COMMENTARY

Enabling Warp Speed Using the Hypervelocity Innovation Model: A Blue Print for Drug Development in Pandemics

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Pharmaceutical research and development is organized around prioritized investments, delivering on assets with the greatest return of investments. Linear sequencing of trials and financial risks are determinants of speed in an enterprise. There is less flexibility in leveraging expertise around priorities that are thrust on the system by external forces. This commentary provides an insight into enabling warp speed using a hypervelocity mindset for mobilizing resources and scientific creativity for accelerated timelines in response to pandemics. For a description of terms used in this commentary, the reader is referred to Supplementary Text S1.

AN ORGANIZATIONAL APPRAISAL OF INNOVATION: DRIVERS OF RISK-BASED INNOVATION

Innovation requires the ability to take higher order risks. In drug development, there is often a defensive mindset at play and such a risk posture can hamper innovation and reduce productivity.1 Using the validated scale of Hansen and Birkinshaw,2 a survey-based analysis in which 50 pharmaceutical companies of varying sizes participated, the survey revealed high scores on 2 dimensions, namely, difficulty with which ideas got funded, and that there was a risk averse attitude toward investing in novel ideas.1 The survey revealed (summarized in Table S1) that, in general, there was a good degree of collaboration across units and businesses. Idea sources appear to transcend specific organizational boundaries—originating from within and beyond firm’s immediate environment. There was a good degree of idea sourcing within the organization and there is sufficient agility in the organization to leverage fast to patients. These observations suggest that ideation and diffusion are not problem areas in an innovation enterprise. Because the analysis revealed two potential weak links, difficulty in getting ideas funded and a risk-averse attitude, firms are conversion-poor.2 It is poor in selection of concepts for further advancement, likely as a result of intolerance toward risk. This aspect warrants an understanding of how innovation occurs within an enterprise, and, more importantly, what change situations do to the organizations. A change situation is one where an organization reacts to a certain situation that could affect the ways of the firm in unprecedented ways (e.g., the coronavirus pandemic). This aspect is further analyzed as follows.

FACILITATING CHANGE TO PROCESS HYPERVELOCITY CONDITIONS

The speed of drug development is often informally characterized as velocity, wherein there is a passage of new drugs through a stage-gate process. Increasing the velocity of the pipeline flow is often achieved by including innovative tools, decisionable biomarkers, adaptive designs, integrative end to end pharmacometrics, or using health economic modeling and simulations. The term hypervelocity is usually referenced in space research, and signifies super high velocity. The author introduces a new use of the term hypervelocity to describe the pressing patient need in pandemics, which require a heightened sense of speed and resource mobilization in the backdrop of significant uncertainty to deliver therapeutics in the face of pandemics.

An issues that may have contributed to poor conversion rates is the lack of agility in the organization and tolerance toward risks. A risk-averse culture may reflect the presence of greater bureaucracy stifling innovation. The inherently large failure rates for new molecular entity (NME) development (1 in 10 compounds reach the market as a drug) coupled with the slow innovation nature of the NME business predisposes an innovation enterprise to stage its investments carefully. Such a predisposition contributes to an organizational lethargy, which, in the context of the short window of opportunity that exists for opportunistic investments, may create an unsustainable barrier to value maximization.

Hansen and Birkinshaw2 indicated conversion-poor companies will benefit from multichannel funding and safe havens. These approaches supplement existing firm infrastructure for resources and funding and allows a firm to devote protected resources to elicit concerted action. Let us further examine these aspects.

In a pipeline-centric model (as we call prioritized-investments model), there is a single pipeline and single funding and resource pool. For example, a firm may opt for a particular therapeutic area focus for such investments. When a change situation occurs (e.g., a repurposed product for a new indication) the new situation now competes with the prioritized investments for resources and funding. Invariably, the new drug candidate for that therapeutic area gets a higher priority and the repurposing of the molecule may receive a lower priority. Although the former

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Table 1 Drivers for innovation performance for the hypervelocity innovation model: a road map for warp speed

| Strategy                  | Processes                                      | Resources                                      | Organization                  |
|---------------------------|------------------------------------------------|------------------------------------------------|------------------------------|
| Hypervelocity             | New second pipeline apparatus that is agile and nimble | Skunkworks model that relies on fast to proof of concept | Reward structure that incentivizes risk taking and idea conversion |
| Strategic alignment between accelerated innovation and business strategy | Creation of an entrepreneurial culture | Staffing with top talent freethinkers and employees that exhibit an opportunistic attitude | Facilitative, productive dialog fostering co-evolution |
| Accountable innovation practices – leading from the top | Value chain that starts with the best ideation to validated prototypes showing proof of concept | Focus on dynamic capabilities and core competencies | Transformational and crisis leadership |
| Patient centricity        | Accelerated development timelines               |                                                | Commonsense approach to decision making, not complex algorithm routines on risk |
|                           | Focus on continuous improvement and learning from best practices |                                                | Emphasize creativity over operational excellence and stewardship |

provides an anticipated benefit more than 10 years in the future, the latter provides a more imminent benefit in enhancing patient value.

In a patient-centric model (as we define hypervelocity model), there may be multiple pipelines and multiple sourcing models created with more directed investment funding pool established to support emerging diseases or pandemics. This might, for example, lead to funding from external sources either government or nongovernmental organizations. The funding of such ideas is at a noticeable fraction of that required for the NME, and can be stage-gated to weed out the low probability ideas and select ones with high probability of technical and commercial successes for full development.

The hypervelocity enabling apparatus should be nimble, leveraging the power of “skunkworks,” with little managerial oversight to avoid hindering its mission. This creates a safe haven for emerging realizable opportunities, which may fall by the wayside in the firm’s current organizational structure.

The cultural environment within the patient-centric apparatus will be entrepreneurial in nature. Individuals, teams, and managers will be expected to exercise entrepreneurial alertness and attitudes toward risk taking. Like Hamel proclaims, entrepreneurs create new wealth while stewards conserve. Over time, the conserving attitudes paralyze the organization’s ability to remain vigilant to new business opportunities. There may be hybrid models where there may be a primary pipeline apparatus that plays a conserving role, while a second pipeline apparatus can be opportunistic, tolerant to risk-taking, and be entrepreneurial. Creating an overall organizational balance between these two forces will also develop agility in thinking while creating a buffer between long-range and short-range goals.

Such an organizational mindset change will be more aligned with a patient-first strategy, where the singular goal is improving quality of life for patients. It will be incumbent upon firms to establish patient-centric innovation as a priority for the company, and directly take ownership for innovation productivity. This will send strong signals aligning innovation priorities as a key link to company business strategy to the rest of the organization on enhancing product and patient value. Table 1 summarizes the critical determinants of successful innovation performance.

TACTICAL ACTION PLAN TO IMPROVE CREATIVITY AND INNOVATION FOR HYPERVELOCITY INVESTMENTS

There are three principal areas of improvement. These are:

- Creating an agile process that enables rapid screening of ideas into full development at low investment costs—is the idea feasible? If not, terminate quickly.
- Developing innovation teams (“skunkworks”) that are small in size, with sufficient authority to rapidly generate concepts into decisions.
- Creating an enabling culture and a decision framework that provides innovation teams with less constraining oversight to chase hypervelocity conditions.

These areas are further expanded below.

Agile process development

The innovation value chain is divided by distinct stages separated by a gate that filters the concepts. This process allows measuring the probability of success of any given idea as it moves through the process and allows decisions to be made in a timely fashion. A model can balance creativity and value capture. The degree of uncertainty will reduce as the idea moves through the various stages of the value chain. A hypervelocity poster organization should transition from reactive thinking to proactive thinking, as it relates to managing an innovation model within a stage-gated process.

A crowd-sourcing model can be used to generate ideas. Ideas for these opportunistic investments can come from internal and external sources, including precompetitive knowledge-sharing networks or public-private partnerships or consortia. Simple rules can be readily applied, including refraining from criticism, allowing freewheeling, and idea improvements. Once ideas are brainstormed, a next step may be understanding the whitepaper feasibility of that idea. The primary goal of this stage is to complete a theoretical feasibility analysis. The advantage of this stage is to identify showstoppers immediately and identify whether a concept may technically necessitate an unusually high resource requirement (such as a unique or somewhat inaccessible patient population). Once the idea is deemed
feasible, the concept is reviewed by a network of experts before transitioning into experimental investigations. During the experimental phase, prototypes of the product concepts are developed and tested to see if the product meets desired objectives (e.g., designing a proof of concept trial for a vaccine for coronavirus). Once the data are available from such a trial phase, a technical review is initiated and a recommendation is made for full development leveraging big data and real-world evidence.

Innovation teams and empowered actions
Another critical organizational improvement is in developing the right team to execute on the opportunistic-investments model, modeled after the “skunkworks” concept by Rich and Janos. This will facilitate a change from reactive to proactive thinking. The NME asset development teams (NME teams) are positioned in a way that embodies linear thinking. Such linear thinking is a constraint for creativity and innovation.

More specifically, these innovation teams need to exercise creative realism in the Finke's creativity model as opposed to the conservative realism that exists in asset development teams. This is because innovation teams need to be highly imaginative and highly connected to the expert knowledge to be able to visualize the full scope of the patient and product value. Innovation teams are to exercise divergent thinking, again contrasting to convergent thinking that may exist in asset development teams. Building internal and external networks and collective creative cognition will lead to the generation of dynamic capabilities, core competence, and resilience of the organization.

APPLICATION OF THE INNOVATION FRAMEWORK TO THE CORONAVIRUS DISEASE-19 THERAPEUTIC DEVELOPMENT

The current coronavirus pandemic has presented an opportunity for engaging warp speed with the hypervelocity innovation model described here. Because this is a global health urgency, such an asset development will fall outside of the firm’s immediate prioritized innovation stream. From the time of the World Health Organization (WHO) alert on coronavirus disease 2019 (COVID-19) genetic sequencing in January 2020, a firm with capabilities in infectious diseases drug development and/or vaccines would have initiated a skunkworks team to define the scope of hypervelocity development of repurposed drugs and/or novel vaccines. In discussion with global health authorities, preliminary agreements on the proposed course of action and approvability would be sought.

Figure 1 describes the model in comparison with the traditional model. The model is built in two distinct phases, paper feasibility and experimental feasibility.

1. Paper feasibility would involve the following:

Whether the asset has potential efficacy in patients with COVID-19?

The more prudent way is to understand how a potential drug works, and whether there is anything in the emerging biology of coronavirus that makes the drug worth studying. Any past antiviral efficacy assessments are considered together with drawing parallels from other emerging infectious diseases (e.g., HIV, Ebola, etc). This paper feasibility would also assess the viral cell cycle and the vulnerability points within the cell cycle.

Are there safety and exposure margins to test the concept in humans safely?

If there is an asset already in clinical development, then there may be existing data that identified a dose and regimen that is generally safe and well-tolerated to evaluate in clinical trials in patients with COVID-19. Understanding the emerging natural history of disease and evolving symptomology of patients with COVID-19 can assist in identifying unique considerations from a safety perspective.

At this stage, drugs, such as chloroquine, hydroxychloroquine ivermectin, and azithromycin, may have been terminated because of questionable efficacy and safety aspects. Combinations may need to be pursued instead of monotherapy, leveraging learnings from HIV-1 therapeutics evolution.

2. Experimental feasibility would involve the following:

Whether the drug inhibit severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) and if so, at what concentrations?

Once there is presumption of efficacy but uncertainty in how the drug could work in terms of the mechanism of action (i.e., whether the drug directly effects the virus or affects something in the downstream pharmacology), the next step is to run a cell-based incubation in vitro test in SARS-CoV-2 isolates. That test would yield the half-maximal inhibitory concentration values of the drug. At this point, using modeling, one can understand whether clinically equivalent concentrations can be achieved, and whether the drug has a direct effect.

Translation of in vitro findings to human drug effect and identifying a dose and dosing regimen.

Whereas in vitro activity is helpful, it represents an artificial system wherein the virus is directly exposed to the drug. Mathematically modeling the data can assist with the design of accelerated hypothesis generating experiments. Once there is an half-maximal inhibitory concentration against SARS-CoV-2 isolates, leveraging tools like physiologically-based pharmacokinetic modeling to pick the dose and regimen for use in a clinical trial can be done. They assist with determining the pharmacokinetic exposure coverage with various dosing “what if” scenarios. More sophisticated models, including drug-disease models, would leverage other features of the drug, including potential safety features that might otherwise limit full exploration of dose range in humans.

Executing real-world clinical study (seamless phase I–III study design)

Selecting the patient population that will have the highest probability of success. The complete spectrum of symptomology and comorbidities associated with
COVID-19 complicates selecting the right population for the investigational asset. Understanding the points of vulnerability around the cell cycle as well as the stage of infection, relative to time of infection to the onset of symptoms, are crucial for identifying the right stage of disease. Early trials in this regard focused on severe disease as patient populations included those that were hospitalized and on mechanical ventilators. Model informed approaches can be used to select patients with mild disease, moderate disease, and/or severe disease based on biological plausibility.

Choice of comparator and end points. Seamless interactions with regulatory agencies allows the trial to be conducted in an adaptive, model-informed manner. At the start of the pandemic, there was no standard of care for COVID-19, and the focus of regulators were on the most prudent design, which was a randomized, placebo-controlled trial. With time, however, many presumptive standard of care options emerged, most notably remdesivir and interferons. A seamless integration approach can be accomplished using flexible, adaptive trials that explore multiple objectives.

There are many end points to consider, including mortality, time to mortality, hospitalization, time to hospital discharge, symptoms, and biomarkers. Building the trial in such a way that addresses both learning and confirmatory objectives is key. In this regard, leveraging real-world evidence as applied in rare diseases affords an accelerated pathway to registration (21st Century Cures Act), based on compelling weight of scientific evidence using biomarkers and novel trial designs.

Choice of clinical trial sites. To ensure operational success for the trial, it is expected to leverage open source networks and consortia with nonprofit and nongovernmental organizations to ensure the broadest possible pool of patients were available to mitigate against the uncertainty of a global pandemic. The paucity of truly global trials in the early phase of this pandemic has generally limited a comprehensive understanding of generalizability with regard to policy.

It is anticipated that such behavioral alterations to enable hypervelocity can result in agility within an enterprise.

SUMMARY

The author has proposed firm level enhancements for enhancing hypervelocity creativity and innovation, such as those necessary for pandemics. These modifications are designed to increase the conversion rate of ideas into viable products in the shortest possible time.

Three key lessons emerge from this analysis. These include:

- **Innovation builds on existing incremental knowledge** – The success of the opportunistic-investments strategy is deeply linked to prior knowledge from the product and therapeutic area expertise. Making pandemics as future-proof as possible is an example of incremental innovation.
- **Leverage the power of collaboration** – Creativity is enhanced in groups, the source of intangible synergy of teams. This coupled by crisis leadership will enable the hypervelocity model.

*Figure 1* Contrasting the conventional vs. hypervelocity innovation model.
• **Compatibility to the external context** – This is an essential attribute to a hypervelocity strategy, which relies on what patients want and at what speed.

**Supporting Information.** Supplementary information accompanies this paper on the Clinical and Translational Science website (www.cts-journal.com).

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