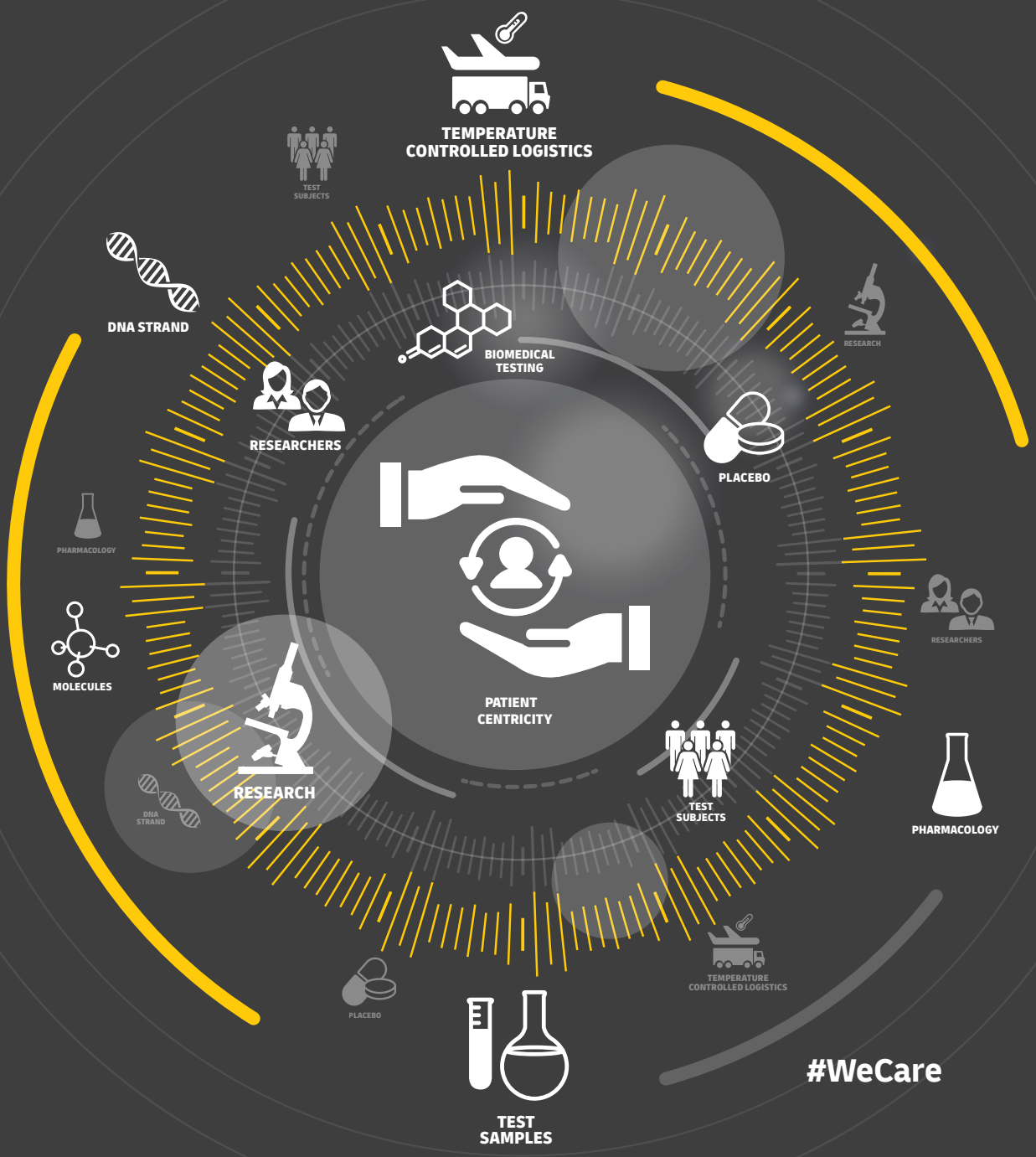

PATIENT CENTRIC DELIVERY FOR CLINICAL TRIALS OF THE FUTURE

A DHL and Frost & Sullivan perspective on the transformation of clinical trials for a more patient centric service.

FROST & SULLIVAN

DHL

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In the world of healthcare, care isn't something you say, it's something you do.
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By doing what's right, not just what's expected.
By taking on the tough challenges, not just the straightforward.
By making things happen when others would walk away.

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Doing what others can't do – compliantly.
Stepping up to give the scale of support this vital industry needs.
Because it's easy to say you care, but another thing to show it.

DHL. WE CARE

Patient Centric Delivery for Clinical Trials of the Future: Preface

As we all know all too painfully well, the COVID-19 outbreak has impacted every aspect of life, including – or even particularly – clinical trial activations, especially in the US. The consequences are profound, immediate, and long-term, affecting three significant areas: data ownership, business model innovation, and clinical trial design.

Data: Under traditional clinical trial methods the data is created, managed, and stored in silos, resulting in duplication and inaccuracy. In future, clinical trials will deploy new ways of working to permit shared access, with multiple stakeholders, raising significant ownership, governance, and security challenges.

Business model innovation: New technologies are enabling a rapid shift toward the development of targeted therapies. Similarly, Food and Drug Administration (FDA) efforts to accelerate biologics development, combined with pharmaceutical regulatory changes and new global trade rules, are collectively disrupting business-as-usual for US biopharmaceutical companies.

Clinical trial design: The constraints of the pandemic has shown the benefits, and weaknesses, of Decentralized Clinical Trials (DCTs), leading to growing governmental intervention to demand strategic inventory management and greater transparency. While participating in clinical trials from home can improve the overall patient experience and can make trials more accessible to under-represented communities, there are big questions to be answered about cost optimization, efficiency, and the supporting logistics.

This paper looks to the future of clinical trials at a global scale, and how we respond to meet tomorrow's complex healthcare challenges.

Contents

Key Questions Answered

1. What is the current state of clinical trials?
2. Where is the focus of pharmaceutical industry shifting, and how does this impact the clinical trial landscape?
3. What is the impact of changing clinical trial regulatory landscape on global clinical supply chains?
4. Why is there a need for decentralized trials?
5. What are the benefits of a Direct to Patient delivery model?
6. What opportunities exist for the Supply Chain & Logistics Service Providers to support the expanding DCT market?

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1. The Changing Landscape of Clinical Research

The global clinical research market is undergoing transformation driven by the mobility restrictions of the COVID-19 pandemic, increasing focus on the development of next-generation monoclonal antibodies and cell and gene therapy to boost the personalized medicine portfolio. There was a substantial decrease in new clinical trial activations, especially for US-based trials, as a result of the coronavirus outbreak. March to May 2020 recorded the most significant dip in clinical research in the United States. Trial activations rebounded following the initial pandemic period (June to September 2020), though less for US-based trials.

Recovery from the pandemic: With the rollout of the COVID-19 vaccines, therapeutic trials launched monthly, and suspended trials resuming operations, sponsors face increased competition for sites, investigators, and regulator bandwidth, requiring rigorous planning, active local monitoring, flexibility, and close partnerships with sites and patients to maintain timelines.

The growing pressure to meet trial demands while ensuring patient safety has resulted in the adoption of digital methods of data collection and patient onboarding (Electronic Clinical Outcome Assessment, Electronic Patient-reported Outcome, Remote Source Document Verification, and Electronic Informed Consent). The Global Clinical Research Organization market is estimated to reach $59.2 billion by 2026, of which North America is forecast to contribute 37% of the total market.[1]

Enabling patients to participate in trials from home requires timely access to the Investigational Medicinal Product (IMP), trained nursing staff to administer the IMP, the availability of mobile applications, sensors, or devices to ensure reporting of any adverse events or interactions with the investigator through televisits.

The use of these solutions comes with the challenge of data gaps, noise, and biases, requiring rigorous validation and standardization.

Investor-backed technology vendors take the lead in the United States to support trial operation recovery: Despite the challenges, newly-issued Food and Drug Administration (FDA) guidelines and fresh rounds of venture funding continue to fuel the efforts of technology vendors, such as Science 37, Medable, and THREAD Research, to accelerate the development of high-end decentralized clinical trials (DCT) enabling solutions.

The ensured safety and ease of participation in remote trials has doubled trials in the United States compared to 2019 and is expected to expand over 7 times by 2026. Moving trials closer to the patient's home introduces clinical research to a wider pool of patients and physicians practicing in remote communities. Clinical research is projected to grow exponentially once regulations on the cross-border use of technology, patient-data ownership, and IMP shipment are harmonized, and workflows to conduct DCTs are standardized.

The need for customized logistics solutions: For logistics solutions providers, the shift away from traditional direct-to-patient clinical trials means addressing multiple focal coordination points, such as manufacturers, CROs, local pharmacies, home nursing providers, and individual patients, depending on the trial protocol.

Direct-to-participant (DtP) services require pick-up and delivery within extremely tight timeframes and usually over long distances. There is an increasing need for specialized solutions to avoid frequent deliveries to patients, such as small access-controlled refrigerators that can store drug products in patients' homes in remote, low-resource locations. Abiding by good distribution practices and storage standards and maintaining a secure chain of custody as per regional regulations are imperative.

1 Post-COVID-19 Trends Disrupt the Global Contract Research Organization (CRO) Market, Frost & Sullivan, May 2021

Clinical Trials of the Future

- Site and sponsor at the center
- Poor patient enrollment
- Poor patient diversity
- High patient drop off
- Discontinuous endpoint assessments with risks of missing data points
- Trial designs are digitally driven

- Majority of trials conducted in US and EU
- Limited scope of innovation in patient outreach and redundancy in workflows
- Trial amendments are costly and time consuming

- Data entered via an intermediary (study team)
- Clinical data created and stored in silos, resulting in duplicity and incaccuracy

- Patient at the center
- Pre-qualified patient enrollment
- High patient diversity
- Improved patient experience and retention
- Continuous digital endpoints that can be tracked 24x7
- Trials can be executed through partial virtual visits or through completely digital sites

- Open to ease of geographic expansion to emerging markets of Asia and LATAM
- Use of clinical trial simulation, electronic health records etc. to improve trail efficiency
- Flexibility to adapt new trials workflows in real time based on pre-qualified rules

- Data entered virtually (ePRO, apps, sensors) or through human intervention (nurse, study team)
- Unified view of clinical data and accesible through anywhere

Figure 1: Clinical Trials of the Future. Source: Frost & Sullivan

2. Innovation & Business Model Disruption in Clinical Trials

Refocused Priorities of the Pharmaceutical Industry

Innovation driving the biologics development: New technologies, such as next-generation sequencing, artificial intelligence, multi-omics technology platforms, and single-use bio processors, enable the shift toward the development of targeted therapies, such as next-generation monoclonal antibodies and cell and gene therapies with better clinical outcomes. The top-selling drug globally is Humira®, a monoclonal antibody, and as of early 2020, biologics comprised 7 of the top 10 bestselling drugs. In 2021, the biologics market is estimated to be worth $298.4 billion, with antibody therapeutics contributing to 55% of this market[2]. Manufacturers now focus on collaborating with regional companies to develop bi- and tri-specific antibodies with high potential to be put on the shelf as immunotherapy agents posing as a critical driver to boost growth in this segment.

Figure 2: Refocused Priorities of the Pharmaceutical Industry

China leads the cell and gene therapy clinical research: Cell and gene therapy contributes to 2.8% of the biologics market and is forecast to grow at a compound annual growth rate of 39.7% until 2024[3]. As of 2020, three cell and gene therapies are approved by the FDA, and one is under the FDA's priority review since May 2021. Of the 671 clinical trials listed for chimeric antigen receptor T-cell (CAR T-cell) therapies in June 2020, China contributed 357 trials, while the United States contributed 256[4]. China leads in the development of cell and gene therapies, with over 218 CAR T-cell therapy assets under development. The growing preference toward China as a lucrative launch market is demonstrated by its inclusion in global multi-site clinical trials.[5]

Patient emphasis on value-based therapeutics drives growing research and development (R&D) costs: The transition toward targeted treatments that are more effective or better tolerated in smaller groups of patients generates a need to co-develop diagnostic tools to identify the individuals most likely to benefit, adding to the already rising R&D costs per new molecular entity[6]. It is increasingly important to examine the cost-effectiveness of a therapy under development that can affect reimbursement decisions, resulting in a shortened time to market. The economic impacts of the pandemic are expected to dampen a patient's ability to afford high-value therapies leading to fluctuating demand.

COVID-19 vaccine and therapeutics development: A huge focus in the fight against COVID-19 has been on the development of effective vaccines and therapeutics against the virus across the globe. Innovation in COVID-19 therapeutics is led by the US companies, more so by the small biotech companies. Although there was a surge in the number of therapies entering development pipeline until Jun 2020, successful vaccination drives and

2 Curative Oncology and Rare Disease Therapies Transforming the Global Biologics Market, 2020–2024, Frost & Sullivan, Jul 2020
3 Curative Oncology and Rare Disease Therapies Transforming the Global Biologics Market, 2020–2024, Frost & Sullivan, Jul 2020
4 Wei J., Guo Y., Wang Y., et al., Clinical development of CAR T cell therapy in China: 2020 update. Cell Mol Immunol. Sept 2020, doi:10.1038/s41423-020-00555-x
5 Simultaneous investments in supply chain optimization and decentralized manufacturing expanding the contract cell and gene therapy manufacturing market, 2020–2026, Frost & Sullivan, Aug 2020
6 Schlander, M., et al., "How Much Does It Cost to Research and Develop a New Drug? A Systematic Review and Assessment", PharmacoEconomics, Jul 2021

Figure 3: Need for global cold chain networks and alternative sourcing strategies

dampening effects of the pandemic has decreased the number of new therapies entering the development pipeline, significantly suggesting that the companies will soon re-align their focus on suspended non- COVID therapy development programs. The success of mRNA therapeutics opens doors for its applications in oncology, other infectious diseases and immune disorders. The first efficacy data for cancer vaccines are expected to be out by end of next year or early 2023.

Need for global cold chain networks and alternative sourcing strategies: Delivering biologics, while maintaining the cold chain, whether standard (2°C to 8°C) or deepfreeze (as cold as -70°C) or cell and gene therapy specific- liquid nitrogen stocks and temperature down to -196°C, requires extensive infrastructure that is costly to build and maintain. This increases the reliance of manufacturers on logistics solutions providers. Moreover, lockdown measures create challenges such as a reduced workforce, manufacturing facility capacity limits, and government restrictions on exports. These measures disrupt the supply chains of various biologics catering to chronic diseases, including diabetes and oncology drugs. The burden of the pandemic will add more strain on active pharmaceutical ingredients (APIs) procurement for small-molecule therapy and generics developers due to the overwhelming demand and trade restrictions limiting access to most vendors in India and China. Biopharmaceuticals are spared this pressure as the APIs are mainly proprietary and less dependent on global sourcing. However, securing ancillary supplies, such as cell culture media, filtration media, single-use plastics, bags, vessels, glass vials, and syringes, will be challenging. Bioprocessing materials' supply chain constraints are expected to increase as over 300 COVID-19 vaccines and therapeutic products are in development, and clinical stages are moving toward commercialization.

GLOBAL CLINICAL TRIALS LOGISTICS FOR LARGE PHARMA

Case study
Consolidation of large pharma clinical trial logistics network into a regional distribution model

Customer challenge

- Large increase in studies over 5 years with a flat R&D budget
- Distributing study medication supplies through affiliates, maintaining 72 warehouses, resulting in high buffer stocks at warehouses and long transit lead times
- Inventory overage of 157% on average across entire study portfolio
- Lead time of minimum 4 –5 weeks from completion of secondary packaging to patient kits available at INV sites
- No visibility of stored and distributed clinical supplies at affiliate warehouse

DHL Solution

- 3 hub solution distributing to 80% of investigator sites globally >40 countries
- Processes and staff to manage considerable growth of 60+ new & 140 active studies
- Investigation material with 3 temperature zone requirements (2 –8C, 15 –25C, -20C)
- Additional services including cGMP packaging and returns/reconciliation
- Supply Chain Integrator (SCi) tool for universal shipping and inventory access
- Full system integrated with multiple IRT (IVR/IWR) systems

Customer benefits

- 3 depots serving 45 countries (80% of investigator sites), enabling depot network to de reduced from 72 to 20
- Considerable savings of logistics costs (estimated 40%) and inventory
- Single contact at DHL; management time and communication improved
- Detailed global inventory, shipping and cost data across all studies
- 60+ logistics processes reduced to
- Single EU QP release process and using 1 authorizing body (reduced from 27)

The DHL Advantage

DHL's global GMP depot networks serve full loop service for all temperature ranges such as ambient (room temperature), chilled (2°C to 8°C), frozen (-80°C to -20°C) and controlled (15°C to 25°C) as per the customer requirement.

Moreover, the premium Medical Express service involving specialized features such as priority handling, dry ice inclusion as well as innovative dry ice solutions through partnership with CRYOPDP positions them as preferred partner for companies conducting multi-country trials requiring temperature controlled storage and distribution of investigational drugs and biological specimens.

DHL also offers customized solutions for urgent deliveries with a possibility of same day delivery round the clock, all year in over 200 countries which is critical for biological samples involved in the manufacturing of therapy as in case of cell therapies.

Precise demand planning and end-to-end visibility: Precise demand planning and forecasting are critical for low-volume, high-value products. Just-in-time inventory for specialized raw materials, technology, and the equipment needed to expedite manufacturing efforts in response to localized needs will limit costs and be of central focus. Shipping the cells to and from patients for cell and gene therapies requires a wide range of cold chain networks between 2 and -196 degrees Celsius and usually needs to be completed within the short half-life of the cells undergoing apheresis. The transport of cellular therapies needs optimized solutions to support advanced packaging, tracking, tracing, real-time feedback, scheduling, and monitoring of cell potency to ensure the success of the therapy[7]. The impact of disrupted cell and gene therapy is much larger than that for biologics. With cell and gene therapy, each batch produced is patient-specific, and any disruption or error during manufacturing or supply conditions can impact patient safety and the therapy outcome caused by the time lag to replace with a fresh batch.

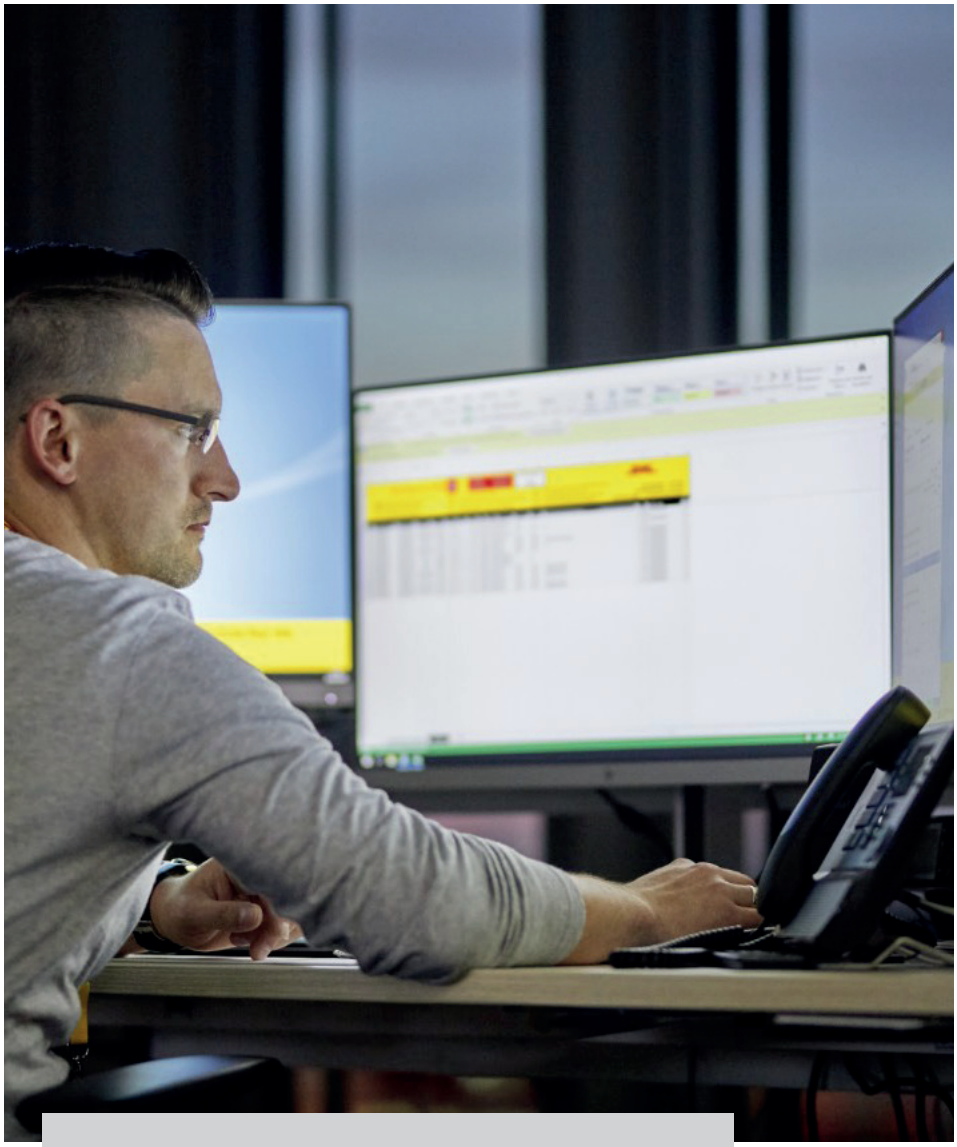


Figure 4: Precise demand planning and end-to-end visibility

7 Simultaneous investments in supply chain optimization and decentralized manufacturing expanding the contract cell and gene therapy manufacturing market, 2020–2026, Frost & Sullivan, Aug 2020

The DHL Advantage

DHL is the world's leading logistics company offering tailor-made supply chain solutions for the Life Science & Healthcare Industry. DHL Same Day white-glove service combine years of mission critical logistics experience, regulatory compliance and global control tower and network; DHL Express ensures compliant processes and fast, cost-effective international transportation in their global network.

The hybrid solution delivers the best out of both products, incorporates further elements like pre-conditioned packaging, pre-clearance and 24/7/365 end-to-end monitoring to ensure full control and seamless execution of all critical steps.

The US Pharmaceutical Regulatory Environment

FDA is driving biologics development: The US FDA incorporates a fast-track approval pathway and designation status for drugs that cater to serious or life-threatening conditions. Most of the drugs used for these diseases are biologics. Under the accelerated approval program, drugs can gain indications quicker than through the regular approval timeline based on a surrogate endpoint.

US-China trade rules disrupting business for US biopharmaceutical companies: Global cell and gene therapy developers headquartered in the United States seek domestic partnerships to manufacture products meant for China markets. Using local companies allows developers to gain operational efficiency and circumvent the complex rules announced in July 2019 that regulate the collection, storage, and transportation of genetic samples and materials in China. The rules limit the number of international companies unless the research projects are conducted in cooperation with Chinese partners and need sharing of IPs generated with local partners.

Evolving FDA guidance for the execution of DCTs: In 2018, the FDA issued guidance on the use of the Electronic Health Record (EHR)/Electronic Source. The Clinical Trials Transformation Initiative released their final recommendations on overcoming the legal, regulatory, and practical hurdles to plan and conduct DCTs in the United States in the same year. However, these are not formally endorsed under any regulatory framework. In March 2020, the FDA issued guidance on conducting clinical trials during the pandemic built on prioritizing patient safety, minimizing risks to trial integrity, and documenting the reasons for any protocol changes and deviations. The industry is awaiting output from the International Conference on Harmonization Good Clinical Practice renovation project that is expected to address considerations related to the conduct of DCTs by 2022 in the United States and the European Union.

Figure 5: FDA is driving biologics

The DHL Advantage

DHL's Customs Control Tower System solution is ideal for managing customs activities across various countries especially during the pandemic when the IMP shipment regulations across regions are constantly evolving.

The solution can limit risk of fines and penalties as well as ensure timely delivery by harmonizing customs processes and increase internal compliance. It provides a central electronic archive for customs-relevant documents while ensuring complete transparency with respect to incremental costs due to any last minute change in destination or requirements.

Figure 6: DHL Control Tower

Growing governmental intervention demanding strategic inventory management and greater transparency: The US government may enforce localized sourcing in the long term considering trade restrictions with China. The industry is heading toward transparency delivered on the back of automation and collaborative suppliers. Efforts to use blockchain technology in the pharmaceutical supply chain have been initiated by the MediLedger Network, established in 2019. The network comprises pharmaceutical manufacturers and wholesalers that leverage blockchain technology to deliver on the Drug Supply Chain Security Act requirement of developing a track-and-trace system for US drugs by 2023. This system is expected to tackle the movement of counterfeit medicines better; this is especially important for biologics, which cost more than small-molecule drugs. The system can validate the authenticity of drug identifiers throughout the supply chain without any proprietary data being shared openly on the blockchain, thus maintaining the highest security.

Case Study: Improving Position as "Sponsor of Choice"

DHL operates the global order fulfillment center on behalf of the sponsor, allowing better visibility throughout the supply chain and resulting in improved forecasting to match the evolving trial needs and improve product availability on time. The company's ability to promptly implement reverse logistics loop for clinical returns can help significant cost reduction. DHL's services saved a sponsor 25% shipping costs by resolving the inefficiencies in supplying diverse clinical ancillary supplies that required dynamic warehousing, shipping and return of stock around the world.

IMPROVING YOUR POSITION AS "SPONSOR OF CHOICE"

Case Study
Increasing Clinical Trial Partner relationships

Customer challenge

- Inefficiencies in supplying diverse range of clinical ancillary materials
- Storage issues at investigator sites in over 80 countries around the world
- Excessive warehouse and transport costs, from storing, shipping and returning unnecessary stock
- Eroding relationships with CROs and investigator sites

DHL Solution

- New global order fulfilment centre that increased visibility throughout the Supply Chain
- Ensure compliance over 150 different regional transport and storage protocols
- Implemented an improved reverse logistics loop for clinical returns

Customer benefits

- Significant improvement in product availability
- Improvement in forecasting, allowing capacity to better match demand
- Greater partner satisfaction & improved partner relationships
- Estimated 25% reduction in shipping costs

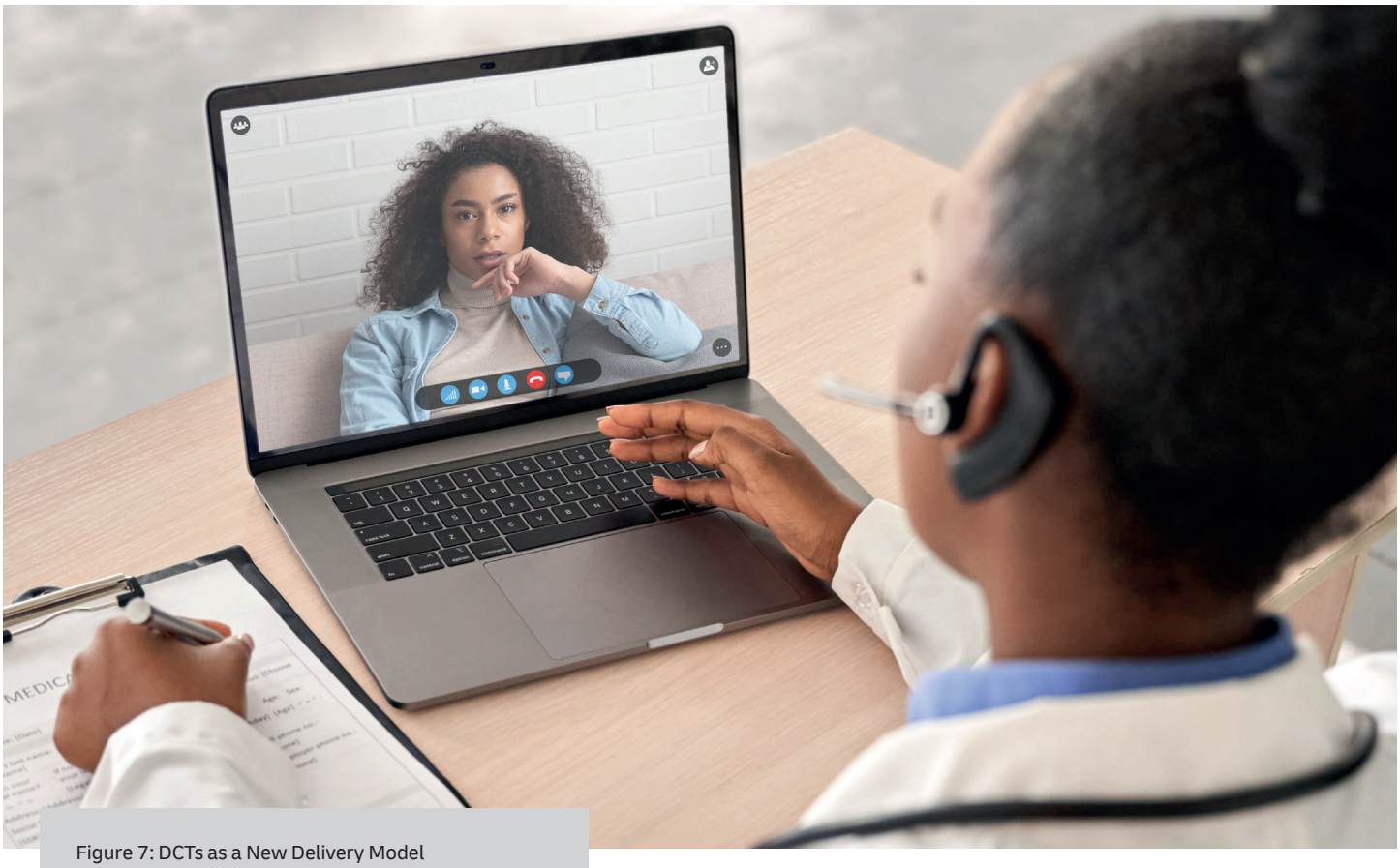


Figure 7: DCTs as a New Delivery Model

3. Patients at Home

Decentralized Clinical Trials as a New Delivery Model

Interoperability of digital solutions

Omni channel patient recruitment

DTP / DFP IMP storage solutions

Secure and standardized workflows

Full spectrum at home health care services

Figure 8: Pillars of efficient DCT delivery

The need for patient-centric designs: Over the past decade, there has been an 86% rise in the number of endpoints reported in a single clinical trial, as per the Tufts Center for the Study of Drug Development report. The need for frequent and lengthy site visits, disruption in personal routines, and exclusion due to geographic barriers make trial participation burdensome for patients, resulting in missed recruitment targets in 61% of the trials[8]. Patient identification and outreach are significant drivers of the costs and inefficiencies of research and can account for 32% of the trial budget.[9]

The pandemic is accelerating the adoption of DCT: Large pharmaceutical companies ran pilot virtual clinical trials before the pandemic to evaluate the cost-benefit of digitizing the clinical trial process. However, skepticism around societal acceptance, large technology setup, training costs, and the focus on on-site operation efficiency and limited use cases have stopped the industry from moving toward virtual clinical trials. Part of the resistance comes from patients who prefer in-person interactions with investigators, especially for complex therapies needed in oncology and rare disease trials that have undefined medical endpoints. Travel restrictions exerted by the pandemic have further exacerbated the trial participation burden for both patients and site investigators, resulting in temporary suspension, or in some cases, termination of planned clinical trial operations during the first quarter of 2020. Quick measures adopted by the FDA and pharmaceutical companies to ensure continuity of clinical trials in the United States, such as embracing alternative ways to collect safety and efficacy data and support trial participants, have allowed patients to participate in trials from the comfort of their homes. As such, the pandemic has accelerated industry-wide acceptance of tele-health and remote monitoring tools in trial operations.

8 Ken Getz ,Tracking the Patient Engagement Movement and its Impact on Clinical Research Execution, CSDD, Tufts University School of Medicine, Sept 2019

9 Huang, G. D., et al., Clinical trials recruitment planning: A proposed framework from the Clinical Trials Transformation Initiative, Contemporary Clinical Trials, vol. 66, pp. 74–79

Industry-wide efforts are driving DCT adoption: Sponsors and CROs are ramping up efforts to build capabilities around delivering decentralized trials over traditional paper- or site-based trials to ensure trial continuity following the FDA's emphasis on patient-centric trial design to ensure safety during the pandemic. Based on a Pharmaceutical Product Development survey in 2020, 24% of sponsors are in the process of establishing DtP solutions[10]. The industry is likely to transition into a hybrid model of clinical trials where initial interactions or select endpoint assessments requiring physical intervention are conducted in local research sites while follow-ups are executed through a virtual setup or home visit by a trained healthcare professional. Based on the growing awareness and acceptance, evolving infrastructure, and favorable regulatory outlook, the DCT market is forecast to reach $16.4 billion by 2026. The United States is expected to lead the DCT market, followed by Western Europe, owing to the growing venture capital investments in technology companies that support DCT solutions for data management, patient recruitment, clinical trial operations, existing technology infrastructure, along with skilled healthcare professionals to support the clinical outcome assessments outside the medical set-up and growing patient acceptance.[11]

DCTs empowering the sites and investigators to support trials efficiently: Wider adoption of DCT will benefit not only patients but also the clinical research sites and investigators. Less time will be spent documenting outcomes, collecting data, and physically moving patient records, freeing up time for patient care through clinical guidance and support. This change is bound to reflect improved patient retention and future willingness to participate in trials. Site investigators will have more bandwidth to engage in additional studies, expanding the clinical trial market. Real time remote monitoring solutions adopted in DCTs can limit the growing burden on site/ investigators due to complexity of trials related to new-generation antibodies and personalized therapeutics.

DCTs enabling trial cost optimization and improved clinical outcomes: Sponsors and CROs can benefit from the potential cost reduction due to the incorporation of digital technologies in their DCT offerings. Telehealth visits cost 50% less than traditional in-person visits. A study suggests that using source data verification accounts for 25% of the trial cost[12]. Moreover, direct data capture and standardized use of patient-reported outcomes through apps, wearables, and other technologies deployed in DCTs can enhance the quality of safety and efficacy of the data generated. These tools allow data collection to be frequent, continuous, and accurate, and reduce the reliance on patients to remember or document scheduled visits. DCTs allow direct tracking of compliance and adverse events and facilitate expedited market entry for safe and efficacious therapies.

Growing DCTs require a fertile ground for collaboration: Technology vendors, such as Science 37 and THREAD Research, grew exponentially during the pandemic as they built comprehensive solutions around the pillars of efficient DCT delivery through partnerships with logistics solutions and home health service providers. However, leading CROs, such as Covance, ICON, and PPD, which have partnerships for Direct to/ from patient (DtP/DfP) IMP and access to skilled medical home-nurse networks are more focused on building interoperable platforms and enhancing patient reach with multichannel recruitment solutions through partnerships, acquisitions, or expanding in-house expert technology teams.

10 Decentralized clinical trial survey report, PPD, 2020
11 Global Decentralized Clinical Trial (DCT) Growth Opportunities, Frost & Sullivan, 2021
12 5 ways that decentralized clinical trial approaches can reduce study costs, Thread, Aug 2021

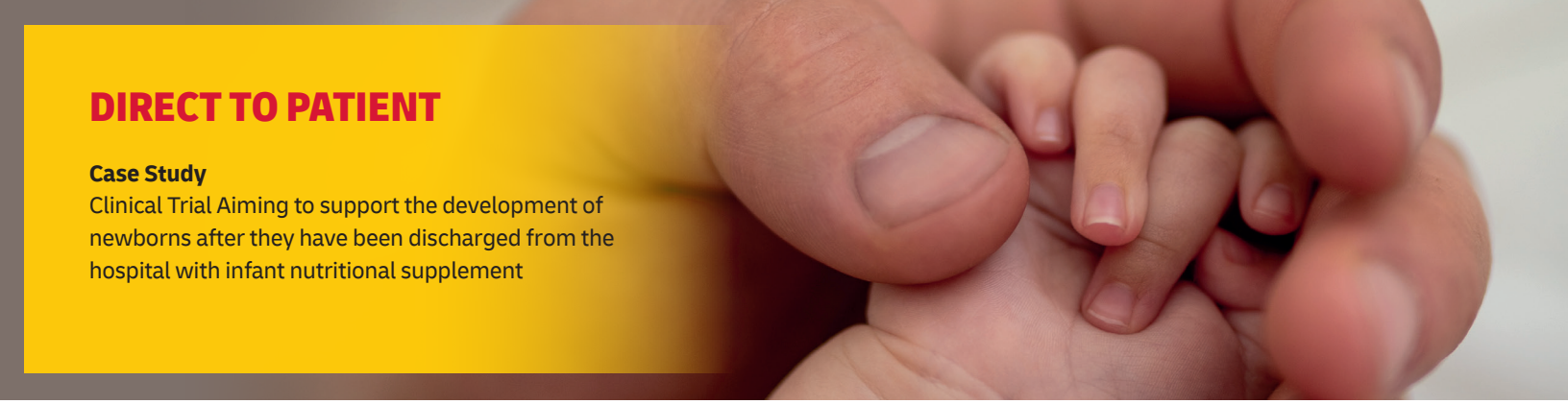
The DHL Advantage

DHL's Same Day online web portal can facilitate delivery of IMP to the patient's home as well as home pickup of biological samples for delivery to the lab while maintaining complete confidentiality of patient personal information within strict delivery windows as small as 2 hours within order placement.

DHL can support CROs and DCT technology vendors through their specialist packaging solution for temperature-controlled hazardous goods, dry ice, high-quality smart sensors, returns process, 24/7/365 real-time shipment monitoring. Thus DHL serves as a single point of contract for all clinics participating in the trial and ensuring operational ease.

DIRECT TO PATIENT

Case Study
Clinical Trial Aiming to support the development of newborns after they have been discharged from the hospital with infant nutritional supplement



Customer challenge

- High Volume of shipments: clinical trial spans multiple clinics across the US each serving several patients
- Strict delivery window of 2 hours within placement of order
- Nature of study is blind: required a way for patient names and addresses to be shielded from customer, but not interfere with the delivery

DHL Solution

- Customized point-to-point ground transportation delivery from clinics to patients homes
- Ability to schedule appointments
- Online system with support and onboarding provided to clinicians
- Continuous and proactive monitoring with intervention, if necessary
- 24/7/365 availability

Customer benefits

- Single point of contact for all clinics, administering the trials
- Streamlined ordering process using DHL Same Day's online web portal.
- Confidence in safe and fast, end-to-end process, and handover of the supplement to the patients at the right place and the right time

Figure 8: Direct to Patient (DtP)

Figure 9: Need for Improved Patient Heterogeneity in Clinical Research

Need for Improved Patient Heterogeneity in Clinical Research

In 2020, of the 32,000 patients who took part in trials for innovative medicines, 75% were from a single ethnic origin. Participation of racial and ethnic minorities such as African Americans and Hispanics is only between 2% and 16%, although they make up 32% of the US population;[13] hence, there is growing urgency to ensure an accurate representation of patients in clinical trials. Clinical trial outcomes of recently conducted COVID-19 therapeutics also highlight the importance of maintaining patient diversity for the success of any treatment or vaccine development initiatives.

DCT paving the way to achieve patient diversity: DCTs allow improved communications through patient engagement, community outreach, advocacy and education, study design, site selection, and research methodology. It is anticipated that the growing acceptance of DCTs, along with the structured guidance of the FDA issued in November 2020 on broadening patient eligibility criteria and redesigning clinical trials, will enforce consideration of the following strategies by sponsors and CROs to ensure better patient diversity:

- Broaden the inclusion criteria and design trials around the needs of patients, especially from lower socio-economic groups or with insufficient income, which restricts their participation due to travel costs. These could include ailing older patients who may need transportation support, daily-wage workers who cannot miss workdays to attend multiple on-site visits, or individuals who often travel for work
- Select investigators associated with community-based centers with higher coverage of diverse patient populations and better patient relationships
- Use clinical trial simulation (CTS) to allow sponsor companies to test different trial designs with target cohorts before exposing patients to any treatments
- Incorporate diverse patients' needs from phase 1 trials as opposed to phase 3 trials
- Engage with patient advocacy groups to find a wider range of pre-qualified patients to improve compliance and retention throughout the trial duration
- Reduce the burden of participation by eliminating the need to be on-site every second week by incorporating remote monitoring or at-home nurse services when necessary

13 Statistics from 2020 US census. Census.gov

Figure 10: Impact of improved patient heterogeneity

Impact of improved patient heterogeneity: Reducing patient wait times to interact with clinicians at busy clinics can motivate more patients to participate in trials. The convenience of participating in decentralized trials from home can improve the overall patient experience and make trials more accessible to under-represented communities globally. Opening studies to a larger patient pool reduces the need to overcompensate during recruitment for the drop-off rate of approximately 30%[14]. The use of the CTS process generates qualitative data on the engagement and experiences of patients and can be used to inform protocol design. The need to receive community support, transportation and childcare coverage, clarity on time commitment, and personal benefits of participation, especially for ethnic minorities or socio-economic groups, can be incorporated early in the trial protocol and workflow, thus improving adherence to protocol and overall retention.

In a recent longitudinal study supported by Medable, which targeted a rare genetic variant of dry age-related macular degeneration that affects 2% of the population, 11,000 participants needed to be identified, pre-consented, and screened. Medable's technological capabilities enabled the recruitment of underrepresented patients who were contacted and prescreened from their respective homes. Data capture was conducted via mobile apps and at-home genetic test shipments and pick-ups were arranged. Traditional methods would have limited the patient pool to those in the vicinity of the research sites and required patients to travel, making it difficult to recruit an adequate number of qualified patients in a short timeframe[15]. To succeed in reducing health inequalities, companies need to align their entire clinical trial operations around the real-life needs of the diverse populations they serve.

14 5 Ways that decentralized clinical trial approaches can reduce study costs, Thread, Aug 2021
15 The centricity of decentricity, Medable, 2020

4. Delivering the Right Logistics Solution

The pandemic underscores the importance of capable end-to-end logistics partners to service every component of the clinical development supply chain to ensure cost-effectiveness, traceability, and accountability throughout the packaging, storage, and transport processes to meet the evolving demands of the clinical research industry. Logistics solution providers need to incorporate automation, strengthen global cold chain networks, leverage data-driven demand planning solutions, and enhance data security frameworks to emerge as long-term partners to sponsors and CROs.

Figure 11: Integration and visibility

Imperatives in Delivering Clinical Trial Logistics of the Future

1. Integration and visibility: The DCT delivery model calls for a radical change in the traditional clinical trial supply chain framework. There is a growing need for drugs to be directly shipped to the patient and samples and expired or damaged drugs sent from the patient to the laboratory or local pharmacy/ research site. Once the acceptance and adoption of DCTs achieve scale, logistics solutions providers will play a more prominent role as partners to biopharmaceutical manufacturers. There will be a focus on integrated partners to support the logistical needs of the clinical development program. It will be imperative for supply chain partners to coordinate the chain of identity and custody in real-time through precision recording and documentation methods that allow full traceability as often as once per hour and safety checks to track material labeling accuracy. Enabling visibility into patient-specific product batches and infusion schedules through efficient linking of geographic data tracking with temperature monitoring, active management of the patient's attendance on-site, and coordination and timing of pre-treatments will be considered crucial value-added services within the supply chain management of personalized therapies. The success of the existing efforts to use blockchain in the pharma sector can form the basis of transparent workflows throughout drug development and distribution without compromising data security, which becomes extremely important at the scale of multi-country decentralized trials.

2. Digitization in data and regulatory intelligence management: Growth in the direct-to-patient model of clinical trials will require real-time tracking of regional customs laws to avoid delays. ÏMP accountability and shipment laws vary across state lines in the United States and different countries. For example, although DtP shipments from the site were permitted to ensure patient safety during the pandemic, some European member states, such as France, Netherlands, and Italy, restricted DtP by courier directly through the sponsor due to ethical and practical concerns regarding personal data protection[16]. Intelligence on product registration status with the FDA or legal status of the product in the state can impact whether IMP will require review by the destination state. Delays in import

16 de Jong A.J et al., "COVID-19 and the Emerging Regulatory Guidance for Ongoing Clinical Trials in the European Union; Clinical Pharmacology and Therapeutics", vol. 109, no. 6, Jun 2021

Key considerations for Logistics Solution Providers serving the pharmaceutical industry

- **Need for minimizing carbon footprint, through process improvement or technology use**
- Optimize warehouse storage space and inventory holding
- Minimizing use of single use packaging such as Styrofoam and incorporate multi-use packaging solutions
- Develop sustainable specialty supply chains for the customers through consolidated shipments

- **Freight capacity constraints, temporary suspension of clinical trial activities, regulatory compliance pressures**
- Build ability to ramp up or down as per the trial needs
- Keep up to date on global trade regulations and ongoing national compliance programs

- **Demand for DtP/DfP services**
- **Demand for cold storage facilities (IMP's, biological samples, test equipment)**
- **Need for advanced data security**
- Engage with the customer during protocol design
- Build resilient global cold chain infrastructure to support cold chain to the last mile.
- Leverage technologies such as blockchain to ensure transparency and data security and for AI for improving efficiency in network planning and predictive demand

- **Shift to a single logistics vendor offering better visibility and control**
- **Improve delivery timeline/ operational efficiency**
- Become a one stop shop strategic partner offering a tailored digitally enabled supply chain platform supported by a flexible global network of highly trained personnel and regulatory expertise and real time, end-to-end visibility throughout the life cycle of drug development

- **Need the transparency and accountability throughout the lifecycle of the drug development**
- Follow GXP standards from transport and storage processes to depots

- Support shipment stability through sensors for tracking temperature, light, pressure, humidity and tilt throughout the journey

Figure 12: Key considerations for Logistics Solution Providers serving the pharmaceutical industry

DHL- ONE STOP SHOP LOGISTICS PARTNER FOR THE BIOPHARMACEUTICAL AND R&D SUPPLY CHAIN NEEDS

Clinical Research Supply & Logistics Value Chain

Inbound transport	Global GMP depot storage networkk
Deconsolidation	GMP secondary packing / Lab kittings
Global visibility & tracking tools	Global logistics control tower
Next flight out service	Dedicated outbound transport
Returns management	Certified destruction
Specialized courier services	Risk assessment & shipping lane verification
Temperature controlled / reusable packaging	Biological shipments
DTP services	IMP storage

Real-time end-to-end visibility platform

Temperature ranges from -196°C to +25°C

GOP, GMP, GCP compliant: IMP License

23 Clinical Trial Depots serving 80 countries

170 Countries served by Medical Express and/or DHL SameDay

50,000 Cold chain shipment

>200 DHL certified life sciences professionals

250 Pharmacists in our warehouses

Source: DHL & Frost & Sullivan

Figure 13: Biopharmaceutical and R&D supply chain needs

clearance may affect the drug's efficacy due to the prolonged exposure to temperature-controlled environments during shipping. Incorporation of DtP IMP shipment process workflows into the trial protocol early on can expedite import clearance.

3. Customization in clinical trials impact logistics models: Due to the dynamic nature of patient enrollment in digitally-enabled trials, there is a need to consolidate supplies in a central location. Management of shipments to local investigator sites or patient homes as a consolidated shipment of everything required for the trial (i.e., IMP, administration equipment, instructions, protocols, monitoring equipment, and consumables, such as syringes) will alleviate confusion, simplify inventory management, and expedite the study from months to days. However, there is a growing risk of increased wastage and the pressure to address sustainability challenges by logistics solutions providers. They will have to drive innovation in process or packaging materials continuously, e.g., using reusable packaging when appropriate for shipment type, location, and drug product or incorporating a system to use returnable temperature-monitoring devices where relevant. Adoption of AI-based supply chain technologies such as demand sensing and inventory rebalancing is expected to rise within the pharmaceutical and biopharmaceutical processing materials supply chain as the industry recognizes its advantages to map out demand based on virus spikes across different geographies.

4. Agility through collaboration and partnerships: Logistics solutions providers are expected to offer agile and cost-effective solutions based on the trial participation from across borders to ensure continuity. A global cold chain network of depots and fleets capable of supporting a wide range of temperature requirements for different biological samples, cells, IMP, or equipment from manufacturing to the end consumer will improve the success of clinical trials. The majority of finished cell and gene therapy products need to be stored at -150to -180 degrees Celsius, with the final product having a shelf life as low as 24 hours after thawing. Instead of building these specialized capabilities, global CROs must collaborate with logistics solutions providers to suit their trial needs.

Figure 14: Supporting biopharma and CROs throughout the entire clinical development life cycle

DHL, a global leader in logistics industry with end-to-end offerings, serves as an excellent example of a partner that supports biopharma and CROs throughout the entire clinical development life cycle. DHL offers collection and delivery of time-sensitive shipments while maintaining product integrity under rigorous temperature-controlled storage throughout its network, serving more than 80 countries. The control tower system ensures the quick and smooth transition of clinical trials through import/export controls that minimize customer delays in the IMP shipment or risks associated with failure to deliver the shipment in optimal condition. DHL tracks and reports each shipment from departure to delivery using a customizable self-contained system—Global Customs Connect—ensuring complete traceability until the IMP safely reaches patients. The premium medical express service involving specialized features such as priority handling, dry ice inclusion, and innovative dry ice solutions through partnership with CRYOPDP (offering temperature-controlled logistics solutions) positions DHL as the preferred logistics partner for clinical research sites and laboratories. DHL's international express network also provides customized solutions for urgent deliveries with the possibility of same-day delivery round-the-clock. Its global Good Manufacturing Practice (GMP) depot networks serve full loop services for all temperature ranges such as ambient (room temperature), chilled (2 to 8 Celsius), frozen (-196 to -20 Celsius), and controlled (15 to 25 Celsius) as per customer requirements.

Patient Centric Delivery for Clinical Trials of the Future: Conclusion

The COVID-19 pandemic has underscored the importance of capable end-to-end logistics partners that can service every component of the clinical development and trials supply chains. In the face of a rapidly changing global market, geopolitical chaos, shifts in consumer needs, scrutiny from regulators, rising operational costs, and emphasis on sustainability, tomorrow's logistics solution providers must ensure cost-effectiveness, full traceability, and total accountability at every step – packaging, storage, transportation, and delivery. To meet these challenges, leading logistics solution providers are incorporating automation, strengthening global cold chain networks, deploying data-driven demand planning solutions, and enhancing data security frameworks. Open, honest, and authentic partnerships between clinicians, government, CROs, and logistics solution providers, will deliver better global healthcare for all.

The DHL Advantage

More than 9,000 life sciences and healthcare specialists work across DHL's dedicated global network so that pharmaceutical, medical devices, clinical trials and research organizations, wholesalers and distributors, as well as hospitals and healthcare providers, are connected across the value chain, from clinical trials to point of care, and every step in between.

DHL's portfolio for the healthcare industry includes 150+ pharmacists, 20+ clinical trials depots, 100+ certified stations, 160+ GDP-qualified warehouses, 15+ GMP-certified sites, 135+ medical express sites, and a time-definite international express network covering over 220 countries and territories.

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