White Paper

Vaccines and Bio-Logics: Managing Quality and Compliance within your Cold Chain Supply Network

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Back-Ground

Over forty years ago the 27th World Health Assembly resolved to build on the success of the smallpox eradication program and established the Expanded Program on Immunization (EPI) to ensure that all children, in all countries, benefited from life-saving vaccines.

The newly launched EPI at that time recommended the use of vaccines to protect against six primary diseases: tuberculosis (BCG), diphtheria, tetanus, pertussis (DTP vaccine), measles and poliomyelitis. As time has gone on there have also been local programs introduced around the globe to prevent specific outbreaks of particular childhood maladies, such as:

- In Liberia a new program for protection against one of the leading vaccine-preventable killers of children as the country today celebrates the introduction of pneumococcal vaccine (PCV).
- In India, improving measles control and polio (now 3 years without a major outbreak).
- In Haiti a 5-in-1 pentavalent vaccine protects children from diphtheria, tetanus, whooping cough, hepatitis B and Haemophilus influenzae type b (Hib) which causes pneumonia and meningitis.

There have also been many other globally focused programs, not just for childhood immunization, but also to protect against the growth of infectious diseases like:

- Influenza
- HIV/Aids
- Pneumonia
- Hepatitis
- HPV Vaccination for girls aged 9 to 13 years old

Obtaining Vaccines and Local Financing

Usually immunization programs are multi-year in nature and the WHO and UNICEF have published guidelines on developing a comprehensive multi-year plan (cMYP) for immunization, which includes recommendations on how these programs can be financed. Outlines of the tools available to help with obtaining this financing are available on the WHO website (www.who.org).

In addition to this, the Gates Foundation, PATH, plus UNICEF and its member groups, do provide some funding for global programs to vaccinate both children and adults against many of the common life threatening diseases in specific targeted regions.

Ultimately it is a costly proposition for any country or global entity to set up vaccination programs due to the high cost of these specialized medicinal products, most of which need strict control of environmental condition. Therefore, it is either recommended or defined by regulations, that condition management practices called cold chain monitoring and management, are employed for the manufacture, storage and distribution, both long range and locally within the region.

Vaccines Storage and Supply

Vaccines are highly sensitive and complex biological products. The manufacturing process of vaccines involves the manipulation of living organisms and incorporates significant risks of production failures.

Vaccines therefore depend on a highly regulated environment that ensures the strict enforcement of quality at all stages of the production, storage and transportation processes. Specific features such as the limited shelf life and temperature sensitivity of vaccines require careful stock and supply chain management that needs to be taken into account during the whole procurement process.

As noted earlier, vaccines are in the most part government funded, donor funded, or privately funded, and often distributed without any

end-user charges. Therefore loss of the local supply, or stock, can have a significant impact on ample supplies being available to meet the goals of the local immunization program and creating the need to find additional quantities or funding, to meet program goals.

Vaccines are mostly of a preventive nature and are administered to otherwise healthy individuals, most commonly children. The risks arising from poor quality vaccines are considerable. Adverse effects, or even deaths, caused by using poor quality vaccines can destroy public confidence in immunization programs and put additional lives at risk. Quality should always be of overriding importance, coupled with patient safety.

The CDC has a Vaccine Storage and Handling Tool Kit publication available: http://www.cdc.gov/vaccines/recs/storage/toolkit/storage-handling-toolkit.pdf

This document is comprehensive in nature and outlines the types of storage devices (refrigerators) that should be utilized, and includes details on how the condition of the products can be monitored on a regular basis to insure compliance to cold chain storage recommendations, usually between 2°-8°C and never allowed to freeze.

In addition to this, the WHO has a PQS (Performance, Quality and Safety) Program whereby they evaluate and certify specific types of products that should be used for cold chain logistics and management procedures and processes. This includes shipping containers, storage units, and temperature and condition monitors to ensure that documented manufacturer requirements for product storage and handling are maintained at all times. This also includes recommended types of certified thermometers and data loggers that can record a full 30-day condition log and have the ability to show temperature excursions and indicate alarm conditions if and when these may occur.

Types and Brand of WHO PQS – Certified Products, Why They are Needed

Immunization programs are global in nature, as previously noted, and this includes programs in the United States as well as all regions around the globe.

Vaccines and other cold chain products can be stored not only at vaccine distribution points but also at wholesaler warehouses, clinics, pharmacies and even a doctor's office. Therefore all of these locations are required or recommended to follow Good storage practices for cold chain and vaccine products. This includes using a temperature monitoring device to ensure that the 2°-8°C temperature range is maintained and no excursions occur.

When temperature excursions do occur and these are not captured, the products can cause serious harm if these medicines are given to a child, or indeed a patient of any age. Apart from the patient safety issues, loss of large quantities, and sometimes smaller batches, of vaccines can result in significant delays to immunization programs and a significant financial loss to the manufacturer, shipper, and/or the agency or country sponsoring the program.

If storage and transport conditions are monitored on a regular and recommended basis, any minor or immediate excursions can be detected as these occur, and corrective actions can be taken to prevent loss of products.

To monitor cold chain conditions, a simple device would be a certified to NIST traceability standards thermometer with alarm capabilities, if and when temperature excursions occur. To protect against any expected temperature fluctuations within the range of normal use, such as frequent door openings and cycling of the refrigeration/freezer units, the thermometer should have an external temperature probe

inserted in a bottle containing glycol as a buffer against the expected temperature fluctuations. The probe and bottle are placed inside the refrigerated storage unit to actively monitor conditions within the unit, and the thermometer is left outside so that the temperature can be monitored and manually recorded twice daily (per CDC recommendations).

Although this would suffice potentially for a doctor's office or small clinic, it relies very much on regular monitoring of the indicated temperature and a paper log of the daily conditions – i.e. human intervention on a regular basis.

The CDC has recently sent out an advisory that, instead of a thermometer, a data logger with an internal memory for logging/recording temperature on a regular basis, (every 15 minutes is recommended) should be used.

Preferably, and as a CDC recommendation, these devices should be certified to NIST traceability standards, and come with the compliance certificate from a test lab with accreditation conforming to ISO 17025 standards. These units should also have an external probe inserted in a glycol bottle to act as a temperature buffer, just like the thermometers, with the ability to alert staff if any temperature excursions occur. The units should also have their temperature logs downloaded every month to store as a permanent record for potential audits.

In addition to the CDC recommendations, it is advisable to utilize a monitoring device that is certified to WHO PQS standards, and DeltaTrak has a vaccine monitoring device that meets all these standards and requirements.

New Regulations - Cold Chain Risk Assessment and a Risk Mitigation Plan – Part of Your QMS?

Not only have global healthcare organizations defined best practices for handling cold chain products, but local entities, like the Chinese Health Organization based in Hong Kong, have issued strict guidelines related to cold chain product management aimed at immunization programs and vaccines. http://www.pco.gov.hk/english/resource/files/Module_on_Immunisation_Children.pdf - (Section 3.3 for Storage and Handling Procedures)

There were also a number of other global regulations introduced last year, for example:

In the EU, new Guidelines released on March 7, 2013, focused on Good Distribution Practice (GDP) of Medicinal Products for Human Use – (2013/C 68/01) – Implementation period of 6 months after March 8, 2013.

The Chinese FDA introduced new Good Supply Practices (GSP) guidance – (Implemented on June 1, 2013) – with an implementation period of 3 years.

Even though both of these regulations cover all aspects of best practices for managing the life sciences and medicinal products supply chains, these guidelines also define specific recommendations for cold chain products management within storage facilities, warehouses, and during transportation.

The trend with all new compliance regulations aimed towards GDP, or GSP, is to secure the supply chain against falsified medicines entering the distribution network, define more stringent regulations on cold chain management, and require that a risk assessment and risk mitigation plan is included as part of the company's quality management system (QMS).

The five common key areas related to risk in the supply chain are:

1. Internal Risks
2. Network Risks
3. Industrial Risks
4. Environmental Risks
5. Compliance Risks

(Note: Each of these common areas should have been figured into any previous Risk Assessment reviews, as well as part of the fully documented Risk Mitigation plan, which should now be part of any QMS.)

A short list of the other key areas of risk in your cold chain network that need to be included in your Risk Mitigation Plan - are:

1. Anywhere there is human intervention – should include detailed Work Instructions and SOPs with clearly defined personnel training.
2. Having a back-up plan for staffing and alternative shipping points for critical supply products, with environmentally controlled facilities.
3. A list of approved alternative vendors for cold chain shipment containers and temperature monitoring devices.
4. Automated temperature monitoring of storage facilities and transport systems, with alerting when excursions occur, and fully documented shipment records.
5. An audit plan for your data storage vendors and cloud services providers, with regular audit program for all critical outsourced services vendors.

Just like any regulation where audits are an accepted part of the compliance confirmation process, it will now be incumbent upon the auditor to review the Risk Mitigation plan as part of the Quality System review.

What about environmental controls for storage facilities and delivery to the patient, or clinic?

In regards to the recent global regulations related to cold chain management, as noted, the recommendations are very specific about requiring automated environmental controls within storage facilities, with out-of-limits automated alerting. Both of the newer regulations extend this to beyond storage areas, and now include transportation and delivery from source to patient.

The certified vaccine data logger with the glycol bottle, discussed earlier, is ideal for monitoring a refrigerator where vaccines may be stored locally at a clinic, hospital, pharmacy, or even a doctor's office. However, a larger facility needs a system that is capable of monitoring multiple areas of a building with data collection at a central point. Also the glycol bottle unit is not meant to be used in the transit environment where on demand real-time monitoring is usually required with a GPS capability to show location for potential security and vehicle tracking.

Based upon the newer GDP and GSP regulations, the requirement exists for an automated environmental management systems to monitor the condition of vaccines and other temperature controlled medicinal products that are stored in warehouses, or major distribution centers.

Such systems need to be able to keep a complete record of the environment for review and/or audit, plus have the ability to alert responsible parties when alarm conditions are detected.

The systems that are offered from DeltaTrak, either have a local database for storing the data records with the ability to send alerts, or send the data to a secure access cloud database.

The advantage of a cloud database, like ColdTrak offered by DeltaTrak, is that condition data can be reviewed either locally, or remotely, in real-time mode, or by selecting the ability to have alerts sent by text, email, or as a real-time condition indication.

Unfortunately, as many people are not familiar with all the elements of these new regulations, they rely upon data recorders, or loggers that need to be manually downloaded to a system daily or weekly, hence potentially not providing real-time alerts to problems as they occur.

Not only do these newer regulations require or recommend the automated monitoring systems for storage facilities, they also require the same monitoring for transportation of these controlled products to ensure that the manufacturer's temperature management recommendations are maintained – up to the final point of delivery!

This requires a cellular or Wi-Fi enabled system that can work in any location where there is common access Wi-Fi or cellular service that the control unit can connect to for transferring collected and/or real time data to a cloud service database.

Ideally the best solution would be one that can be utilized in either a fixed location (e.g. a warehouse) or during transport (i.e. within the cab of the truck). A telematics wireless solution offers a cellular connection with GPS data plus temperature information which is collected from the data loggers installed either in a warehouse or mounted within a vehicle. This could, in theory, utilize the data collected from the data loggers in either environment – whether the materials are stored in the warehouse or being transported.

The Future for Compliance and Regulations

It would be hard to forecast what will happen in the future without a crystal ball, but what seems to be occurring is that there is an increase in regulations related to managing cold chain products, vaccines, biologics, and for preventing falsified medicines from entering the supply chain.

In addition to this, there are now requirements for a fully documented Risk Assessment and Risk Mitigation plan to be part of any Life Sciences company's QMS – this will almost certainly be a trend that continues.

The other positive trend, as can be seen with the recent EU GDP regulation and CFDA GSP regulation, is much more commonality in new regulation content, which is hopefully a move towards a global compliance approach, as opposed to a local or regional approach.

In the main cold chain compliance, quality and the prevention of falsified medicines entering the supply chain are getting much more attention and focus as more regions of the globe are manufacturing drugs and other controlled substances.

Countries like China, India and Russia are producing many of the Active Pharmaceutical Ingredients (API's), plus bio-similar's and generic drugs that will be filling the gaps between cost and need. Hence, the need for globally focused regulations which will make for a more consolidated approach to product quality and condition compliance.

There should never be a consideration of too much control, or too many quality initiatives within the Life Sciences industry. The primary focus should always be towards patient safety and ensuring efficacy and quality of the drugs provided to the patients.

The consequences of providing "bad drugs" to a patient can be severe, often resulting in death, and can ultimately affect a company's reputation, not to mention their bottom line.

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