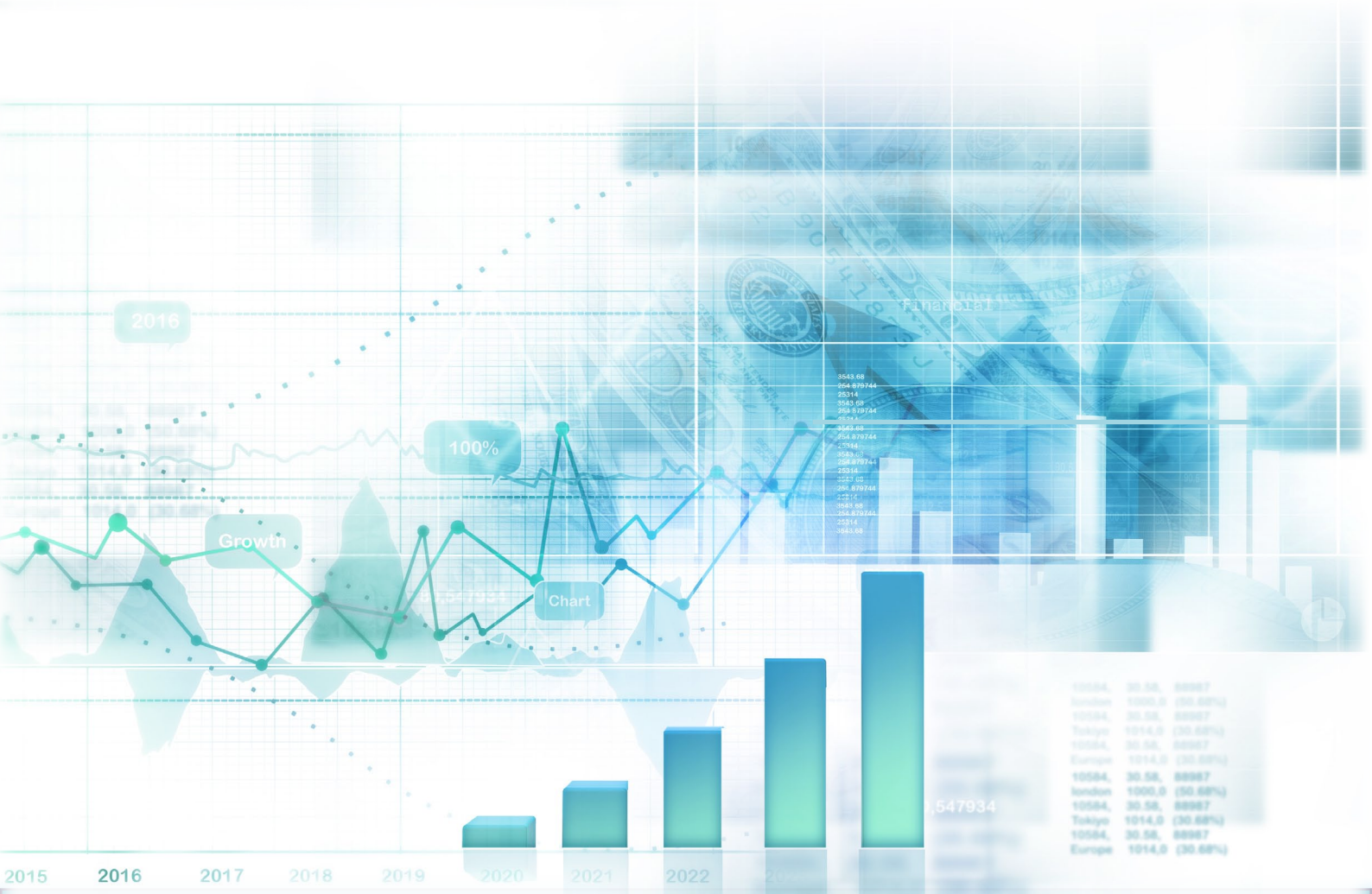

Stability Data Sharing in Canada's Cold Chains

Pharma Logistics IQ

15TH COLD CHAIN GDP & TEMPERATURE MANAGEMENT LOGISTICS SUMMIT – CANADA

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Stability Data Sharing In Canada's Cold Chains

Lately, the need for heightened awareness and use of stability budgets within cold chain has been an industry focus. In a recent article Dr. Bishara and Dr. Erik J. van Asselt explained that a stability budget: "Refers to the quality of a product to resist, under specified conditions, irreversible change in its identity, strength, quality, and purity at various temperatures above and below the labelled claim storage temperature.

"....The drug degradation] rate depends on several factors including but not limited to the physical and chemical properties of the active pharmaceutical ingredient, formulation, pH, temperature, water and oxygen sensitivity, light sensitivity and primary packaging." (6)

In explaining the importance of deploying a stability budget, Dr. Bishara noted that "the effect of not knowing your stability budget, calculating it correctly, and most importantly, implementing it on a quality-based standard, is that you may discard medicines and vaccines that are good – or approve the utilization of pharmaceuticals and vaccines that have been exposed to excursion that has resulted in the degradation, lack [of] efficacy and potency. So by knowing your budget, calculating it correctly, and implementing it during the supply chain in case there is a deviation or an excursion heat or freezing you will be able to make quality-based data decision on what to do with this material."

The time out of storage (TOS) can then be calculated and compared to allowable excursion time. By using the allocated TOS, packaging and manufacturing stages can be conducted in ambient temperatures for cold chain products. Manufacturers can then benefit from improvements in machinery and employee performance. However, this could impact the product's shelf life, so this time needs to be measured and balanced. TOS can be useful in managing temperature excursions. Hazards within transportation represent larger threats to the cold chain with the prospects of physical contact, handovers and unforeseen delays.

When considering Canada's extreme temperature ranges and vast territories, it is clear that the region's cold chain stakeholders would benefit from the flexibility provided by stability data. In reality, however, there is a lack of end-to-end transparency along the supply chain with stability data. Reasons for this are driven by the legal responsibilities attached to decisions made with excursions.

Louise Labelle, Affiliate Quality Leader, Zoetis explains that manufacturer importers are reluctant to share this information because there is more than one factor to take into consideration with excursion decisions. Depending on the nature of the product and the temperature excursion, an assessment needs to be made. For example, there may be several excursions for a specific lot during manufacturing, packaging, inbound transportation, storage or outbound transportation. For some products the duration of the excursion is additive and wholesalers don't have a comprehensive history of the product to make an evidenced decision. "Despite this, manufacturers and importers are the ones who are responsible for any adverse events of a product."

Ahead of the 15th Annual Cold Chain GDP & Temperature Management Logistics Summit we explore the state of affairs in the general industry as well as specifically to Canada in regards to stability data use in the cold chain.

Standards

The PDA's guidance, on stability budget protocols and their application has been praised for its contribution towards global standardization. Technical report number 53 of the PDA guidance was especially important. Dr. Bishara noted that to shirk the use of a stability budget could be perceived as an indicator that company is not following modern industry best practices. Regulators are likely to enquire about stability and the protocol deployed to generate the data and the implementation of a stability budget. Rafik stresses that to avoid implementing a stability budget is in fact taking on a risk – dependent on the inspector they are allocated and whether that inspector decides to focus on the stability budget. Stability protocols will inform handlers of a product's failure boundaries due to extreme temperatures. Senstitech notes that the stability budget – pertaining to time and temperature - should ideally be distributed through the entire lifecycle, with fixed periods dedicated to manufacturing and storage. Excess time should be utilized upon distribution. [1]

However, some have asked whether the stability budget should be left solely for any excursions in the last mile. Stephen Mitchell, E2E LP Quality Lead, GlaxoSmithKline notes: "The only point I would make on this is that the stability budget should be built into the last mile. It is not something that people should be using to plan for their core distribution process centre. The principle is that you can't budget to include boost your stability budget in a normal supply chain process, I think that is quite important. At the end of the day, you do not know what your patient is going to do with the product once they have received it. The stability budget really is intended [for] that end of the supply chain." [2]

The Correct Balance

Pharma products usually have accelerated stability testing conducted at high temperature pre-market, so this information is already available. For pharma cold chain products, accelerated stability testing is usually conducted at 25 Celsius at several time points; up to the expiry date. Although, Louise Labelle notes that there is not much stability data available at extreme temperatures for cold chain products (pharma & biologics), more and more companies are now performing those studies. For biologics cold chain products stability studies at extreme temperature could be conducted at different temperatures (20 Celsius, 25 Celsius or 37 Celsius) up to 7 days depending on the nature of the molecule. The challenge is more at very low temperatures below freezing point, we have less data but more and more companies are conducting stability data on new products.

Companies are often reluctant to run stability studies, due to their expense. Louise Labelle has observed that these studies are being conducted for more and more new products, but less so for older products. She clarifies that manufactuers importers are reluctant to share the stability data because ultimately they are the ones legally responsible for any adverse events attached to the product. As wholesalers and such do not have information on the history of the product's transit and make a decision without contacting the manufacturer importer, they could be taking a big risk. It needs to be considered whether the product

is a pharma, a bio, what is the dosage form etc.

The basic level data to be shared will outline the temperature boundaries that the product can remain stable within. Without access to this technical data an entire shipment of pharma product can be put into destruction, which can be transferred into a loss of hundreds and thousands of dollars. Placing this data on the submission file for Health Canada could be productive to ensure that it will be included in the budget

Bein in the pharma industry since 1986, Louise Labelle has seen various perspectives on this subject in her career, working for wholesaler AmerisourceBergen from 2007 to 2013 which are in the states and Canada. When working as part of the wholesaler she would attempt to retrieve the information from the pharma manufacturers but found that most of them would not divulge the data, except for maybe solid dosage forms. Louise Labelle has also worked within the function of the manufacturer importer.

She acknowledges that wholesalers wish to have the information to cover themselves in case of a temperature excursion during storage or transportation. However, Louise Labelle highlights: "If the wholesaler would make sure to have transportation conditions that maintain temperature conditions within labelled conditions of the products, probably we would not need to have this discussion."

Cost Efficiency

Within one season, Canada's climate can rest at a variety of temperatures which will challenge temperature controlled transport lanes. Stability budget awareness will allow for more manoeuvrability with challenging steps in the lane, eg - unloading/loading maneuvers and handling at distribution centers or warehouses. These stages may be too complex or expensive to navigate without stability flexibilities. Senstitech notes that decision trees are useful to navigate scenarios set to encounter a lot of thermal variability. These trees will help structure the process so cost-efficient actions can be made with distribution and monitoring. Supplementing this tree with weather information will bolster the method to become a more predictive model.1

In the Canadian market the stability budget is regarded is regarded as a spend by pharma companies more than an investment in their supply chain flexibility. However, stability budgets can save a whole shipment from destruction. Work needs to be applied between the logistics and quality departments to restore investment patterns to stop spends from being sporadic.

It is favored to ship to label claim in Europe and

Going Beyond Label Claim

such, however shipments outside of this are based on stability data. There is an additional complexity when relying on stability data to verify that excursions will not degrade a product's efficacy or quality. The manufacturer is often the only party that in fact as access to such data. Transparency along the entire lane, although necessary, is not easily managed or documented when it comes to stability data. In regards to CRT shipments there may be limited data to specify the uncontrolled conditions beyond label claim. This will incur a lack of uncertainty on whether temperature controlled solutions can guarantee product integrity.[1]

Forecasts for the future of stability data usage in Canada

It's not in the legislation per say to have some stability data on your product, but some can see that easily becoming one in Canada in the very near future. In Europe, new labels are starting to be see where you have the tolerance on the temperature the product can accept. So that is something that a pharma company will not be able to disregard like the Canadian market seems to show right now. It's likely to become a huge requirement for pharma manufacturers in Canada.

Louise Labelle: "Well, I would say that the possibilities are low. Again depending on the dosage form, chemical molecule, stability of the product. Some companies will share the info and will define in their quality agreement the notion of minor, major, critical deviations, excursions, and should add the timeline to respond to the wholesaler.

"When I was on the wholesaling side, I negotiated with some manufacturers to add information pertaining to temperature excursions for some products –mostly solid dosage forms in an addendum to the quality agreement (ex. Above 37 Celsius up to 48 hours or below – 20 Celsius for 7 days….). In general for sensitive products (liquid, suspensions, ointments, creams…), the manufacturers and importers will not provide this kind of information.."

To explore more on stability budgets consider attending the 15th Annual Cold Chain GDP & Temperature Management Logistics Summit

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