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REVIEW

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Ensuring quality and integrity of vaccines throughout the cold chain: the role of temperature monitoring

Umit Kartoglu [a] and Henry Ames[b]

[a]President and CEO, Extensio et Progressio, Collonge-Bellerive, Switzerland; [b]Sensitech Life Sciences, Beverly, MA, USA

ABSTRACT

Introduction: Vaccines have continually proven their inestimable value to the world through the eradication of smallpox, gains achieved toward a polio-free world, and controlling other vaccine-preventable diseases. Although vaccines require certain temperatures and conditions to maintain their potency, supply chain controls vary greatly at different legs of the global journey. Vaccine manufacture is closely managed, but inconsistencies plague the cold chain when vaccines are shipped and stored in variable conditions. Monitoring vaccine temperatures throughout the cold chain is of paramount importance to ensure quality. The emerging COVID-19 vaccines present the world with new challenges and additional opportunities to establish best practices for safeguarding human health.

Areas covered: We review the risks associated with the vaccine cold chain that require temperature monitoring throughout shipment and storage. Electronic and chemical monitoring devices are compared along with data needs. Regulatory oversight and guidance are also discussed.

Expert opinion: Regulatory oversight has contributed to the creation of a risk management and quality culture among private sector players in the vaccine field. Meanwhile, the public sector (the main player at the country level) remains largely untouched by regulatory oversight. Adherence to best practices shall only be possible with increased regulatory oversight of public sector operations.

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1. Introduction

Immunization is one of the most successful and cost-effective interventions known in the field of health [1]. Immunization saves two to three million lives every year and has enhanced life expectancies. Through a ten-year global effort, immunization freed humanity from smallpox in 1980 [2] and has also played a central role in the efforts to establish a polio-free world [3]. Today, vaccines have become a strategic tool to facilitate an exit from the COVID-19 pandemic [4]. Even in countries where a high vaccination coverage is achieved, there is a renewed burst of cases and a rising death toll in what's become 'a pandemic of the unvaccinated' Dr. Rochelle Walensky, the Centers for Disease Control and Prevention's (CDC) Director said recently [5].

It is widely known that vaccines require appropriate temperatures and conditions to ensure their potency, but less known are the complexities, risks, and failings involved in the associated cold chain, through which vaccines leave manufacturers, travel round the world, and ultimately reach a patient's arm. This paper focuses on the role of temperature monitoring combined with proper handling to ensure the quality and integrity of vaccines throughout the cold chain.

Vaccine researchers employ cutting-edge technology built on many years of research and development to create today's breakthrough vaccines. However, the most effective and vital vaccine can have little impact on human health if products are unable to reach their destinations, or if they arrive impaired and thus are ineffective.

All vaccines are sensitive to heat, some to freezing, and some to light. They need to be kept at a certain temperature range based on the stability characteristics of each vaccine and need to be protected from exposure to heat and cold. The cold chain system comprises an extensive array of equipment, tools, procedures, and staff that facilitate maintaining vaccine effectiveness from the point of manufacture to the point of administration.

Cold chain problems occur in all countries and at all levels contrary to the belief that deficiencies are mainly observed in developing countries. The Effective Vaccine Management Initiative launched by the World Health Organization (WHO) documented poor compliance with temperature monitoring targets at all levels of the cold chain in more than 45 countries [Garnett A, Unpublished data]. Interestingly, the majority of problems evidenced at the country level do not require significant investments.

Most pharmaceutical products travel through a significantly complex supply chain with many handoffs and owners along the way. As products change hands from manufacturer to primary wholesaler, secondary wholesaler, pharmacy, hospital, or clinic, stitching together the environmental monitoring across each segment of the supply chain becomes incredibly challenging – and therefore is not typically performed. The lack of visibility leads to unidentified and inadequate monitoring in segments of cold chain management thus resulting in adulterated products.

CONTACT Umit Kartoglu umit@kartoglu.ch President and Ceo, Extensio Et Progressio, 1A chemin du Pre-d'Orsat, 1245 Collonge-Bellerive, Switzerland
This article has been republished with minor changes. These changes do not impact the academic content of the article.

Article highlights

- Vaccines are time and temperature sensitive biological products and are affected by exposure to freezing temperatures, to heat and to light. When vaccine potency is lost it cannot be regained. It is therefore essential to ensure vaccine quality.
- The primary crux of the vaccine cold chain is temperature monitoring. As all vaccines need to be maintained within a specific temperature range, continuous monitoring of vaccine temperatures is imperative, particularly as products travel through varying conditions.
- Electronic devices are superior to chemical systems based on their data capabilities that meet the requirements of key players in vaccine cold chain operations.
- Introduction of new vaccines (especially COVID-19 vaccines) brought more complexity to cold chain operations and therefore to temperature monitoring.
- Following manufacturing, vaccines typically reach end users through a highly complex cold chain operation, going through a number of 'touchpoints' or process and service exchanges between organizations and individuals. Touchpoints present substantial risks of improper handling during these exchanges, typically resulting in temperature violations.
- Regulatory oversight has contributed to the creation of a risk management and quality culture in the private sector. Although the public sector is the main player at the country level of vaccine management operations, the public sector is mostly untouched by regulatory oversight. The ability to demonstrate compliance with good storage and transport practices shall only be possible with increased regulatory oversight of public sector operations.

Although cold chain products need to be temperature monitored from manufacture to the point of use, stricter monitoring occurs at the higher levels of the cold chain. The main reason for this is that the regulatory pressures and auditing of proper storage, handling, and distribution is mainly focused on these higher levels. Thus, less regulatory scrutiny is encountered deeper into the supply chain.

The public sector, however, has been largely untouched by the quality and risk culture demanded by regulatory authorities for pharmaceutical products and vaccines. For instance, a Ministry of Health could establish a cold storage facility without oversight from the national regulatory authority in contrast to the way manufacturers are closely monitored by regulatory authorities. Manufacturers are required to qualify temperature-controlled storage areas and produce evidence of temperature monitoring in storage areas, security and fire protection, temperature mapping, refrigeration equipment maintenance, and calibration of temperature control and monitoring devices. Most importantly, in the private sector, a technically competent person is (and must be) appointed to manage storage areas, whereas in the public sector a non-specialized worker could be given such tasks without any training.

There are a number of factors that impact how and when a product is monitored across the very complex pharmaceutical supply chain. Given that regulatory pressures are generally focused earlier in the supply chain at the manufacturer level, a vast majority of temperature monitoring services are contracted directly with drug manufacturers or dictated by the manufacturers and documented in quality agreements with their downstream supply chain partners.

The situation is quite different for COVID-19 vaccines mainly due to the limited availability of stability data. In this sense, as it pertains to good cold chain management practices, the distribution of the COVID-19 vaccine is unique in a number of ways. First, the process is largely controlled by the manufacturers. Many of the financial transactions are taking place between manufacturers and the destination country's government. This uncharacteristically streamlined chain of custody simplifies the burden of ensuring product quality and patient safety. Furthermore, the streamlined flow of goods helps to drive accountability, as well as visibility for ensuring product efficacy. The increased public visibility and new-found education and awareness about the importance of proper temperature control of COVID-19 vaccines has, no doubt, had a positive impact, helping to ensure that vaccines are not adulterated at any point along the cold chain.

2. Temperature sensitivity of currently available vaccines

In order to protect vaccines from exposure to both high and low extremes, they are required to be stored and transported within certain temperature ranges that correspond to their stability characteristics. Today's classical cold chain was developed mainly for two types of vaccines: those with temperature sensitivities dependent on the complex nature of the three-dimensional structure of vaccine antigen and those with temperature sensitivities dependent on adjuvants and additives. However, many new vaccines cannot be assigned to these two-category cold chain, which adds greater complexity to cold chain requirements and to temperature monitoring.

WHO classifies vaccines based on their stability characteristics defined through real-time stability studies at 5°C, as well as accelerated stability studies conducted at 25°C and 37°C. Figure 1 and 2 illustrate the freeze and heat stabilities of traditional and new vaccines plotted in ordinal scales based on their freeze and heat sensitivity [6]. COVID-19 vaccines are not plotted in these figures because real-time and accelerated stability studies are not available. However, a full list is given in Table 1 (including the COVID-19 vaccines) indicating their transport requirements based on their available stability information [7].

Figure 1 mainly illustrates two major categories for traditional vaccines based on their freeze sensitivity. Figure 2 shows new vaccines with greater variation in both heat and freeze sensitivity including the most recent thermostable vaccine Rotasiil® Thermo. It should be noted that Table 1 applies only to international air shipping of vaccines as classified by the WHO.

3. Managing cold chain risks

Quality Risk Management (QRM) has become engrained in the pharma industry with regulatory authorities demanding more and more risk-based approaches in all processes of manufacture and transportation of products. International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Q9 defines quality risk management as a 'systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle' [8].

Table 1. Classification of WHO prequalified vaccines based on their thermostability and presentations for international air shipment.

Class A – Highly heat sensitive and not impacted by freezing	**Recommended shipping temperatures**	
	Lower limit	**Upper limit**
Oral polio vaccine bivalent types 1 and 3 Oral polio vaccine monovalent type 1 Oral polio vaccine type 2 Oral polio vaccine type 3 Oral polio vaccine trivalent	None	8°C
Class B – Heat sensitive and not impacted by freezing	**Recommended shipping temperatures**	
	Lower limit	**Upper limit**
bacille Calmette–Guérin COVID-19 vaccine (Janssen, Moderna) Ebola vaccine (Mvabea and Zabdeno) Haemophilus influenzae type b (lyophilized) Influenza, pandemic H1N1 (lyophilized) Influenza, seasonal (lyophilized) Japanese Encephalitis vaccine (live, attenuated – lyophilized) Measles Measles-Rubella Measles-Mumps-Rubella Meningococcal A conjugate Meningococcal ACYW-135 (conjugate vaccine – lyophilized) Moderna COVID-19 vaccine Rabies vaccine (inactivated – lyophilized) Rotavirus (live attenuated – lyophilized) Rotavirus (live attenuated – liquid, applies only to products from Bharat) Rubella (live attenuated – lyophilized) Varicella Yellow fever	−30°C	8°C
Class C – Heat sensitive and impacted by freezing	**Recommended shipping temperatures**	
	Lower limit	**Upper limit**
COVID-19 vaccine (Corbevax, AstraZeneca, Covishield, CoronaVac, and BIBP) Diphtheria-Tetanus Tetanus-Diphtheria (reduced content) Diphtheria-Tetanus-Pertussis (acellular) Diphtheria-Tetanus-Pertussis (acellular)-Hepatitis B-Haemophilus influenzae type b-Polio (inactivated) Diphtheria-Tetanus-Pertussis (whole cell) Diphtheria-Tetanus-Pertussis (whole cell) -Haemophilus influenzae type b Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B-Haemophilus influenzae type b Haemophilus influenzae type b (liquid) Hepatitis A (inactivated) Hepatitis B Human papillomavirus (quadrivalent, bivalent and nine-valent) Influenza, pandemic H1N1 (liquid) Influenza, seasonal (liquid) Japanese Encephalitis vaccine (inactivated) (liquid) Meningococcal ACYW-135 (conjugate vaccine) (liquid) Oral cholera vaccine Pneumococcal (conjugate) Polio vaccine (inactivated) Rotavirus (live attenuated) (liquid) Tetanus toxoid Typhoid (polysaccharide and conjugate)	2°C	8°C
Class D – Ultra low temperature	**Recommended shipping temperatures**	
	Lower limit	**Upper limit**
COVID-19 (Comirnaty) Ebola vaccine (Ervebo)	−90°C	−60°C

This table is to appear in Rev.1 of the WHO Guidelines on the international packaging and shipping of vaccines, 6th edition (Submission of 1st revision of the 6th edition of WHO Guidelines on the International Packaging and Shipping of Vaccines to Isaac Gobina/WHO, unreferenced, see 'Notes').

This approach was also reflected in the most recent two regulatory guidance document updates from the United States Pharmacopoeia (USP), and the European Commission [9,10].

Following manufacture, vaccines typically reach end users through a highly complex cold chain operation. A salient feature of these operations is the number of 'touchpoints' or process and service exchanges between organizations and responsible individuals [11]. Touchpoints present substantial risks for improper handling during these exchanges. Due to the potential of abuse at these junctures, a touchpoint is typically defined as a 'critical control point' at which controls, and checks can be applied to prevent or reduce a hazard or risk to an acceptable or critical level [12].

Table 2 gives examples of touchpoints and types of risk controls in an air transport operation of vaccines [11].

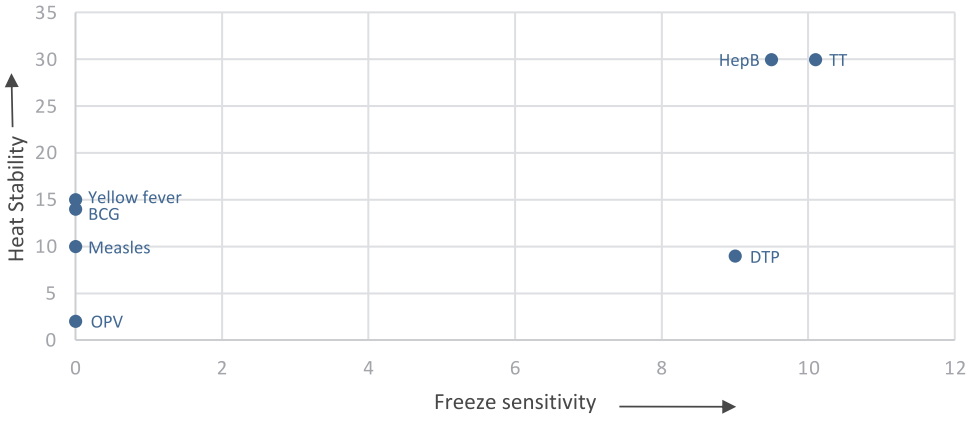

Figure 1. Freeze sensitivity and heat stability of traditional vaccines [6].

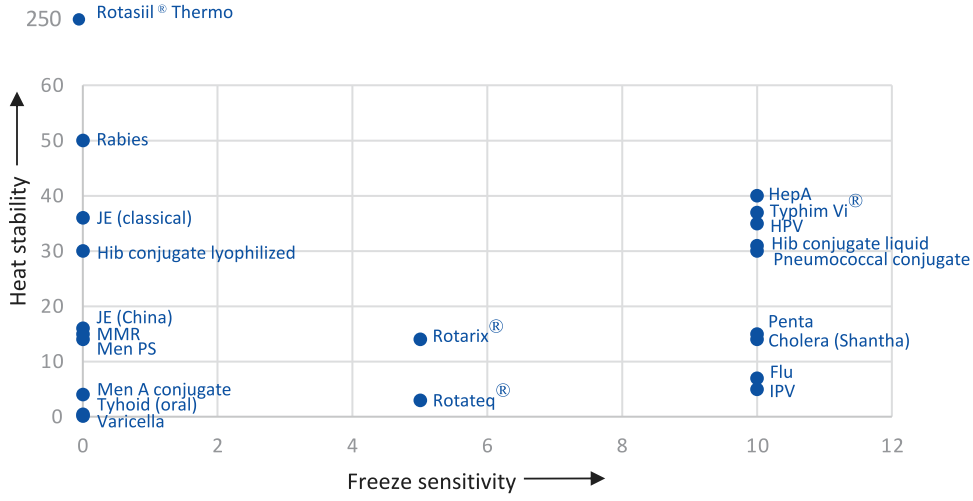

Figure 2. Freeze sensitivity and heat stability of new vaccines [modified from Ref. 6].

4. The need for information drives the design of temperature monitoring devices

The primary crux of the vaccine cold chain is temperature monitoring. However, maintaining appropriate temperatures as products travel through varying conditions presents considerable challenges.

From the QRM perspective, temperature monitoring is a 'detective' type of control measure. Such monitoring detects alarm violations and alerts workers to take necessary actions. In typical international shipments, there are three major players: manufacturer, logistics service provider, and the recipient. We are considering the United Nations (UN) procurement agencies together with the recipient to simplify the discussions under this title as UN procurement agencies are involved on behalf of the recipient country.

All parties want vaccines to reach their destination in good quality. However, the need for information obtained from temperature monitoring devices may differ among the players. The recipient country may want to know whether there was any temperature excursion that would affect the quality, which would trigger rejection of the shipment, but they may have no interest in the cause. However, the cause of the alarm could be the major point of interest for the logistics service provider as well as the manufacturer. Ultimately, the recipient wants straightforward, clear information that indicates whether or not to accept a shipment.

Rejection criteria are very seldom clearly defined. Even the WHO prequalified international shipping indicators require recipients to contact the procurement agency if any of the alarms are triggered. Thus, the recipient can only elect to accept the shipment under two conditions [7]:

- that no alarms have been triggered, and
- that if the −0.5°C alarm has been triggered for more than one hour, a freeze-sensitive vaccine passes the shake test.

With all other alarms, the procurement agency is required to be contacted for evaluation of the alarm details to decide whether or not to accept the vaccine.

Table 2. Selective critical handling processes and types of risk controls involved in a typical air transport operation of vaccines (modified from WHO).

Critical handling process	Risk control
Product preparation and conditioning at shipper's location	• Electronic temperature monitoring of storage facility, i.e. • refrigerator, freezer, cold room, warehouse. Humidity monitoring where appropriate. • Defined conditioning and staging time specifications for packaging components – temperature and duration, compliant with design and operational qualifications
Product loading at shipper's location	• Defined process, checklist • Application of International Air Transport Association (IATA) time- and temperature-sensitive product label • Defined actions in the event of delays

Ground transport from shipper location	• Use of refrigerated or temperature-controlled vehicle
	  • Temperature defined and preconditioned before loading
	  • Electronic temperature monitoring; humidity monitoring where appropriate
	• Serviceability checks on equipment
	• Defined actions in the event of delays

Warehousing (en route)	• Use of IATA Standard Acceptance Checklist for Time and Temperature Sensitive Healthcare Shipment • Temperature monitoring; humidity monitoring where appropriate • Availability of batteries, electrical connections, or dry ice to maintain correct temperature of active containers • Availability of sub-zero, refrigerated, or controlled room temperature storage when required • Defined storage instructions • Defined actions in the event of delays and mishaps en route
Airport tarmac/apron	• Minimize time exposed to ambient temperatures • High priority ramp handling • Covered storage when transiting through multiple airports • Use of passive protection tools such as thermal blankets • Defined actions in the event of delays
Aircraft hold	• Avoid positioning near cargo door • Cargo hold temperatures maintained between +15.0°C and +25.0°C • NOTOC (notification to captain) defining cargo hold temperature setting or use of dry ice in active containers

When selecting the most suitable device for international vaccine shipments, it makes sense to investigate the data requirements that the major players look for in an international shipment, as these needs inform the temperature monitoring device design. The information needs can be summarized as follows:

- Whether preset alarms have been triggered
- Details of each alarm (highest and lowest temperatures reached and their durations)
- Highest and lowest temperatures reached beyond alarm limits (but not exceeding the time limit) without triggering any alarm
- Timing of the alarm (when it happened – to understand where in the transport chain a problem has occurred)

Table 3 analyzes the capabilities of electronic and chemical indicators in meeting these data needs. Vaccine vial monitors (VVMs) as chemical devices are kept outside of this analysis since VVMs are not considered as transit indicators alone. Details about the VVMs are given in the following section.

As for chemical devices, both threshold and cumulative types, the accuracy of the data has a much wider span compared to electronic devices. For example, since the establishment of the Expanded Programme on Immunization (EPI) by WHO in 1974 until 2006, the freeze indicator that was used in international shipments of freeze-sensitive vaccines had an accuracy of ±1.5°C [13]. Now, electronic equivalents of this category measurement accuracy are ±0.5°C or better [14]. Similarly, the cold chain monitor card with ±1.5°C accuracy was the device of choice in the early days of the EPI, but now WHO recommends the use of electronic devices with ±0.5°C or better accuracy for the same purpose [7]. In general, chemical devices warn users that 'it has happened' without any details of the extent of the violation both in terms of high or low temperatures reached and about their duration.

5. The distinguished role of VVMs as chemical devices

At this point, we need to distinguish VVMs from all other chemical devices. VVMs are the only devices in vaccine management that have an inherent role at all levels of the vaccine supply chain, as they are attached to a vaccine vial and present at all times from manufacture until consumption [15]. However, VVMs only capture the heat exposure over time and not freezing conditions. The dynamic response of these time and temperature integrators (TTI) relative to temperature exposure is governed by the Arrhenius equation (as is the case with the stability of pharmaceuticals and biological materials), more specifically the activation energy (AE) which defines an amount of heat (energy) required to facilitate a change in the reactive material. In this sense, VVMs differ from all electronic temperature monitors because they are used at certain legs of the vaccine supply chain, and exposures cannot be cumulatively evaluated by the users across the duration of the cold chain. Of course, electronic devices can monitor the entire cold chain from beginning to end, but such monitoring is done only for study purposes.

Table 3. Comparative analysis of electronic and chemical device capabilities in meeting data needs for temperature monitoring of international vaccine shipments.

Data need	Electronic devices	Chemical devices
Whether preset alarms have been triggered	Any alarm condition (single or cumulative) can easily be programmed in electronic devices	Certain technologies have limitations in programming any alarm condition with chemical devices
Details of each alarm (highest and lowest temperatures reached and their durations)	All possible	Not possible. Chemical devices will only indicate that the condition has been violated without any precise details of the highest/lowest temperatures reached and their durations
Highest and lowest temperatures reached beyond alarm limits without triggering any alarm (but not exceeding the time limit)	All possible	Not possible
Timing of the alarm (when it happened – to understand where in the transport chain it has happened)	All possible	Not possible

However, VVM is not a transit or shipping indicator. In VVMs' operational life cycle, the duration of transport and especially the international transport is minimal. It is almost impossible to notice a product change unless shipping has been unduly prolonged and/or products are exposed to extremely high temperatures for extended periods of time which is very unlikely.

Because of their availability at all times, VVMs offer additional uses to vaccine managers by exploitation of the stability of each vaccine to the greatest possible extent. In addition, VVMs minimize distribution costs while increasing the flexibility of handling vaccines in the field. VVMs pinpoint cold chain problems, facilitate efficient management of vaccine stocks, reduce vaccine wastage, and facilitate immunization outreach.

6. The superiority of electronic monitoring devices over chemical monitoring

Electronic monitoring devices offer many advantages as compared to chemical monitoring, thus demonstrating a clear superiority. Not only do electronic devices provide greater temperature accuracy but they also overcome user ambiguity and furnish more detailed information as compared to chemical monitoring. Following is a detailed comparison of electronic versus chemical monitoring for vaccines (and other sensitive products).

6.1. Time and temperature accuracy

Time accuracy specifications for chemical indicators vary widely. Some manufacturers of chemical indicators do not provide time accuracy parameters. In comparison, the typical time accuracy of an electronic device is on the order of ±0.01% of elapsed time, or less than a five-minute error per month of operation. Typical published temperature accuracy claims for chemical indicator thresholds are ± 1.0–2.0°C, as opposed to electronic devices that provide temperature measurement accuracy on the order of ± 0.5°C.

6.2. Measurement repeatability (precision) and hysteresis

Electronic devices offer highly repeatable (precise) temperature measurements. A high degree of 'closeness of the agreement' of repeated measured temperatures under the same environmental conditions is readily attainable with electronic sensor-based technology. In addition, the directionality of temperature changes (increasing/decreasing) has little impact on the precision of the measurement obtained by electronic sensors (low hysteresis). In comparison, chemical indicator temperature measurement repeatability and hysteresis effects are not widely known.

6.3. Stability and drift

The change in resistance or drift of a solid-state ceramic glass-bead semiconductor thermistor is minimal, on the order of 0.02°C to 0.15°C after 12 months of continuous exposure to temperatures between 25°C and 100°C [16]. The ceramic oxide material utilized in thermistor sensor construction is typically encased within glass, hermetically sealing the temperature-sensitive material from exposure to environmental conditions that can alter the characteristics of the material. Chemical indicators utilizing monomers, enzymes, or esters can be susceptible to drift and instability due to exposure to environmental conditions such as high or low storage temperatures, humidity, ultraviolet light, and chemical vapors.

6.4. Post-use validation

In addition to pre-deployment validation, electronic indicators can be post-use validated. If there is any question or concern regarding the accuracy of results displayed by electronic indicators, they can be returned to the factory, 'reset' and retested and validated within a controlled environment. Chemical indicators cannot be reset and retested after activation and deployment.

6.5. Custom threshold/alarm settings

Electronic temperature indicators can be easily tailored to unique product needs (stability data), packaging/pack outs variability, and specific conditions of a particular transportation segment. Chemical indicators are generally offered in a limited number of time-temperature threshold variants.

6.6. User interface ambiguity

Chemical-based TTIs incorporate a user interface that is dependent on either color-matching of the reactive material or the determination of the 'migration' distance of the reactive material relative to a graded time scale. In both cases, the user

must infer the results based on a subjective interpretation of what is presented. Chemical phase-change devices for freeze indications generally present less subjective results. However, they still rely on the release of a dye or a color change to the reactive material, which is open to interpretation and naturally to error [17]. Electronic indicator user interfaces and displays offer clear, unequivocal results of the status of the time-temperature alarm states.

6.7. Multiple alarm settings

Many electronic devices can be programmed with several independent time-temperature alarm conditions, either single-event or cumulative, high, or low. In addition to the ability to tailor the setting to the unique transport situation, one device can be deployed to monitor both high and low temperature conditions; no need to procure, stock, and deploy multiple devices or manage seasonal adjustments as required with single time-temperature threshold chemical indicator deployments.

6.8. Integrated start delay

Electronic indicators are often available with a measurement start delay that allows the device to equilibrate to 'stable' storage and shipping conditions prior to monitoring the alarm states. This capability inhibits false-positive alarms due to dynamic thermal responses of the packaging and pack out. Chemical indicators are passive devices that are continuously affected by their environment, and therefore susceptible to temperature fluctuations.

6.9. Pre-deployment storage and shipment requirements

Many chemical indicators must be stored and shipped in controlled conditions prior to deployment. In some cases, this requires manufacturers to ship the indicator on dry ice and store on-site in freezers. In other cases, chemical indicators must be protected from freezing prior to use. In comparison, electronic indicators offer broad storage and shipment temperature ranges prior to deployment and are 'inactive' and therefore unaffected by temperatures prior to initiation. In addition to onerous storage and shipping conditions, some chemical indicators require specific temperature storage pre-conditioning to prevent a premature response.

6.10. Product reliability

Electronic devices are inherently more reliable than chemical indicators due to the low failure rates and stability of electronic temperature sensors (and supporting circuit components), and the high-yield automated assembly and test processes utilized in their construction. In comparison, chemical indicators utilize polymers, enzymes, or esters, which by design are reactive to their environments. These compounds require careful synthesis and elaborate analysis to provide some measure of repeatability relative to dynamic responses to temperature.

6.11. Ultraviolet light exposure

Some chemical indicators, particularly TTIs manufactured from diacetylene monomers, can be adversely impacted by exposure to ultraviolet light. Electronic indicators are impervious to exposure to UV, as well as typical chemical vapors present in transportation environments.

6.12. Fixed trip record display

Chemical indicators are passive devices that are continuously affected by their temperature environment. As a result, their condition will reflect the entire history of their exposure, including after a shipment is received. These devices can indicate false-positive alarm states relative to the trip history because of post-receipt temperature exposures. Some electronic indicators allow the user to stop the monitoring function upon receipt of the device, thereby creating a fixed record of the trip within the indicator and eliminating post-receipt temperature confusion.

6.13. Alarm excursion history data

Some electronic indicator products can display alarm excursion history data such as a time stamp identifying when a specific alarm has been triggered. Chemical indicators cannot provide information about temperature excursions relative to when specific thresholds were breached.

6.14. Combined features

Real-time temperature monitoring combined with other features such as detecting humidity, location, and breaches gives additional important information both for decision making and interventions as needed. Real-time monitoring can be used not only in transport but also in monitoring storage areas especially when combined with event logger systems that report door openings. Chemical devices cannot be combined with such features.

6.15. Self diagnostic capabilities

Some electronic indicators contain internal self-diagnostic capabilities to ensure proper temperature measurements prior to deployment. Chemical indicator technology cannot facilitate self-diagnostics.

6.16. Toxicity and cross-contamination

Most electronic indicator products are encased in materials that are non-reactive and non-corrosive and in many cases are United States Food and Drug Administration (FDA) approved for product contact. In comparison, chemical indicators may contain materials that could present contamination concerns.

6.17. Supply chain disruption and inventory management

Chemical indicator customer acceptance quality-level inspection testing, shipping, handling, and preconditioning processes are more complex than those experienced using electronic indicators. Therefore, chemical indicators present more risk for successful inventory management. The inherent stability and ease-of-use of electronic devices minimizes supply chain risk for customers.

7. Electronic versus chemical monitoring device validation

In addition to the above listed attributes establishing electronic device superiority over chemical devices, it is worth discussing the validation of both devices. Electronic temperature indicators can be fully validated prior to activation and deployment. By virtue of the technology, each indicator device can be tested for accurate operation during the manufacturing process, thereby establishing the veracity of the measurement characteristics for 100% of all devices shipped to a customer. Every indicator can be verified within a specific set of time and temperature conditions and electronically 'reset' at the factory in preparation for customer deployment. Single-use devices (both electronic and chemical) cannot be validated in this fashion as any validation or testing at operational time and temperature settings would be destructive [18].

As stated in the guidance issued by the USP, 'Monitoring devices – Time, Temperature, and Humidity,' under 'Calibration of temperature – and humidity monitoring devices,' it is clearly explained that: 'Single-use electronic and chemical indicators should follow Good Manufacturing Practices with appropriate testing controls. Electronic indicators require proper calibration. Single-use indicator performance can be qualified by the supply chain user by sampling and testing of multiple production lots. For time- and temperature-integrators that calculate MKT, the performance of a batch can be assessed statistically by subjecting an appropriately sized sample to elevated temperature conditions for a set period and observing the results. Manufacturers should adopt appropriate acceptance criteria. It is acceptable to use the release test performed by the manufacturer of the indicator (based on the certificate of calibration or the certificate of analysis and the expiration date) in lieu of calibration or qualification.'

In line with the calibration/validation of the devices, electronic indicators are typically offered individually serialized and shipped with documentation supporting the validation process. Chemical indicators are generally marked with lot numbers again in line with USP recommendations.

8. Vaccine supply chains and temperature monitoring become more complex with the introduction of COVID-19 vaccines

Cold chain management encompasses many challenges including revamped product portfolios, requirements for good storage and distribution practices, regulatory expectations, quality management, and risk assessment factors. These challenges have become even more complex with the introduction of next-generation COVID-19 vaccines. To date, immunization programs have managed two temperature chains: 2°C to 8°C and −15°C to −25°C. With a specific mRNA product, the ultra-low temperature requirement of −90°C to −60°C was introduced. Although Ebola Zaire rVSVΔG-ZEBOV-GP live attenuated vaccine requires ultra-low temperatures both for storage and transport, the need was limited to certain countries experiencing Ebola outbreaks in Africa [19].

In addition to ultra-low temperature requirements, currently COVID-19 vaccines also differ from childhood vaccines because of their limited stability information. The main reason for this limited stability data is the abbreviated period these vaccines were studied between their development and emergency use authorizations. However, vaccine manufacturers continue with ongoing stability studies, and new storage and transport conditions are disclosed as new information emerges. For example, it was first announced that Comirnaty from Pfizer/BioNTech remains stable only 24 hours in a refrigerator (2°C to 8°C) once thawed. This information was later updated twice based on the new stability information revealing that thawed vaccines can be kept at 2°C to 8°C for up to 5 days, and then up to 31 days [20,21]. Currently, stability data indicates that the same product can now be stored at a − 15°C to −25°C range for up to 2 weeks [22].

New COVID-19 vaccines do not necessarily follow typical cold chain distribution routes, and special arrangements are designed to deliver vaccines to vaccination points, therefore special attention is required for the duration of storage.

Different temperature regimes also require different settings in electronic temperature monitoring devices. This requirement applies both to transport and storage of vaccines. WHO has grouped prequalified vaccines into four classes based on their stability budgets [7]:

Class A – Highly heat sensitive and not impacted by freezing

Class B – Heat sensitive and not impacted by freezing

Class C – Heat sensitive and impacted by freezing

Although vaccines requiring ultra-low temperatures for storage and transport do not appear in this classification, WHO is in the process of creating a new 'Class D' for ultra-low temperature vaccines (Submission of 1st revision of the 6th edition of WHO Guidelines on the International Packaging and Shipping of Vaccines to Isaac Gobina/WHO, unreferenced, see 'Notes').

The electronic temperature monitoring devices recommended by WHO for transport and storage consider this classification. The COVID-19 vaccines with emergency use authorization fit into this classification (with the addition of ultra-low temperature Class D); however, current WHO prequalified electronic shipping indicators cannot be used with their pre-set alarm points because they will not be able to cover the known stability characteristics of these vaccines. Currently, vaccine manufacturers use electronic data loggers with preset alarms for international transport.

This complexity highlights that one of the most essential elements of managing vaccines is sufficient human resources and ensuring that participants are equipped with the right knowledge and skills.

9. Regulation of the supply chain and temperature monitoring

Various global regulatory requirements must be met by both public and private sectors of the vaccine industry while storing and distributing temperature-sensitive products. This compliance is critical to ensure the quality and efficacy of the product throughout its lifecycle, so that the product is not compromised or adulterated. In general, three types of institutions issue regulatory documents: national regulatory agencies; other regulatory bodies, for example, the IATA and the ICH; and international organizations, for example, WHO and the Parenteral Drug Association (PDA).

National regulatory agencies of Member States (e.g. USFDA [9], Health Canada [23], the European Medicines Agency (EMA) [10], and the Medicines and Healthcare Products Regulatory Agency (MHRA) [24,25]) issue guidelines for temperature control of drug products during storage and transportation. Revisions are made to these guidelines regularly including those from the USP, Health Canada, and the European Union. The most significant revisions were implemented for the 'Good Storage and Distribution Practices for Drug Products' [9], 'Monitoring Devices – Time, Temperature and Humidity' [18] and the brand-new 'Good Distribution Practices – Supply Chain Integrity' [26]. These regulatory documents indicate the principles for setting standards as well as providing guidance for appropriate actions. Regulations describe 'what' needs to be done, and they are 'guidelines' by nature, not obligations. However, it is in industries' interest to follow regulatory guidelines. Some of the European Union countries have converted EMA guidelines into laws which adds another level of pressure for their follow-up and implementation. Under the USFDA's 'Food and Drug Cosmetic Act,' a company is prohibited from introducing an adulterated product [27]. The MHRA publication 'Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2017' lays out very detailed expectations of calibrated accuracy for temperature monitoring [25].

None of these guidelines explain 'how' these suggested practices should be accomplished. At this point, in addition to their own guidelines, WHO and PDA-type organizations have published technical documents detailing how these principles could be implemented. In this regard, WHO's 16 technical supplements on best practices to support the harmonized 'Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products' can be highlighted as an important contribution [28,29].

The USFDA's 'Federal Food, Drug, and Cosmetic Act 501(a)(2)(B)' states that a drug is adulterated if the facilities or controls used for its 'manufacture, processing, packing or holding' do not conform to/are not operated or administered in conformity with Current Good Manufacturing Practice (cGMP) [27]. And, equally important, 'holding' is defined as when a drug is 'distributed, transported, or warehoused for distribution or transfer.' In this sense, temperature monitoring is considered one of the most critical components of the user's Quality Management Systems (QMS).

The ICH Q9 'Guideline on Good Manufacturing Practices (GMP)' also requires manufacturers to ensure that the contractors for transportation of the products know and follow the appropriate transport and storage conditions [30]. In this regard, temperature monitoring is an inherent component of GMP.

'Temperature Control Regulations' published by the IATA contains all the information and requirements for shipping temperature-sensitive products [31]. IATA also sets a list of considerations and awareness for large-scale handling, transport and distribution of vaccines, pharmaceuticals, life science and medical products and highlights the importance of temperature monitoring in its 'Guidance for Vaccine and Pharmaceutical Logistics and Distribution' [32].

10. Can thermostable vaccines remove necessity of temperature control?

Improving both heat and freeze stabilities of vaccines have been studied for many years and due to various restraining factors, limited examples exist today. In 2012, WHO has introduced an innovative approach to vaccine management called 'controlled temperature chain (CTC),' which allows vaccines to be exposed to temperatures outside the traditional cold chain requirements for limited period of time under monitored and controlled conditions [33]. MenAfriVac® became the very first vaccine prequalified for CTC which allowed a single excursion up to 40°C [34]. In principle, the CTC approach eliminates the need for cold chain during the last mile.

Other methods to develop thermostable vaccines involve many regulatory, technical, commercial, and intellectual property challenges, which may provide public health benefits but do not necessarily translate into commercial advantages for vaccine manufacturers [35,36]. Some current vaccines have excellent stability when stored and transported outside of cold chain restrictions, such as hepatitis B, human papilloma virus, oral cholera, and tetanus toxoid vaccines. Although thermostable vaccines reduce the dependency on the cold chain, the need to constantly monitor temperature persists as compliance must be demonstrated.

11. Expert opinion

Maintaining optimal conditions for the shipment and storage of vaccines is essential for delivering life-saving protections against infectious diseases around the world. Along with appropriate environmental conditions, the primary need for ensuring vaccine potency is monitoring temperatures throughout the cold chain and gathering data that demonstrate requirements have been upheld to safeguard the quality and integrity of the products.

Monitoring, recording, and reporting vaccine temperatures throughout the supply chain provides documented evidence that is essential to validate vaccine quality from the manufacturer's point of origin to the point of vaccination. From the QRM perspective, temperature monitoring also provides a means of detecting cold chain equipment failures and

other operational issues that enable the introduction of control and mitigation measures.

The availability of new technologies and the capabilities of electronic devices provide great opportunities to effectively manage the supply chain.

For monitoring, electronic devices overweigh chemical systems in meeting data demands that provide reliable information to cold chain managers. Electronic devices also provide more detailed information about the violations that are critical both for acceptance/rejection as well as for insurance purposes. Details such as timing and the extent of a violation can only be revealed if electronic devices with applicable features are employed. Such critical details cannot be provided by any of the chemical devices.

Real-time temperature monitoring combined with other features such as humidity, location, and breach detection shall be the norm in the future, especially for expensive products and goods that travel on routes with security threats. In this sense, the authors believe that in the future we shall see less and less use of chemical devices in temperature monitoring of vaccines and other biologicals. VVMs differ from all other chemical devices due to their added value as monitors of heat exposure at the unit level from manufacture to the point of use. VVMs will also continue to be a critical tool with the most recent 2D barcode integrated version [14].

As in all vaccine operations, responsible personnel with ample knowledge are critical for monitoring temperatures and maintaining proper environments. Personnel equipped with the appropriate training and skills are better equipped to recognize and respond efficiently to temperature excursions.

New and more stringent temperature monitoring requirements for breakthrough COVID-19 vaccines have introduced more complexity to cold chain operations. Generating new information about the stability of these vaccines (e.g. new storage conditions for the Comirnaty vaccine) has placed additional challenges on national immunization programs to adapt their logistics operations accordingly. Although these changes are positive in nature, restructuring is still needed to ensure that programs implement and maintain optimal operations. Adapting to the demands of the COVID-19 pandemic has helped immunization programs to become more responsive and flexible. On the other hand, internationally, all cold chain systems have gone through a reality test with the introduction of COVID-19 vaccines, which also help in building more resilient systems globally.

Regulatory requirements have supported the private sector in creating a risk management and quality culture, though the public sector has largely been untouched by regulatory pressure. Although vaccine logistics operations are outsourced in some countries, globally vaccine management operations are mostly handled by the public sector. In order to implement comprehensive and systematic temperature monitoring at all levels of the supply chain, the public sector should embrace the risk management and quality culture. This can only be achieved through regulatory oversight of public sector operations.

Although thermostable vaccines, which would be resistant to heat and/or freezing, could reduce pressure on the cold chain, they will not eliminate the need to monitor temperatures. In order to document that the required conditions are met, temperature monitoring will remain in practice.

Notes

As a consultant, U Kartoglu has authored both the 6th edition and the first revision to the 6th edition of WHO 'Guidelines on the International packaging and Shipping of Vaccines' under Isaac Gobina's supervision. Class D packaging for ultra-low temperature shipments as a new vaccine packaging was established in the 1st revision. The revision is expected to be published in early 2022.

Declaration of interest

U Kartoglu has worked with WHO as a consultant on authoring the guidelines on the international packaging and shipping of vaccines including requirements for candidate COVID-19 vaccines as well as revising specifications and verification protocols for temperature monitoring devices. He has also worked as a consultant for Temptime Corporation, Insite Enterprises, Inc., Sensitech, Inc., and UNICEF on vaccine-quality related issues. The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. H Ames works as General Manager for Life Sciences at Sensitech, a Carrier Company. Sensitech manufactures temperature monitoring products and provides expert services to help customers protect their temperature sensitive products. He also serves as a member of the Parenteral Drug Association's Pharmaceutical Cold Chain Interest Group and sits on the International Air Transport Association's Time and Temperature Task Force. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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ORCID

Umit Kartoglu http://orcid.org/0000-0003-0868-0007

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