Cold-Chain Temperature Monitoring: Approach and Suitable Devices

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Temperature sensitive goods such as vaccines, biological components, drugs, corneas, blood, etc are highly perishable if not kept at appropriate conditions. They may lose their potency, spoil or become unsafe to use upon temperature abuse, unless correctly stored, packaged and shipped. In the last 5 years the means of protecting and monitoring such sensitive products has increased exponentially. Various concepts, based on indicators and on electronic devices have been tested, the results verified, and the product introduced. The modern world with high consumer sensitivity, high technology / high value products and a strong demand for quality, reliable record keeping, verification and traceability, demands an electronic solution. On the other hand, cost and loss reduction as well as customer satisfaction and customer loyalty are part of the picture as well. This lecture will present a brief outlook at the issues surrounding temperature abuse, and name some specific solutions to this problem.

1. General Problems observed with Sensitive Goods

The physical and chemical properties of a product on its date of manufacture undergo unpredictable changes by the time the same product is put to its intended use by the end user, or in case of the pharmaceutical industry - is administered to a patient. Figure 1 shows the typical distribution chain such a product may experience. Different means of transportation and a number of unloading and reloading operations are a potential threat to the intended storage and handling conditions. Several external parameters may influence the level of quality either instantaneously or as a function of intensity and time. Figure 2 shows some of the influences a product may be subjected to during its life cycle. This presentation focuses on temperature related effects on products and how to monitor them.

2. Temperature related Loss of Quality vs. Level of Temperature Abuse

Based on stability data, all pharmaceutical products receive a shelf life. A modern quality assurance approach should specify a shelf life which includes the time span between date of sale and date of intended use on the patient. The date of manufacturing and the expiration date (when the product reaches the level of minimum acceptable quality) determine the life time of a product with the assumption that the product was stored under certain conditions (specifically temperature).[i] Depending on the intended result one may look at the entire temperature history of a product or may focus just on the time and temperature outside the recommended conditions – the so called level of temperature abuse.

3. Temperature Exposure During Storage and Shipment

Typical temperature conditions for storage and transport of pharmaceuticals may be specified as :normal conditions (+15 to 25°C, depending on the climate zone up to 30°C, dry); between 2 and 8°C, no freezing (cold chain products, 5°C +-3°C); below 8°C; between -5°C and -20°C, frozen; below -18°C, deep frozen. Typical tolerances: temperature +- 2°C, humidity +-5%. The number and variety of different specifications in health care and industrial applications is surprising; the following examples are just a small illustration: - Orthopedic cement, keep below 40°C; - Red cell concentrate, don't freeze, keep between 2°C and 6°C; - Diagnostic kit, keep below 10°C; - Water based paint, keep above 5°C, keep below 48°C; - Chocolate; keep below 25°C. Any exception to the recommended environment condition represents a threat to the product and may potentially shorten the real shelf life.

4. Different Solutions to Different Problems

In order to keep goods within the specified temperature limits ice packs / dry ice or refrigerators / freezers can be used. The standard method of shipping e.g. vaccines is to use Styrofoam or polyurethane insulated shipper boxes packed with dry ice or ice packs. The goods are packed while at refrigerator (4°C) temperature. The entire process is validated prior to practice. The chosen means of transport, the length of travel-time and the acceptable level of risk determine the type of packaging and the level of protection selected. The selection of monitoring devices is not independent of these criteria. However, it includes further information such as: is the devices reusable, will it or can it be returned, does the receiver have access to the requested equipment to read the devices, does the sender want his counterpart to read the detailed data, who should decide whether or not to use the product in

case of minor abuse. Another criteria can be single or multiple use of the device. Single use may be preferred whenever the return shipment is uncertain (due to cost, commitment or long distance) or when the recipient with his experience, equipment, education and level of reliability is unknown. Multiple use devices including RFID tags are most efficient where you have a “closed system”, within one company, between High Tech. Partners or whenever customers (for safety reasons) suggest it or require it.

5. Technologies and Devices Available: Indicators, Electronic Indicators, Data Recorders, Active RFID-Tags with sensors, Blue Tooth technology, etc

According to the specification of monitored goods the temperature indicators (as defined in BS7908: 1999[ii]) can be described by function as : Temperature Indicators; - Ascending function, thaw or threshold indicator, typically -20°C to several 100°C (below +30°C activateable as of storage requirement); - Descending function, freeze indicator, typically 0°C down to –6°C. The second group consists of : Time-Temperature-Indicators; - Partial temperature history (indicator does not change below a certain temperature, threshold) and - Full temperature history (indicator operates over the full temperature range). Both indicator types can be either activated (start changing with temperature over time) upon production or can be activateable on demand, which has consequences regarding storage of the indicators, prior to use. Time-temperature-indicators are categorized in BS 7908:1999 by runout-time tolerance at constant temperatures as A: up to +-2,5%, B: +-5%, C: +-10%, D: +-20%. The technologies on which the indicators are based vary from melting point and solidification temperature, metal expansion, polymerization, viscoelastic migration, electrochemical corrosion, enzyme based reaction- to liquid crystals. Most of the indicators start to show a change in color when passing a defined threshold or show a continuous distance coloration with time. Both of these visual changes allow the observer to recognize and interpret the information by human eye which is especially beneficial where no computer is available at the time of reception.

Nowadays modern temperature data loggers are replacing the good old chart recorder. Temperature data loggers are becoming small and cheap enough to travel frequently or even regularly with shipper boxes, cases or pallets and record temperatures during passage through the cold chain. Throughout the distribution chain one can find three categories[iii] of such logger systems: - Fixed systems, integrated in networks or as stand alone units, used with cold rooms, refrigerators etc; - Vehicle temperature logging systems (as sophisticated as the GSM-connected Frigoblock) and portable data logging systems(for multiple use or single use). This presentation focuses on portable temperature data logging systems with one temperature sensor for multiple or single use. Whether a logger or an indicator is selected depends normally on the required accuracy and precision, available hard- and software at the recipient, price / value relationship of the monitoring system including labour cost vs. value of the product itself and- last but not least, ease of use and understanding. Unfortunately, such monitoring devices are some times simply considered as part of the packaging which often leads to the assumptions of limited value and low importance. On the contrary, by adding such a device one is able to judge the amount of exposure upon reception and hence “secure” the product including, packaging and transport cost. Furthermore, a replacement of a questionable shipment could be sent earlier and reduce the lost time, especially important in case of scheduled vaccination campaigns etc. When preparing the introduction of temperature data loggers one may want to look especially at, - accuracy and precision, - hard- and software stability, - quality of documentation, - battery and memory capacity, - internal date, - ease of data transfer to PC, - PC soft ware quality and ease of use. When selecting indicators one would focus on: Functional requirements like – ascending or descending temperature dependency; - partial or full temperature history; - activation on demand or pre activated (upon production), - ease of handling and interpretation of the visual information. As well as general features such as: storage temperature requirements; shelf life; lifetime after activation; Temperature range; tolerance of threshold temperature; tolerance of runout-time. Most of the portable temperature data logging systems are used to validate transportation processes for perishable goods such as vaccines, diagnostics, corneas, blood, food etc. After introduction these processes are covertly tested frequently as part of the normal quality control system or in order to evaluate complaints. Only with high value, rare or high risk goods such as medicine in bulk form, genetic material, transplants, blood components etc., are portable temperature data logging systems used regularly. Temperature indicators and Time-Temperature indicators with full or partial temperature history are used to either monitor temperature abuse during the entire life time, in conjunction with the expiration dating or to monitor temperature limits over a defined period or distance. In any case a quick, easy to understand and cost

efficient visual information is requested as a base for the decision to accept or reject a product, process or shipment. This supported the development of single-use Data Logger such as the Q-Tag[iv], see Figure 6. The benefit there is the accuracy and the ease of use. A shortfall is the lack of data readout to a PC for analysis. Some of the single-use Data Loggers are even reusable, 3 to 5 times or, due to battery life time, for a certain period of time . This feature is only of help where you have the ability to return the device, within one organization, location etc. The latest developments are so called active, sensing RFID[v] (radio frequency identification) tags or labels. The battery-free units are well known from libraries, parking chips, security tags etc. In order to monitor temperature permanently a battery and a temperature sensor is connected to the tag. So called PowerPaper[vi] batteries (a printable battery technology) allow the tag to measure and store exeedings of temperature limits while outside the RF field of the reader. The tag mimics a partial temperature history function. The lack here is the missing display. The recipient must be equipped with the appropriate reader unit fitting this particular system and of course with a PC. The Blue Tooth technology is discussed a lot. Regarding temperature monitoring it stands just for a high speed data transfer technology. The Logger would basically not change in function, it would allow to read from longer distance at higher speed. In addition with the far higher cost the issue with battery capacity and lack of display remains the same. Figure 3 shows some loggers and figure 4 typical indicators. Figure 5 shows a typical application for loggers and indicators. Figure 6 provides pictures of a Q-Tag and an active RFID tag.

6. Commercial Aspects

Suitable temperature loggers cost US$ 50 to 500. Independent of the logger cost is the labor cost of about 100 USD per monitored shipment, not mentioning the risk of entire loss of data and logger during return shipment. Single use temperature data logger range from US$10 to 30 with additional labor cost of 30 to 50 USD plus return shipment cost of 20 USD. Active RFID tags vary from 2,5 to 5 USD, with additional cost for reader equipment plus 5 USD labour cost. Full history time-temperature-indicators are available from USD 0,05 to 0,6 and partial history indicators from: USD 1 to 4. Temperature indicators vary from USD 0.3 to 1.0

7. Conclusion

Because of increased demand for better quality in all of the relevant industries and decreasing manufacturing cost for indicators and loggers the variety of available units is growing. The trend seems to go towards indicators with partial temperature history, so called “temperature abuse labels”. This solution is less sophisticated than full history ones. However, easier to interpret and to understand. There is also a clear trend towards single-use loggers and active RFID tags. The successful introduction of active RFID will depend significantly on improved features and lower cost. Temperature data logger and time-temperature-indicators are getting more attention during storage and shipment nowadays to monitor environmental temperature or product temperature to prevent unacceptable losses in quality and safety. There are a variety of temperature and time-temperature indicators as well as temperature data loggers with and without display available in the market and, of course, on the Internet. The need for precision, accuracy, traceability, ease of use and interpretation, unit cost and total cost involved per monitored shipment determines which solution will be used.

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[i] Dr.Brain R. Mathews; Expiry; Expiration date:
The date placed on the container/labels of a drug product designates the time during which a batch of the product is expected to remain within the approved shelf-life specification if stored under defined conditions, and after which it must not be used. WHO definition: The expiry date given on the individual container (usually on the label) of a drug product designates the date up to and including which the product is expected to remain within specifications, if stored correctly. It is established for every batch by adding the shelf life to the manufacturing date.

[ii] British Standard BSI 7908; 1999 Packaging – temperature and time-temperature indicator- performance specification and reference testing. London, British Standards Institution, 1999.

[iii] Chilled foods, Stinger and Dennis, 2000

[iv] Berlinger Company, Switzerland

[v] KSW-Microtec, Germany; and their distributor

[vi] PowerPaper Company, Israel