5 Methods to Accelerate Drug Development through Clinical Supply Chain Improvements

The drug research and development (R&D) cycle and supply chain for pharmaceuticals have been thrust into the spotlight by the ongoing COVID-19 pandemic. Numerous antiviral and vaccine candidates are progressing through clinical trials and hold promise for a comprehensive solution. Among the factors that impact the timeline to approval of any safe and effective treatment, clinical supplies play a role crucial to successful study execution. A considered application of innovative methods to clinical supply chain management can unlock value by simultaneously reducing costs and expediting time to market. This next-generation clinical supply chain model that we need to weather the crisis today should be the one that we embrace as the new standard for tomorrow.

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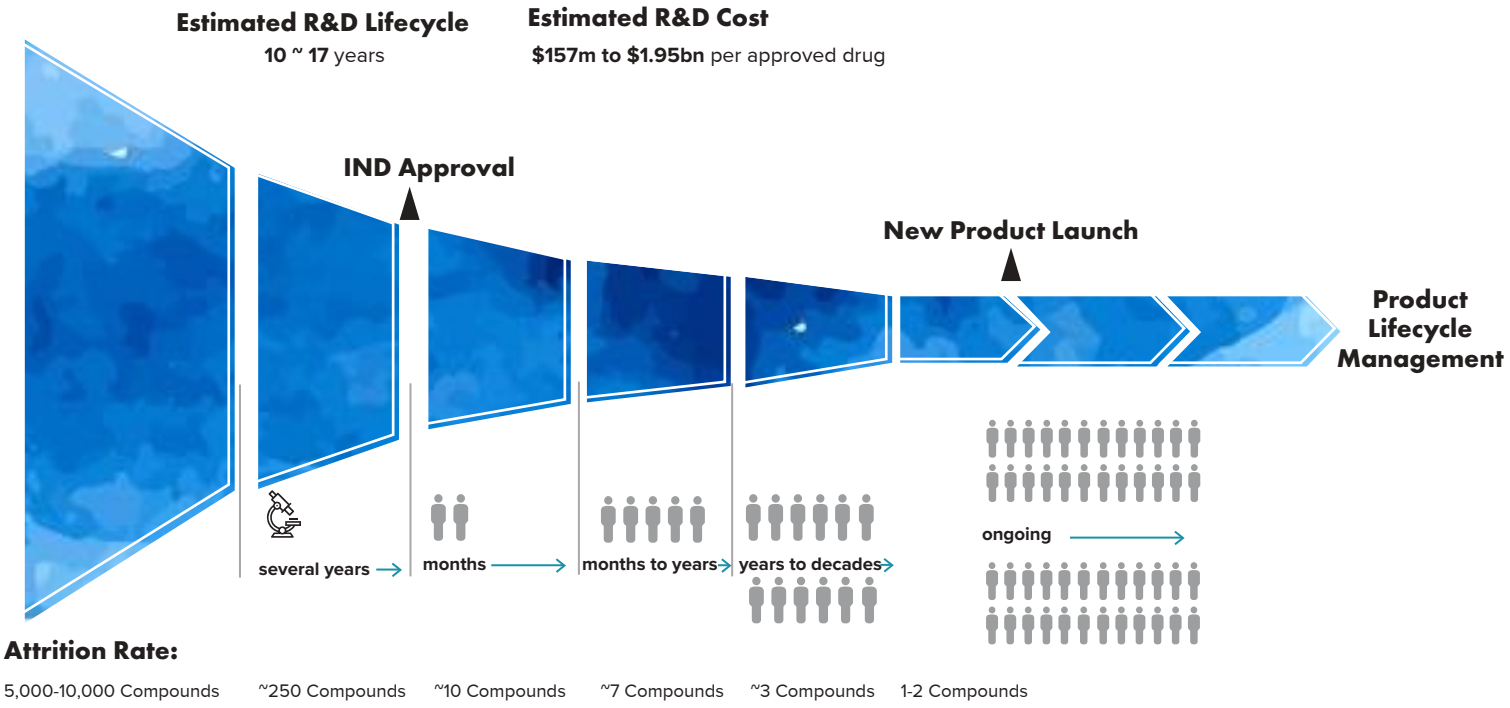
1 Drug Development Lifecycle

Since the end of the blockbuster era at the turn of the century, the drug R&D industry has experienced declining success rates, prolonged timelines and rising costs despite improvements in technology. This phenomenon has been described within the life sciences industry as **Eroom's law**. The typical R&D lifecycle for a new drug extends 10 to 17 years from discovery to commercial launch with expenses ranging from $157 million to as much as $1.95 billion. Conversely, the likelihood of successfully bringing any given investigational molecule from the laboratory to the market is dauntingly low – as poor as 0.01% to 0.02% by some estimates. This painful combination of high costs and low success rates pushes the total R&D investment to bring new drugs to market to a range that borders on the astronomical.

DRUG RESEARCH & DEVELOPMENT LIFECYCLE OVERVIEW



Moreover, although eventual patent expiration has always been an element of the pharmaceutical industry, **beginning in 2010,** a notable wave of high-value blockbuster drugs has lost patent exclusivity. This "patent cliff" has resulted in sharp revenue declines across the pharmaceutical industry, a trend that is expected to continue. The new reality stemming from this growing financial pressure has pushed drug makers to challenge the traditional drug R&D lifecycle and seek to break Eroom's law. From a supply chain standpoint, this has led to an increased focus on reducing clinical trial material costs while improving supply lead times.

2 Crisis Drug Development: A Dilemma in Focus

Prior to the present COVID-19 pandemic, the world outside the life sciences industry had only a limited understanding of the true length and cost of the drug development cycle. However, the current crisis has placed the vaccine development timeline in the crosshairs almost overnight. There can be little debate that humanity is in immediate need of safe and effective COVID-19 vaccines as the ultimate exit strategy to end the pandemic.

As with other drugs, vaccines are thoroughly tested in clinical studies, generally with a **greater number of human trial subjects**. Consequently, the timeline for a vaccine candidate to move from discovery to approval historically ranged from **10 to 15 years,** with the quickest approval taking four years. In the face of the pandemic, however, even this quickest time frame is generally acknowledged to be outside the acceptable range. Unfortunately, the development cycle cannot be simply compressed at the expense of patient safety and efficacy. R&D organizations must produce statistically significant clinical data at a large scale to demonstrate adequate safety and efficacy. Without this, we would be risking inoculating patients with unsafe vaccines that could cause consequences far more harmful than the virus itself.

Neither waiting for standard development lead times nor cutting risky corners is acceptable – so how can we realistically resolve this dilemma?

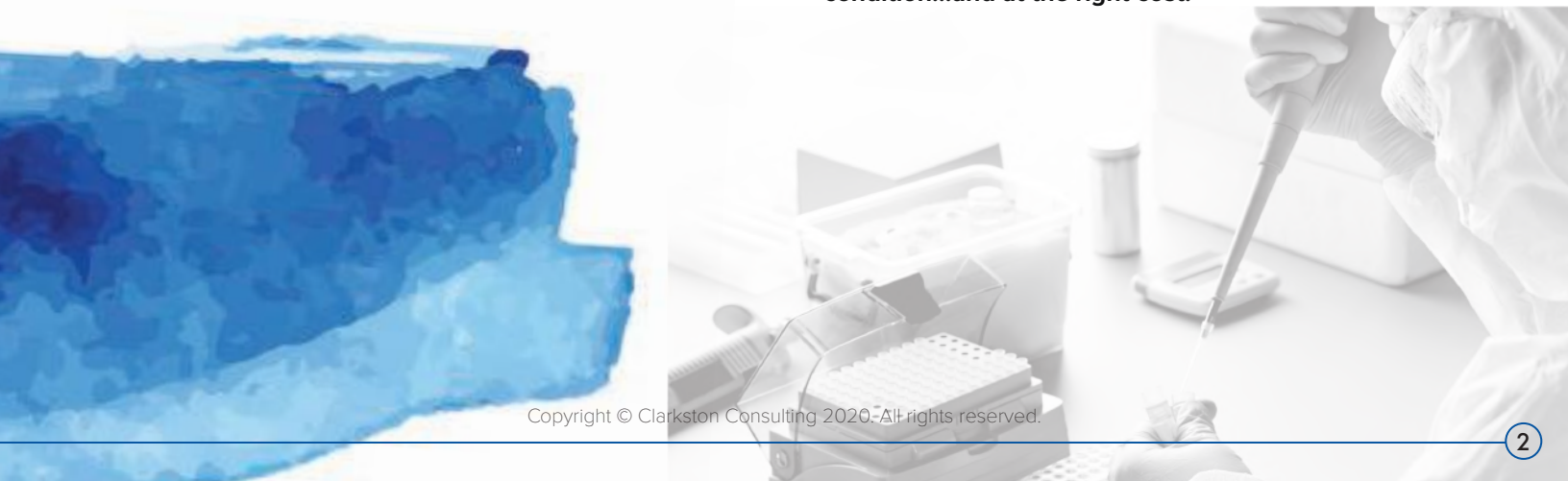
Fortunately, the creative and collective response from key drug value chain players is already offering actionable pathways forward:

- The U.S. Food and Drug Administration (FDA) has implemented the **Coronavirus Treatment Acceleration Program (CTAP),** slashing the agency's response times for COVID-related matters. This round-the-clock collaborative approach has cleared the way for researchers and scientists to launch new studies at an unprecedented pace. Turnaround times for early-stage administrative steps that would previously have taken months are now being measured in hours.

- Industry participants are coming together in an unprecedented fashion, collaborating in response to the global challenge. For example, **Sanofi and GlaxoSmithKline,** two of the world's biggest vaccine developers, started a partnership to leverage each other's proven technology platforms and combined manufacturing scale, aiming to bring COVID-19 vaccines to market in as little as 12 to 18 months.

- Compared to traditional fixed-sample methods, **adaptive clinical trials** allow for more flexible, efficient and faster protocol design and execution based on actual study results, speeding decision-making. **Embracing this adaptive design approach** in COVID-19 clinical programs offers the prospect of significantly increased flexibility, lowered cost and most importantly – compressed timelines.

Vaccine and treatment development, clinical trial designs and regulatory agencies are all making historical efforts to speed a treatment to patients. And as a strategic enabler in the drug value chain, clinical supply chains must match that speed to ensure **the right medicine delivered to the right patient at the right time with the right condition…and at the right cost.**



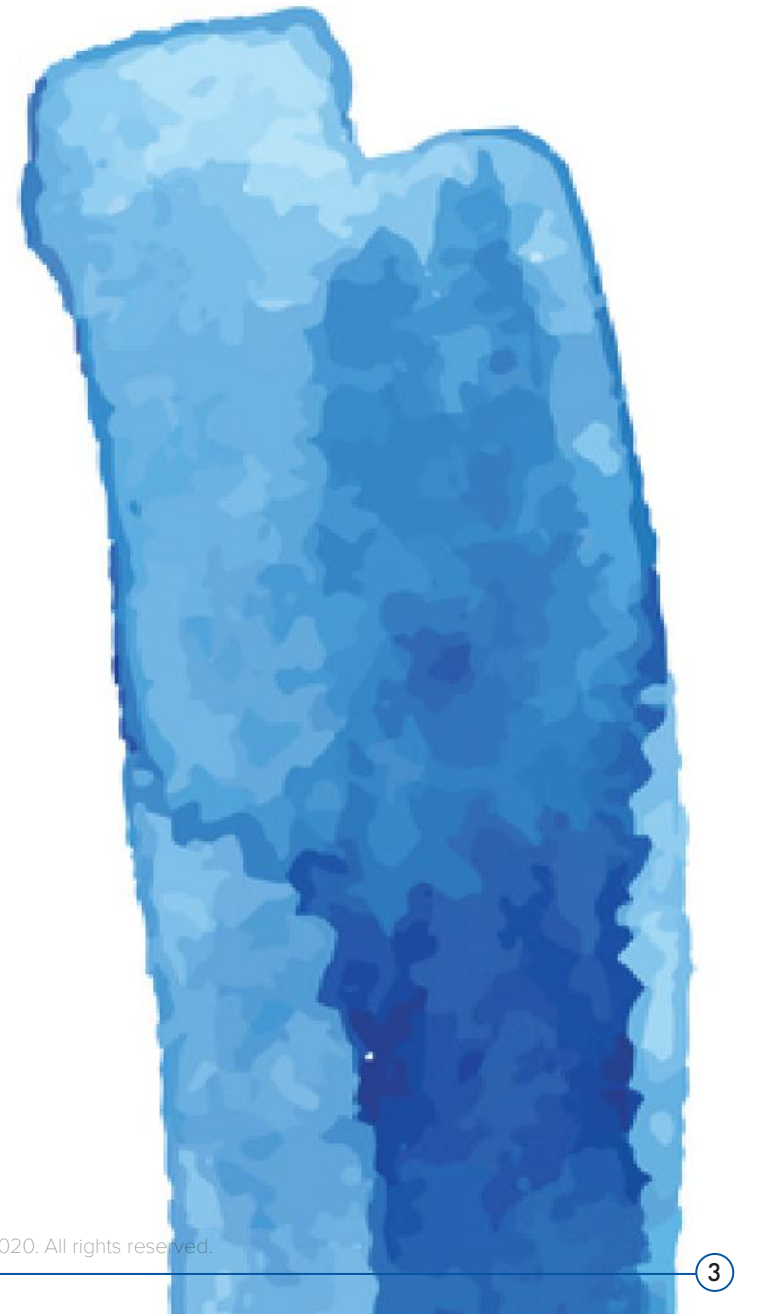
3 Clinical Supply Chain: Existing and Emerging Critical Challenges

Clinical supply chains face great challenges in both planning and execution, especially for late-phase, large scale trials. This frequently leads to a “firefighting” mentality focused on near-term issues instead of a proactive, collaborative view. Such a routinely reactive supply management approach could result in postponed study start-ups, patient disqualifications that potentially jeopardize study viability, and delayed milestone achievements. Key areas of challenges include:

- **Demand Planning:** Uncertain patient enrollment, patient dropouts, complex protocol design and sometimes “fast and furious” global study expansion efforts can lead to unpredictable demand signals. This demand volatility results in sharply limited response time for supply chains.

- **Supply Planning:** Due to clinical trials’ exploratory nature, actual study results frequently require changes to formulation and analytical procedures. This, when combined with low manufacturing process maturity and high-variance yields (especially for biologics), often leads to unreliable supply. Additionally, the long-established “push” supply strategy that prevails among clinical supply chains requires large investigational medicinal product (IMP) production batch sizes. This results in not only large inventory and expiry wastes, but also inflexibility to respond to material change requests. The extended “depot to site” supply chain to support global studies adds further supply risks due to complex labeling and country-specific import/export requirements.

- **GxP Compliance:** In the highly regulated drug development industry where cGMP (current Good Manufacturing Practice), GDP (Good Distribution Practice) and GCP (Good Clinical Practice) requirements must be followed, many IMP supply delays are attributed to human errors in manufacturing operations, data entry, documentation and material handling throughout the clinical supply chain. Exceptions that affect product quality and data integrity add to lead times in conducting investigations, documenting deviations and taking



corrective and preventive actions (CAPA). Depending on the disposition decision, rework may be required, which would further increase lead times of already-delayed IMP supplies.

- **Recent Clinical Trends:** Prior to the pandemic, the FDA had already introduced four designations to speed the availability of drugs in areas of unmet medical needs: priority review, breakthrough therapy, accelerated approval and fast track. The widening application of these expedited designations along with adaptive trial designs has had the positive effect of accelerated timelines. From a supply chain perspective, this further reduces the time to react to the abrupt demand and supply changes. In addition, the increased adoption of decentralized trials has added extra layers of complexity. The modern DtP (direct to patient) model requires even more robust planning and distribution capabilities, real-time temperature monitoring, traceability and control to ensure IMP availability at the right condition at the point of patient use.

- **Pandemic Impact:** The current pandemic has exacerbated these systemic supply chain challenges, as it demands clinical trial material availability in an unprecedentedly compressed time window. Given the stakes for people around the globe and the risk that trial results could be invalidated or drug approvals delayed, there must be zero tolerance for IMP supply disruptions during the crisis.

4 Lean and Innovative: A Path to Future-State Clinical Supply Chain

To drastically shorten the drug development cycle, clinical supply chains must undertake an evolution rather than the traditional stepwise or incremental improvement initiatives. This evolution starts with a new vision and a paradigm shift: in place of the long-standing “push” model that has dominated the clinical world for decades, we must build patient-driven “pull” supply chains that are agile, precise and responsive.

How to bring the next-generation clinical supply chain vision to life?
In my previous post **Seven Clinical Supply Chain Improvements Your CFO Will Love,** I discussed a set of foundational practices that can be quickly adopted to improve clinical supply chain performance. However, to actualize the next-generation clinical supply chain vision and leave Eroom’s law behind – vaccine and drug development companies must move beyond foundational capabilities toward more advanced and innovative supply chain practices. Concurrently, the ***Theory of Constraints (TOC) and Lean Thinking*** should be instilled throughout the value chain to shift people’s mindset and behavior. These proven practices will help guide the R&D organizations to identify, exploit and elevate key “breakable” constraints or bottlenecks across the

end-to-end supply chain. This will reduce uncertainty at the source wherever possible, and “mercilessly eliminate” muda (無駄) activities that are ultimately non-value-added for patients.

Key advanced clinical supply chain capabilities include:

1. **Control Controllable Variables** by creating more predictable demand planning capabilities.

- Involving clinical supply chain stakeholders at the early stage during the protocol development cycle can positively influence study designs and make them more supply friendly. This will help eliminate self-inflicted supply constraints at the source of demand.

- Adopting a fact-based and data-driven decision-making approach to evaluate scenarios can help to optimize flexible study parameters (e.g., randomization designs, visit intervals). This will reduce demand uncertainty and increase dosing agility.

- Replacing labor-intensive and error-prone manual spreadsheets with advanced forecasting and analytics tools will help clinical supply managers quickly convert complex study assumptions into time-phased finished goods (FG) demand, and develop actionable predictive models that drive effective supply planning and risk mitigation.

NEXT GENERATION PATIENT-DRIVE CLINICAL SUPPLY CHAIN CAPABILITIES

1. Predictable Demand Management	2. Agility & Precision Driven Supply	3. Site Handing Efficiency Optimization	4. Lean Thinking & Sense of Urgency	5. True Value Chain Collaboration
Centralized Planning	Planning Bill of Materials	Multi-Echelon MRP Tool		
Scenario Planning/Situations	Monthly “S&OP” /Integrated Planning	Weekly Control Tower Process		

Key Performance Indicators (KPIs)

DEVELOPMENT TIMELINE ACCELERATION | COMMERCIALIZATION SCALABILITY AND SPEED

Foundational Capabilities **Advanced Capabilities**

2. **Agility by Design** through building agility and precision into supply capabilities. Large inventory builds will not achieve perfect service levels at the clinical stage because – unlike approved drugs -- IMPs have inherently shorter shelf lives and are subject to frequent formulation changes.

- **Right-size Production:** Applying proven lean production methods such as SMED (single-minute digit exchange of die) and Six Sigma techniques can drastically cut down changeover times, reduce lot sizes and improve yield. Right-sized, flexible production capabilities are particularly crucial for development-stage companies to achieve the demand-driven, pull supply chain during the clinical phases when demand is much smaller and less predictable compared to commercial products.

- **Postponement/Package to Order:** Clinical supply chains face high demand uncertainty and labeling complexity as a result of the globalization of studies. Under the just-in-time package-to-order model, the final label and pack production of an investigational material is postponed until the demand signal from a specific study becomes more certain. The successful adoption of this supply chain best practice will significantly improve IMP finished goods supply flexibility while optimizing program-wide inventory levels.

- **Precision Cold Chain:** With more and more IMPs requiring complex cold chain handling, the increasing occurrence of temperature excursions (TE) during transportation and storage has become a major pain point for clinical supply mangers. To ensure compliance with the Good Distribution Practice (GDP) guidelines and minimize study delays caused by supply issues, we should learn from the emerging personalized medicine supply chains (such as gene and cell therapies) to build precision cold chain capabilities based on Logistics by Design. The Logistics by Design concept, which grew out of Quality by Design, strives for flawless logistics execution, resulting in speed, accuracy, visibility and control.

3. **Optimize Site Handling Efficiency** by keeping the site perspective in mind. Sites play a vital role in conducting clinical trials but historically optimizing site material handling efficiency has not been a key focus for many R&D organizations. Failing to incorporate site operational perspectives in clinical supply chain designs can lead to additional timeline delays and material waste.

- **Storage Maximization:** Rationalizing IMP pack design to maximize space utilization can greatly improve on-site storage efficiency as clinical sites typically have limited cold chain storage space. For example, a trial site pharmacist once lamented, “Package size…shouldn’t be a ‘shoe box’ for one syringe.”

- **Patient-Driven Resupply:** Leveraging modern Interactive Response Technologies (IRT) can automatically rationalize IMP replenishment decisions based on actual patient enrollment, inventory position and dosing regimen. The future-state clinical supply chain is no longer a one-size-fits-all strategy. As described by the same trial site pharmacist, sites “don’t need 30 vials in stock if [they] use only one every month.”

4. **Right First Time, Every Time** with lean thinking and a sense of urgency to perform in the best interest of patients.

- Start with **Value Stream Mapping** to identify high-impact areas for relentless muda elimination throughout the clinical supply chain. Always ask the question, “Does this activity really add value to patients?”

- Boldly challenge the status quo and identify creative ways to take non-value added activities out of the value chain while ensuring GxP compliance.

- Implement Right First Time and Cycle Time measures beyond the traditional four walls of manufacturing. It is ultimately everyone’s responsibility, regardless of the functional area, to aim for “right first time, every time” and lightning-fast turnaround and response time, if we truly want to achieve a record-breaking timeline.

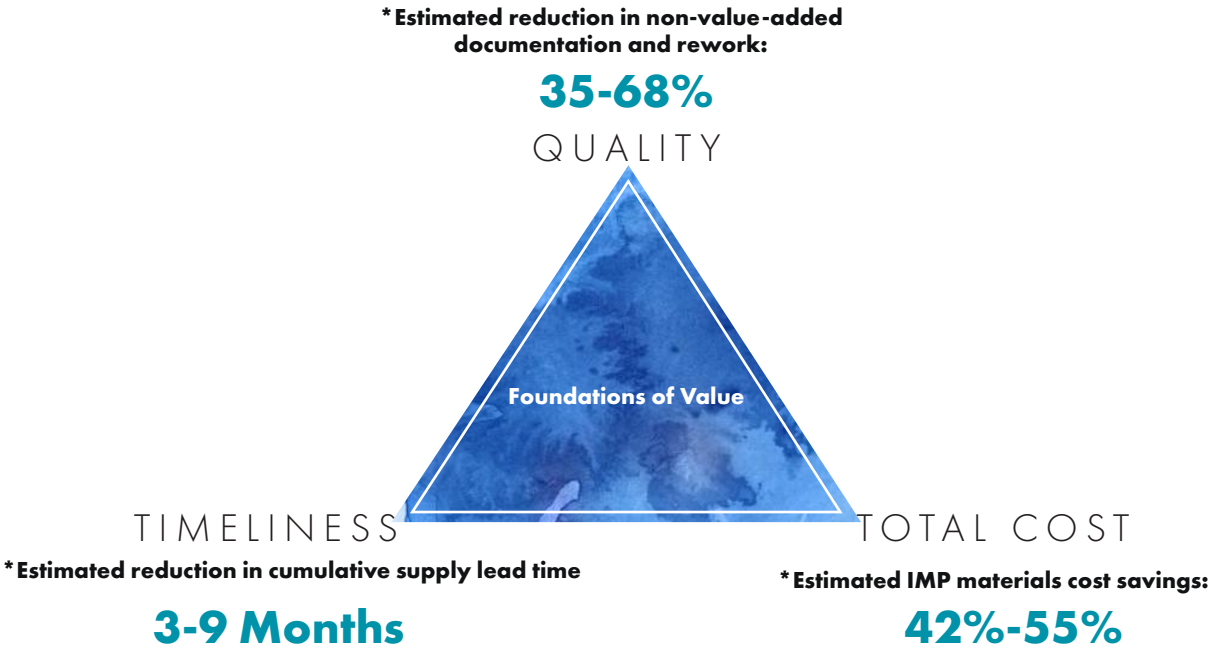
5. **One Vision, One Goal** – True Value Chain Collaboration

- A “Great Divide” phenomenon is often observed within a R&D organization when Clinical Operations (ClinOps), Chemistry, Manufacturing and Controls (CMC), Finance, Clinical Supply Chain, Quality, Regulatory and extended contract organizations have very different agendas and conflicting priorities. Such misalignment frequently results in poor decision making, supply disruptions and timeline delays.

- A true alignment of vision, goals and actions among all critical players spanning the extended value chain is a top success factor to accelerating new drug development cycle.

5 Value Creation – Quality,Timeliness, and Cost

The next-generation patient-centric clinical supply chain is agile, precise, and responsive. If implemented successfully, it will serve as a strategic pillar to support the planning and execution throughout complex clinical programs by creating value to the patients in three core areas: quality, timeliness, and total cost.



*Expected benefits are estimated based on the analysis of industry research and client projects performed by Clarkston Consulting.

- **Quality (Right Product & Right Condition):** Key benefits include (1) reduced human errors and resulting Quality Events, (2) decreased non-value added documentation and rework, (3) improved GxP compliance across the Make-to-Deliver process, and (4) reduced non-conformance and improved investigation product quality to support best clinical study results. While organizations vary, we have found reduction opportunities of 35% to 68% in non-GxP related documentation and rework caused by human errors.

- **Timeliness (Right Time):** Key benefits include (1) shortened manufacturing & quality release times across all material stages from drug substance/API, drug product and finished goods (FG), (2) compressed cumulative IMP supply lead times, and (3) increased flexibility and agility to respond to unavoidable demand and supply changes. Depending on the clinical program design and complexity, reductions of 3 to 9 months in overall IMP supply lead time from plant to plant, plant to depot, and depot to site/patient are achievable.

- **Total Cost (Right Cost):** Key benefits include (1) significantly reduced material scrap and expiry waste, especially when high-value comparators are used, (2) lowered rework and expedited costs, (3) reduced system-wide inventory and non-value added cash burn, and (4) increased overall drug R&D value chain efficiency and productivity, and thus less firefighting and more proactive problem-solving. In practice, more than one third of packaged IMPs ¬– and in some cases as much as 79% – eventually go to waste. A much-needed clinical supply chain transformation could reduce IMP costs by more than half, freeing up R&D budget to fund additional promising pipelines.

6 Conclusion – Thinking Beyond the Crisis

At present, drug makers that are engaged in the COVID-19 vaccine and treatment development are unquestionably taking the center stage. They are in a race against the clock in our fight against the pandemic to bring this humanitarian and economic crisis to an end. However, in addition to the current pandemic related programs, there are more than 300,000 clinical trials that are underway globally, aiming to develop novel medicines that treat serious or life-threatening diseases, especially in those therapeutic areas where treatment is unavailable. The endeavor to drastically accelerate the development cycle should not be limited to the current crisis period. Looking forward, it is an imperative to the life sciences R&D industry overall.

After living and breathing the pain from the reactive, fire-fighting, and siloed supply chain operating models in the past decades, many drug R&D organizations have already embarked on a journey to transform their supply chains to be leaner, more reliable, and more responsive. Now with the pandemic serving as the ultimate catalyst, these organizations should take their clinical supply chain transformation to the next level and make it a true strategic differentiator.

Clinical supply chain should no longer be considered as a simple “order taking” execution arm that is often held accountable but is rarely granted authority. The time has come for clinical supply chains to take their spot at center stage throughout the protocol development, planning and execution cycle. This will allow clinical supply chain to apply next-generation best practices to manage growing uncertainties and ensure IMP availability while optimizing costs. Clinical supply chain has to take its rightful place among the life-saving and history-making heroes.

Being challenged to the limits by the global pandemic, drug value chain stakeholders have aligned, more than ever, to work toward a common goal: developing a safe and effective vaccine in the shortest time clinically possible through utmost innovation, collaboration, and commitment. Such demonstrated efforts during today’s crisis will permanently rewrite the drug R&D playbook and reset the benchmark for standard development lead times for tomorrow. These evolutionary changes will effectively help to break down Eroom’s law and bring many more breakthrough therapies to patients, much sooner and at a much more affordable cost , to ultimately enhance the quality of human life.

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