten demonstrated reduced left ventricular outflow tract (LVOT) obstruction and improve exercise capacity and symptoms in patients with oHCM (2016 PIONEER-HCM publication here). This was the key inflection point in this program, consistent with the CVCP investment thesis. Subsequent randomized control trials demonstrated the safety and efficacy of mavacamten in oHCM, and the drug was approved by the FDA in April 2022 (here).

Concluding remarks

In this blog post, I argue that long-term success in the biopharma industry requires a strategic balance between developing stable products that provide reliable returns and pursuing mega-blockbusters with the potential for outsized gains. I present an investment thesis emphasizing the importance of a dual approach. I explore the CVCP, where the probability of success increases significantly, and mega-blockbusters can be differentiated from stable products. I use an analogy of the flop in poker to reinforce the change in odds that occurs in the CVCP. I outline key principles for minimizing time and capital to reach PoC, increasing the PoS at PoC (and ultimately the PoS for approval), increasing speed to high-value markets, and increasing the ratio of mega-blockbusters to stable products. Through two brief case studies, I demonstrate how biopharma companies can enhance their return on invested capital. Overall, the blog aims to provide actionable insights for biopharma organizations seeking to navigate the complex landscape of value creation and achieve sustainable growth through the delivery of life changing medicines.