



PROPER VACCINE STORAGE AND HANDLING PRACTICES

Failing to keep the cold chain at the required temperature costs lives.

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The quality of the cold determines the efficacy of internal storage conditions.

Evolving quality and design
standards to meet demands of
new research



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MPR-S150H



MPR-S300H

Vaccine Storage and Handling: Current Considerations and Trends

Failing to keep the cold chain at the required temperature costs lives.

Making an effective vaccine faces significant obstacles, but it can't protect people without proper storage and handling, which depend on a complete line of pharmaceutical-grade refrigerators and freezers that maintain the necessary conditions to keep vaccines safe and effective. According to the U.S. Centers for Disease Control and Prevention's **Vaccine Storage and Handling Toolkit**: "Proper vaccine storage and handling are important factors in preventing and eradicating many common vaccine-preventable diseases." Nonetheless, this toolkit points out that every year "storage and handling errors result in revaccination of many patients and significant financial loss due to wasted vaccines." Without the proper storage, a vaccine can lose potency, resulting in "inadequate immune responses in patients and poor protection against disease," according to the CDC. This can only be prevented by storing vaccines—from the raw materials through manufacturing and delivery to patients—within the recommended range of temperatures for a particular product.

A vaccine's temperature must be maintained accurately and consistently. These requirements apply to all stages of a vaccine's lifecycle and impact a wide range of participants in the process, from pharmaceutical and logistics companies to storage and clinical sites. Some of the vaccines in development for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19, create new challenges. For example, the COVID-19 vaccines under development by Moderna and BioNTech/Pfizer are based on messenger RNA (mRNA), which is very unstable, and the vaccines must be stored at -20° C or -70 to -80° C, respectively

(See **Covering the Temperature Range for COVID-19 Vaccines**). Reporting in *Science*, Jon Cohen **wrote** that the ultra-low temperature needed to store the BioNTech/Pfizer means that "delivering it to hundreds of millions—if not billions—of people remain huge challenges."

Scientists see a range of challenges from mRNA-based vaccines. As an example, theoretical chemist Hannah Wayment-Steele of Stanford University and her colleagues **wrote**: "RNA hydrolysis presents problems in manufacturing, long-term storage, world-wide delivery, and in vivo stability of messenger RNA (mRNA)-based vaccines and therapeutics." Several of these obstacles for COVID-19 vaccines can only be addressed with improvements in the cold chain, and those enhancements must reach around the world.

FILLING THE COLD CHAIN GAP

So, logistics and storage companies must provide enough ultra-low freezers to keep the vaccines safe. At clinical sites, personnel must be able to safely handle the frozen vaccines, thaw them, and keep them viable until use. Addressing some of these concerns will require collaborations, such as the **partnership** between vaccine developer COVAXX and logistics company Maersk. Plus, many countries must add cold chain equipment. For example, India's health secretary Rakesh Bhushan, **stated**, "We are in a position to not only augment and strengthen but also add to our cold chain capabilities."

The necessary conditions depend on the specific vaccine. Liquid vaccines that contain an adjuvant, for example, cannot be frozen. The mRNA vaccines for COVID-19 in

development pose novel challenges. For example, RNA contains a hydroxyl group that can be disrupted by hydrolysis, and that makes RNA **less stable** than DNA. Consequently, the vaccines in development for COVID-19 require special cold storage equipment, such as ultra-low freezers. Even before working on these vaccines for COVID-19, scientists saw the **great potential** in building vaccines from mRNA, but researchers also **knew** that most mRNA vaccines needed to be stored at -70°C , which put a premium on developing formulations that could be stored at higher temperatures.

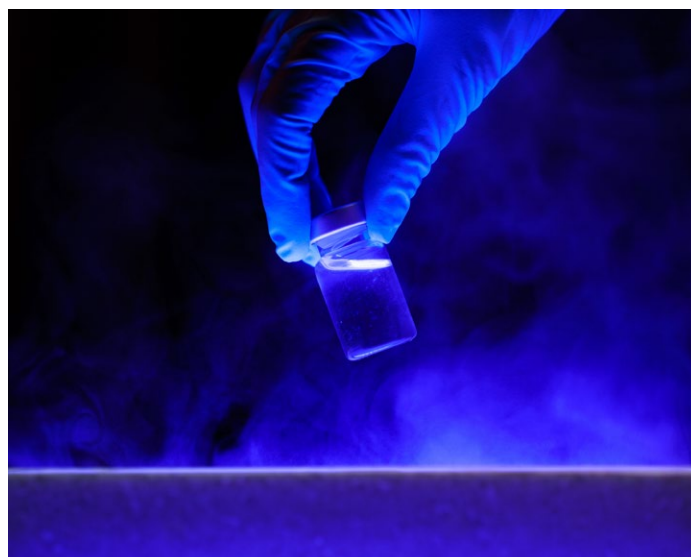
So far, all mRNA vaccines require very cold and stable temperatures. For the BioNTech/Pfizer vaccine for COVID-19, it must be kept at -70°C for distribution and storage and at **$2-8^{\circ}\text{C}$ after thawing**, and even then it's only viable for 5 days; for the Moderna vaccine, distribution and storage require -20°C , and after thawing it's **good for 30 days if kept at $2-8^{\circ}\text{C}$** .

In the United States, the CDC called on states to acquire more ultra-low freezers and some developing countries are hoping for vaccines that do not require such low temperatures. Even Pfizer **pointed out** about its leading vaccine candidate: "Risks and uncertainties include ... challenges related to our vaccine candidate's ultra-low temperature formulation and attendant storage, distribution and administration requirements, including risks related to handling after delivery by Pfizer." Plus, the pharmaceutical company added that there is a "risk that we may not be able to successfully develop non-frozen formulations."

To address such challenges around the world, a variety of pharmaceutical-grade equipment is required across a vaccine's lifecycle (**See Infographic: Maintaining Cold Chain Integrity**).

THE RIGHT COLD

A vaccine's required storage conditions include the temperature and other features. Moreover, creating the right cold conditions for vaccines depends on using pharmaceutical-grade refrigerators and freezers. As noted in **Excellence in Cold Chain Storage**: "Use of non-compliant household or domestic refrigerators for pharmaceutical storage is unsafe and costly."



The cold chain for a COVID-19 vaccine demands more equipment. On September 9, 2020, *The Wall Street Journal* **reported**: "Hospitals, pharmacies and physicians' offices are expected to be vaccination sites, but they have few such specialized freezers." The *Journal* added: "That is prompting a mad dash by logistics, public health and drug-industry officials to cobble together a cold storage supply chain that can deliver vaccines around the country without letting them become warm and ineffective."

Various companies can play a role in expanding the vaccine cold chain. For example, shipping company UPS is building freezer farms around the world. But it will be difficult to serve some regions fast enough. According to the **Asia-Pacific Cold Chain Logistics Market - Growth, Trends, and Forecasts (2020-2025)**, for example: "The Asia-Pacific cold chain market is highly fragmented." The report notes that the key challenges in the region include "large energy and space consumptions along with huge setup and modification costs."

With the right cold storage equipment and trained teams, though, currently available and new vaccines can be kept safe and effective. That can only be accomplished when the equipment and personnel provide the required conditions from raw materials through vaccine administration at a clinical site. Doing that requires preparation, following updated guidelines, and ensuring proper management across facilities around the world. Meeting all of those criteria remains crucial for existing vaccines that fight disease and grows increasingly vital as the world battles pandemics—today and tomorrow.

Covering the Temperature Range for COVID-19 Vaccines

Varying vaccine storage requirements demand precise positioning of equipment around the world.

Cold chain challenges loom ahead for a safe and effective vaccine for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19. On September 4, 2020, *The Wall Street Journal* **reported**: “The race to distribute Covid-19 vaccines to hundreds of millions of Americans could come down to one question: Do we have enough freezers?” With some of the vaccines in development requiring some storage steps at -80°C , the *Journal* adds: “To address concerns about equipment and storage capacity, hospitals are considering plans to buy special freezers.” Stretching that challenge around the world quickly adds up to lots of cold storage equipment.

The precise equipment required will depend on the vaccine, because the leading ones in development require different handling.

THE TOP TRIO

At the time of writing this article, the top candidates for a COVID-19 vaccine take three different approaches: DNA; messenger RNA (mRNA); or recombinant viral vectors. These techniques—known as next-generation vaccines—offer a crucial advantage: They “can be developed based on sequence information alone,” as **reported** by Debby van Riel of Erasmus MC in the Netherlands and Emmie de Wit of the U.S. National Institute of Allergy and Infectious Diseases. “This makes these platforms highly adaptable and speeds up vaccine development considerably, as is clear from the fact that the majority of COVID-19 vaccine clinical trials currently ongoing involve a next-generation platform.”

Some differences distinguish these next-generation approaches to COVID-19 vaccines. For example, DNA is very stable at room temperature, and RNA is not, because it contains a hydroxyl group that can be disrupted by hydrolysis, which makes RNA **less stable**. So, an unstable mRNA-based vaccine requires very stable storage conditions, including -80°C (**See Vaccine Storage and Handling: Current Considerations and Trends**).

Even among the mRNA-based vaccines in development, some similarities and differences exist. In two mRNA-based vaccines being developed, a lipid nanoparticle delivers genetic information for SARS-CoV-2’s spike protein. A DNA-based vaccine can also deliver spike-protein information but via a viral vector. Actual viral-vector vaccines, as described by van Riel and de Wit, “consist of a recombinant virus (that is, the viral vector), often attenuated to reduce its pathogenicity, in which genes encoding viral antigen(s) have been cloned using recombinant DNA techniques.”

COLD CHAIN CRITERIA

The different approaches to making COVID-19 vaccines spawn varying cold chain criteria. The specific conditions required will depend on the vaccine and its point in the overall supply chain.

Among the leading mRNA-based vaccines for COVID-19, distribution and storage require extremely cold conditions. Scientists have **known** for some time that RNA degrades at room temperature and can even degrade some when frozen at temperatures of -20°C and lower. The stability can be further improved through delivery

via a lipid nanoparticle, which **protects** the mRNA from nuclease degradation.

Upon delivery to a clinical site, the vaccines will be thawed, but then a vaccine will only be good for a short period of time. The mRNA-based COVID-19 vaccine being developed by BioNTech/Pfizer can be kept at 2–8° C for as many as **five days** where it will be administered. Conversely, a DNA-based vaccine in development for COVID-19 could be effective for a year at 2–8° C.

The specific conditions will evolve as vaccines move through development and approval. Plus, different conditions will be required from procuring raw materials to giving a vaccine (**See Infographic: Maintaining Cold Chain Integrity**).

THE GLOBAL CHALLENGE

With COVID-19 infecting people around the world, vaccines must be available globally—from urban to rural areas, some of them more accessible than others. Some countries started quickly to improve their cold chains. Singapore, for instance, runs a hub for storing and shipping pharmaceuticals, and it's preparing the facility to handle COVID-19 vaccines. Emirates SkyCargo, an airline based in Dubai, developed a facility just for COVID-19 vaccines, but it can't accommodate the –70 to –80° C needed by some of the vaccines.

To help countries make the most of existing facilities, UNICEF and the World Health Organization **are** “mapping out existing cold chain equipment and storage capacity—in the private as well as public sector—and preparing necessary guidance for countries to receive vaccines.”

As the air hubs in Singapore and Dubai demonstrate, dedicated facilities could be needed for distributing COVID-19 vaccines. DHL, an expert in global logistics, envisions various approaches to vaccine distribution, including direct shipment to point of use and local warehousing. “The benefits of a centralized approach include more efficient processes, increased transparency, and minimizing the redundancies and fragmentation associated with traditional procurement processes,” states the company's **Pandemic Resilience**



whitepaper. “It also brings a scale advantage, which is critical in widespread health emergencies.”

The ultra-low temperature requirements of mRNA-based vaccines could enforce centralized distribution. According to **Paula Cannon**, Distinguished Professor of Molecular Microbiology & Immunology at the Keck School of Medicine of USC, keeping a vaccine at extremely low temperatures all the time “creates a problem both for transportation, as well as storage in a pharmacy or doctor’s office. Initial rollout may well be restricted to large centers that can provide this temperature capability.”

PLANNING AHEAD

If COVID-19 taught the world’s public health experts anything, it’s the need to plan ahead. That includes incorporating the proper cold storage equipment in the needed places—all with a coordinated plan. As DHL stated: “Robust physical infrastructure—including available stock of medical supplies, and access to the required warehousing facilities and logistics capabilities—is key to a successful emergency response.” For example, clinical sites will need the right equipment, including gloves, to handle the shipments of super-cold vaccines. Plus, the people in the distribution system and at clinical sites must all be trained to correctly handle the vaccines.

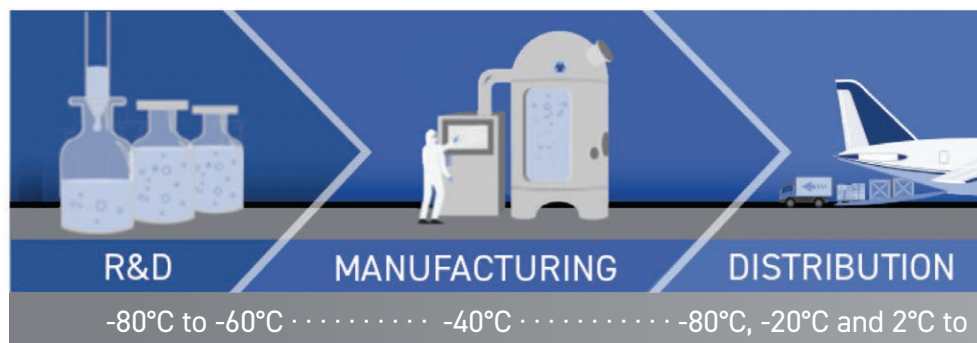
Without this planning, even an effective vaccine cannot slow the COVID-19 pandemic. There’s a lot of work to be done. As ABC **reported**: “nearly 3 billion of the world’s 7.8 billion people live where temperature-controlled storage is insufficient for an immunization campaign to bring COVID-19 under control.” It’s time for all hands on deck in vaccine storage and distribution.

Maintaining Cold-Chain Integrity

The cold chain matters more than ever in the battle against COVID-19 because some of the vaccines in development require very low temperatures from production through patient inoculation. From vaccine manufacturing to distribution and administration, actions taken throughout the process determine the efficacy and safety of a vaccine for patients. In each step, the required cold storage must meet several key criteria: accuracy, uniformity, recovery after opening, and ambient tolerance.

Steps in the process

Using devices, such as bioreactors, a drug maker produces a vaccine's ingredients, which might be transported to another location for formulation and shipping. Then, the vaccines will go to distribution centers, often shipped by air. Most vaccines will require precise temperatures throughout—in some cases, as low as -80°C . From a distribution center, vials of vaccine will go to clinics, hospitals, and other sites to vaccinate patients, and the required temperatures will range from -20 to $+8^{\circ}\text{C}$, depending on the ingredients, formulation, and packaging.



1
Vaccine
Manufacturer

2
Vaccine
Distribution

3
Arrival at
Provider Facility

4
Storage and
Handling at
Provider Facility

5
Public
Administration

Supplying the chain

A complete line of cold-storage devices—such as PHCbi's refrigerators through ultra-low freezers—will be required for protection in every step. All aspects of a specific vaccine and its components and processing will determine the temperature needed along the way. To ensure safety and efficacy, there will be precise temperature specifications for raw materials, R&D, manufacturing, distribution, storage, and handling.



A healthy head start

With various vaccines in development, it's difficult to determine the range of cold-storage platforms that will be needed. As a result, the U.S. Centers for Disease Control and Prevention recommends getting a jump on preparation by installing increased amounts of equipment where needed, from raw-materials producers through clinical sites. Advanced preparation is essential to ensuring that the vaccines currently under development can ultimately make a difference in the fight against COVID-19.



Excellence in Cold Chain Storage

The quality of the cold determines the efficacy of internal storage conditions.

IT'S THE QUALITY OF COLD THAT DETERMINES THE EFFICACY OF INTERNAL STORAGE CONDITIONS.

PHCbi pharmaceutical refrigerators, Biomedical freezers and pharmaceutical refrigerator with freezers combo refrigerators/freezers represent more than fifty years of engineering excellence in cold chain storage and temperature controlled products. From the refrigeration platform to the control center and cabinet configuration, each model delivers an extra measure of protection for safety and viability of high value pharmaceuticals not possible in household or commercial cabinets.

HIGH PERFORMANCE REFRIGERATORS AND FREEZERS

Designed for Vaccine, Pharmaceutical and Medical Product Storage.

PHCbi storage cabinets are designed to meet current The US CDC (Centers for Disease Control and Prevention) pharmacy guidelines for safety and performance.

Use of non-compliant household or domestic refrigerators for pharmaceutical storage is unsafe and costly. It creates liabilities for any audited dispensing pharmacy or health agency that cannot assure the efficacy of vaccines associated with government funded programs or other public health initiatives.

The combination of temperature control accuracy, interior temperature uniformity, quick recovery, resistance to high ambient temperature and multiple monitoring

processes delivers a quality of cold that characterizes PHC Corporation's commitment to engineering, storage safety and reliability.

ACCURACY

PHCbi pharmaceutical refrigerators are factory pre-set at 5°C to assure interior storage temperature is sufficiently above the risk point of temperature-sensitive vaccines and other liquid-based pharmaceuticals.

UNIFORMITY

Quality of cold starts with interior temperature uniformity which assures safety of stored products regardless of location within the refrigerator.

DEFROST

The cycle defrost and evaporator temperature sensor system ensures that defrost occurs only when necessary and automatically, so there is no need to turn off the power for defrosting. Irregular temperature increase during defrost is minimal with no temperature spikes. The evaporation heater also doubles as protection against drops in cabinet temperature caused by a low ambient temperature.

AMBIENT TOLERANCE

PHCbi pharmaceutical refrigerators and biomedical freezers are designed to maintain the quality of cold in warm ambient conditions where temperature recovery, tolerance for brown-out electrical supply on hot days and busy door opening traffic are common.



MPR-N250FH-PE



MPR-S150H-PE



MPR-S500H-PE



MPR-N450FH-PE

PHCbi MPR Series Pharmaceutical Refrigerators and Freezers vs Domestic/Household Products

PERFORMANCE	MPR SERIES	DOMESTIC/HOUSEHOLD
Precise Temperature Setting, Digital Display	Microprocessor Control, $\pm 2.0^{\circ}\text{C}$ Accuracy	—
Uniform Top-to-Bottom Temperature	Forced Airflow, $\pm 3^{\circ}\text{C}$	—
Fast Temperature Recovery	Reserve Cooling Power	—
Ambient Temperature Protection	High Performance Insulation	—
Protection from Vaccine Freezing	Tight Temperature Uniformity To Protect Stored Product From Freezing	—
Design Attributes	Specifically for Vaccine/Biological/Pharmaceutical Use	—
Dual Panel Glass Door	Transparent UV Screening	—
Integrated Systems Supervision	Microprocessor Monitoring	—
Deviation Alarms	Temperature, Door Ajar	—
Remote Alarm Terminal	Standard NO/NC/C - DC 24V 2A Connection	—
Self-Diagnostic Functions	Continuous	—
Access Ports for Independent Probes	Yes	—
Automatic Defrost on Demand, Cycle Defrost	Maintains Stored Product Temperature	—
Independently Controlled Freezer Section	Refrigerator with Freezers Freezer Units Only	—

COVID-19 Vaccine Development is Evolving

PHCbi HAS THE COLD CHAIN STORAGE YOU NEED



New vaccines are emerging in response to the COVID-19 pandemic. Early evidence suggests novel vaccine storage temperatures may require a wider range of the cold chain spectrum. Some vaccines may require multiple temperature storage points prior to administration. Are you prepared for emerging COVID-19 vaccine storage? PHCbi brand products can help¹.

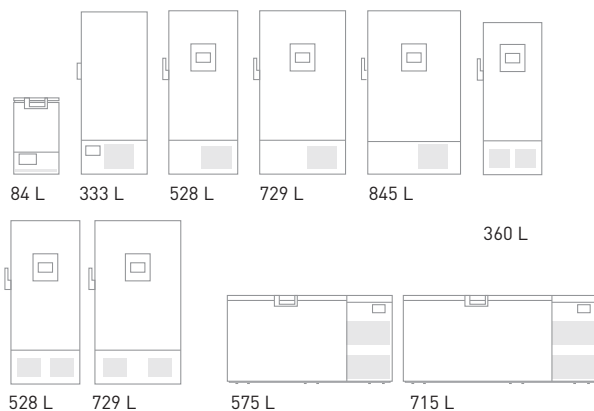
PHCbi brand pharmaceutical refrigerators and biomedical freezers offer a comprehensive selection of storage solutions for high-value vaccines and other biologics. These cabinets are based on high performance refrigeration platforms engineered for reliability, temperature uniformity, fast temperature recovery and tolerance for real-world conditions.

¹ Proposed vaccine storage temperatures are based on initial data from various sources in the public domain at time of publication. Government agencies and individual vaccine manufacturers will mandate required product storage temperatures.

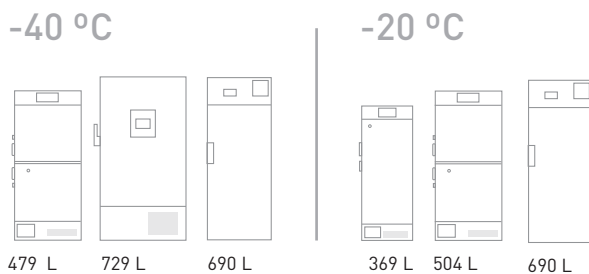
Vaccine Storage Begins with Proper Product Selection

PHCbi pharmaceutical refrigerators and freezers satisfy any storage protocol or space requirement. Robust refrigeration systems and cabinet designs assure temperature uniformity, reliability and energy efficiency. All are engineered to maintain required temperatures for product viability and to achieve rapid temperature recovery after multiple door openings.

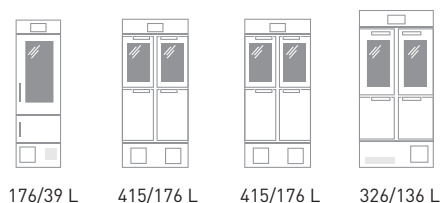
Ultra-Low Temperature Freezers



Biomedical Freezers



Biomedical Ref. / Freezer Combo



Biomedical Refrigerators



-60 °C to -86 °C Emerging Vaccine Types for COVID-19

For storage of mRNA, viral vector and non-replicating viral vector vaccines, as well as specimens.

VIP ULT

MDF-C8V1-PE

PRO ECO ULT

MDF-DU300H-PE

VIP ECO

MDF-DU502VH-PE

MDF-DU702VH-PE

MDF-DU901VHL-PE

TwinGuard

MDF-DU302VX-PE

MDF-DU502VX-PE

MDF-DU702VX-PE

MDF-DC500VX-PE

MDF-DC700VX-PE

-40 °C Vaccine Development Processes

Required for vaccine raw material storage and some pharmaceuticals.

MDF-MU549DH-PE

MDF-DU702VH-PE

MDF-U731M-PE

-20 °C Emerging Vaccine Types for COVID-19

May be required for some emerging mRNA vaccines.

MDF-MU339HL-PE

MDF-MU539HL-PE

MDF-U731M-PE

+2 °C to +8 °C and -20 °C Storage for multiple vaccine types

Both refrigeration and -20°C freezing are established with independent refrigeration systems.

MPR-N250FH-PE

MPR-N450FH-PE

MPR-N450FHD-PE

MPR-715F-PE

+2° C to +8 °C Traditional and emerging vaccine storage

For short-term storage of vaccines days prior to administration.

MPR-S150H-PE

MPR-S300H-PE

MPR-S500H-PE

MPR-S500RH-PE

MPR-1014-PE

MPR-1014R-PE

MPR-722-PE

MPR-722R-PE

MPR-1412-PE

MPR-1412R-PE



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