Leading Minds **Seminars**
Philadelphia 2018
Post Event Report

June 6th and 7th 2018
Normandy Farm | Blue Bell, PA

Seminar hosted by

ELPRO SONOCO THERMOSAFE

Thank You

Thank you for attending the educational and fun-filled Leading Minds Seminar, Patio Party and User Group meetings. We are delighted with the positive feedback and how enthusiastic people were to learn during the entire couple days.

Here is what some of the attendees said:

"I enjoyed learning more about
Direct to Patient cold chain distribution."
Sean McCudden, Merck

"Blockchain was a great topic. For 2019, I'd like to see greater depth and it's applicability for temperature data."
Alan Davis, K. L. Harring Transportation, LLC

"The patio party was enjoyable in that I got to meet and talk to several other participants and people from ELPRO and Sonoco."
Craig Schwartz, Merck

At Leading Minds, we believe people learn by doing or discussing. Thank you for coming willing to share and eager to learn!

A very big thank you for all speakers, discussion leaders and chairperson, Geoff Glauser.

Session Summaries

The following pages contain valuable discussion highlights and key learning points from each of the Leading Minds Seminar Philadelphia 2018 sessions.

9.10 | USP Updates to <1079> Risk Mitigation, <659> Packaging and Storage Requirements, and the Use of MKT Calculating Controlled Cold and CRT

Chris Anderson | Cardinal Health

Key USP regulatory updates include:

- USP <1079> Good Storage and Distribution Practices for Drug Products is moving from the current "Good Practices Approach" to a "Risk-Based Approach". The good practices approach could overlap with regulatory perspective while the risk-based approach provides education and builds on knowledge.
- Updates will include (1) Scope, (2) Risk based approach to the storage and transportation of drug products, and (3) Risk mitigation strategies (as part of a QMS).
- Scope will include: Manufacturers of drug products, radiopharmaceuticals, biological, and biotechnological products, Repackaging, Healthcare providers, Pharmacies, Importers and exporters, Wholesale distributors, and Third-party logistics providers.
- The risk-based approach starts with Product & Process Knowledge moving towards Risk Identification, and then to Mitigation Strategies. These strategies include Documentation, Training, Qualification/Validation, and Resources. These all roll up as part of the Quality Management System (QMS).
- USP <1079> will not include MKT definition and calculations, Temperature storage ranges, or Allowable excursions. These will all be referred to in <659>
- New stimuli article to the revision process for <659> and <1079> will be available soon. This is authored by Chris Anderson, Desmond Hunt, and Robert Seevers.
- Examples of acceptable versus unacceptable controlled storage were discussed and reviewed.
- USP <1079> updates will be published in Pharmacopeial Forum in July 2018. After a period of comments and review in 2018, beginning February 2019 the USP expert committee balloting begins and the updated chapters will be published soon thereafter.

9:50 | Community Forum Discussion: Sufficient Stability Data

Geoff Glauser | US Health & Human Service

This session allowed participants to share experiences of what regulatory authorities are accepting in types of studies and stability data during filing.

Experiences shared include:

- Technical report 53 says how a product reacts during freezing and thaw tested with multiple lots. This is to prove the product behavior and degradation. A vaccine loses 80 % of its efficiency once it has been frozen.
- Is stability budget always accepted? Example:
  A product for Brazil: filed testing proved a stability of 16 weeks outside 22 °C with a label claim 2–8 °C. Still initially the government of Brazil did not accept the excursion.
- What are the best methods to develop stability data that regulators will accept?
  - Define the freezing point for the product and the point where the characteristics for the product change.
  - Six months of data to 1 year of data is used to establish the expiration.
  - For long term stability, 1 year to 3 years of data should be used.
- Be mindful of Label Claim and long term storage.
  Some labels have a long term storage claim. Example for pharmacies; 48 hours at ambient after preparation.
- Manufacturers want as long as possible expiration dates. Some companies are prepared to pay for that. Example; for every additional year 3 % of the purchase price.
- But some still wonder how much data is required? Long term stability data or within label claim?
  This all depends per country and almost the person who is looking at it. No fixed answer here.

10:50 | Stability Data In-Practice Part II: Comparing Company Approaches to Using a Stability Budget

Discussion led by **Michael English** | Merck

The discussion examined different approaches for determining a stability budget.

One of the main takeaways was that your stability data must ensure your distribution model can deliver product within quality specifications.
The attendees were given an activity to review a distribution lane and determine the required stability budget at each step.

Review of the activity included a lively discussion on the difficulties of managing the budget throughout the process. A common goal for the group was to be able to provide the patient with as much of the stability budget as possible.

10:50 | Stability Budget In-Practice – Biogen Perspective

Jennifer Sloan | Biogen

Key learning points were:

- Biogen's stability budget is used to determine how long it can stay outside of label claim for the purpose of being able to plan for unexpected events.
- Planned TOR includes Label/Pack/Load/Unload/ Shipping/visual inspections.
- The stability budget is shared with no one, as it become unmanageable.
- "Allowed excursions" are not excursions because budget is allocated from the stability budget.
- Stability should be in the filing before approval for the product.
- Not all studies need to be 100 % completed before product launch (in clinical trials supply).
- What tools would make the profile better?
  - Pushing forward stability budget
  - Barcode scan in/out time which can be used in case of excursion
  - Real-time location

11.45 | Breakout Discussion A
Blockchain: Potential Impact to the Pharmaceutical Supply Chain

Dirk Rodgers | Systech

The topic is still new for many and the exact application and case examples in the pharmaceutical supply chain are few. However, the question was discussed how temperature data would fit into Blockchain.

Could temperature data be handled like a crypto currency today in Blockchain? The discussion was quite theoretical. However the group discussed a probable application is to use Blockchain to store temperature profiles. Especially in Clinical Trials, profiles can change during the time of the study; yet they have to be safely stored and maintained. Here, Blockchain and its security features could offer new possibilities.

The group also considered that using Blockchain would require a standardization of formats (profiles, temperature data, etc.). But is that realistic? From Blockchain's principle perspective, we could say temperature data management could be a possible application:

- Currently cloud based
- Geographically distributed
- Trusted and non trusted entities involved

Still, an open question is the transaction speed and the risk of distributed data (with no real track where data is stored).

Please reference the PowerPoint slides for further detailed information.

11.45 | Breakout Discussion B
Exploring How Data Monitoring Technology and Stability Data Can Create Efficiency in Your Cold Chain

Discussion led by **Teresa Parayil** | ELPRO

- Group's conclusion on stability budget definition: The amount of time a product is out of storage/out of acceptable temperature range
- During product development researchers learn how a product acts under different temperature conditions to help define the stability budget parameters
- Develop stability studies with distribution model in view
  - Cycling protocol should cover the temperature extremes
  - Simulated shipping lanes have to be considered
  - Plan for the unexpected – incorporate potential highs & lows
  - Tracking system is essential to understand the viability of the product and efficiently track a stability budget throughout multiple legs of supply chain
- Stability budget use and terms needs to be included in the initial FDA filing
- Stability budget also needs to be established for room temperature products (ambient)
- Release testing – many different substances are tested independently. Easier for small molecules rather than large molecules
- Calculating stability budget – variability in product temperature and timing leaves room for error
- Clarity for end user is the key – clear labeling on how much time the product can be out of range
- Widening shipping temperature range may offer more flexible stability budget

In summary:

- In general stability budgets are evaluated after an excursion occurs
- Evaluating stability budget in real time allows product sponsor to be proactive and get replacement product shipped to the end user
- Stability budget can be potentially very important to companies if there is an easy way to calculate it
- LIBERO ITS temperature indicator is a potential direct to patient product for many because of the immediacy of the stability budget data.

To find further supporting materials on Stability Budget, and understand ELPRO's position and leadership on the topic – please use these resources:

Stability budget blog and presentation:
https://leadingminds.elpro.com/news-detail/news/is-stability-data-really-a-superhero-using-a-budget-in-practice/ or **http://bit.ly/2zNJjTG**

To learn more about the innovative LIBERO ITS and "one-touch stability budget read-out", go to
https://www.elpro.com/en/news/news/news-detail/artikel/elpro-announces-innovative-box-level-temperature-indicator-libero-its-with-wireless-read-out/ or **http://bit.ly/2mmVIK8**

11.45 | Breakout Discussion C
Finding Cost-Effective Ways to Ship Controlled Room Temperature (CRT) Products

Discussion led by **Aditi Gupta** | Pfizer

- Attendees shared their experiences with CRT shipping practices. Some have had success with reducing costs by closely monitoring lanes and re-evaluating the shipping system used for that lane. If the lane is not as severe as originally thought, it's possible to reduce the amount of thermal protection and maybe proceed with a lower cost solution.
- Hot topics included CRT control at wholesaler during shipments and possibilities to remove temperature monitors on well controlled lanes for cost reductions.
- Most attendees agreed that when possible, reusability of the passive shippers is ideal as long as the reverse logistics are possible.

11.45 | Breakout Discussion D
Using <659> MKT Calculating Controlled Cold and CRT

Discussion led by **Chris Anderson** | Cardinal Health

Chris Anderson led an interesting discussion around finding an excursion and then going backwards 24 hours to establish MKT. Chris was a big proponent, while the rest of the team seemed to push back a little on the concepts.

- There was a long discussion on what parties were able to use the excursion time. How do you give excursion time to a party in the middle of the distribution chain versus at the end?
- Discussion on using modeling to understand the excursion possibility and a shipper being delivered beyond the qualified time.
- The USP is pushing for more participative training.
- There was much discussion on how new technology can help cold chain distribution. Essentially the lot codes are too large to effectively trace anything. There is currently no unique identifier down to the individual vial. Questions around whether block chain could help with shipping durations and decisions. Many questions on the lot sizes and the true tractability of a dose.

1:45 | USP – GDP <1083> Updates, Clinical Trials and Key Factors with Investigational Drug Product Distribution

Jeffery Carrico | National Institutes of Health

- Discussed the history and mission of the United States Pharmacopeia (USP).
- Mentioned that GDP topics are covered in three documents <1079>, <1083> and <1197>. USP's intent was to provide a holistic approach to Good Distribution Practices.
- GDP-related chapters from <1079> and <1197> were compared and consolidated into the <1083>.
- <1083> included four GDP topics covering quality management system, environmental conditions management, importation and exportation management and supply chain integrity and security served as the foundation for the GDP chapters. Generally, they apply to all materials and products, regardless of their regulatory category, e.g. Finished Drug Products, Excipients, API's, Clinical Trial Materials, and Packaging.
- Given the DQSA (Drug Quality and Security Act), enacted on Nov 27, 2013 the USP put on hold the development of the overarching chapter <1083> and focused on the chapter dealing with finished drug products <1079>. USP <1083> is no longer.
- Jeff then transitioned to discussing about investigational drug products (IP) and clinical trials. Clinical trials need to follow a protocol, test safety and efficacy, needs of sponsors may vary, and it may include approved or unapproved medications.
- Given that NIH does about 500+ trials, Jeff covered several key factors with IP distribution including:
  - Distribution risk factors (distance, time, temperature, number and type of handoffs, track and trace and partnership with courier companies)
  - Number of clinical trial sites
  - Audits (pre, ongoing, post and more)
  - Depots and subcontractors
  - Global challenges for IPs
  - Expiration/retest dates
  - Packaging
  - Return of IP to sponsor
  - Unblinding
  - Environmental conditions of IP
- In conclusion, guidance now exists for IP's that will supplement regulations. The attention paid to the good distribution practice for IP's leads to further confidence in the results of a clinical trial. USP will continue to look at developing guidance on the proper storage and distribution of drug products and materials with a current focus on the areas that pose the greatest risk to quality of products as they move through the supply chain.

2:25 | Reusable Packaging that Drives Product Integrity While Meeting Environmental Goals

Vishal Khushalani | Sonoco ThermoSafe

Vishal reviewed the considerations required to implement a successful reuse program. Defining what is reusable and implementing inspection, cleaning, and refurbishment procedures are essential. Return rates will vary depending on your distribution model and this can still result in successful programs with the right approach.

- When return rates are high (>70%) the user will benefit from a solution with lower dimensional weight which lends itself to better insulation.
- When return rates are low (~30%) the user should consider less expensive insulation. This will increase the dimensional weight but decrease the solution cost and allow for acceptable lower return rates.
- Vacuum insulated panels (VIPs) are not the most reusable packaging material. Due to its high cost they require reuse to make them more affordable on a per-turn basis. That said, VIPs do help in reducing the dimensional weight and hence the outbound and return costs making it a viable returnable solution when the return rates are high.
- Many customers have used a staged approach before investing in high-cost reusable solutions. Processes are put in place to return EPS and PUR-based solutions to educate stakeholders across the supply chain and assess true return rates. Once return rates cross 70%, customers transition to better insulation to realize savings in freight and the overall program.
- There are many durable and reusable materials including EPP (used in Automotive industry), PUR, PUR-infused HDPE containers and gelled phase-change materials that can make a very cost-effective and rugged reusable system.
- Customers can today choose to invest in a reusable asset or just choose to “pay-per-use”. Pay-per-use is becoming more prevalent where vendors like ThermoSafe cover most costs (e.g. asset, reclamation, return freight) to encourage customers to save capital dollars, realize instant savings on a per-turn basis and be sustainable.
- Discussed a few asset track and trace technologies such as bar-code, RFID and GPS-based which allow for inventory control and asset visibility across the supply chain.
- Chris Anderson, Cardinal Health, added his context based on several case studies where they reuse EPS and PUR solutions and have demonstrated successful programs leading to large cost savings.

3:35 | Achieving a New Level of Insight into Temperature Data: Case Study

Sharmila Babu | Biogen

Biogen track and KPI their temperature data to

- Meet regulations: risk-based quality measurements
- Vendor performance
- Internal performance; track and trend against PQ

Sharmila gave examples of how vendor performance can be measured by tracking and sending CSV files and PDFs to database. Those metrics are used in business reviews with partners to work toward better compliance; and implement corrective actions, such as new training videos, new instructions, etc.

Biogen classifies excursions by

1) False: administrative error
2) Reportable: Real excursion need root cause analysis
3) Non-reportable
4) On-site: delay in stopping monitors
5) In-transit: tells about the shipper, carrier, custom delays

Key considerations:

1) Start with an objective – with the end in mind. What do you want to know from your temperature data?
2) Compare against industry peers and benchmark – what metrics are working for them?
3) Be careful with what you measure – more data isn't necessarily better.
4) Level the metrics – decide your baselines
5) Seek for improvement initiatives – ongoing

4.15 Breakout Discussion A
Comparing Real-time Monitoring vs. Logistics Milestones for Greater Supply Chain Visibility

Discussion led by **Ed Difilippo** | ELPRO

The lively discussion covered a number of questions. Here is the audience feedback:

When are you thinking of implicating real-time?

- Roadmap item for 2023
- Real-time dynamic packaging start concept

What would be the advantages?

- Quick reaction time
- Hot topic but see it as nice to have
- For Latin America it would use one week or longer advantage to resupply. This is a general problem, which is mentioned always due to this poor custom/broker process.
- Customers don't report or send back info. Real-time will solve this.
- Advantage for Clinical is that patients are not lost due to product excursions. In time, resupply can save a patient for a study.

With real-time is an alarm an alarm?
What is the stop point?

- Challenge with real time is start and stop. Geo-fencing could be the solution.
- GPS must monitor the product temperature not the ambient only.

In an alarm situation who is reacting – shipper or sender?

- Depends on agreement with sender
- There must be communication
- Send notification to shipper is important
- Pro active action with freight forwarder is important

Does everyone see a value in Heat Map?

- It is a requirement in China for some customers

What is holding people back to use real-time?

- Availability of the signal. Bottom of ship
- Cost/benefits. Cost are too high
- GPS is used for security reasons mainly
- Battery capacity is to poor → cannot be used for shipments, which last too long
- Not IATA proof

Group's conclusions:

- Nice to have
- Only needed if required for regulations
- High value products
- Real-time gives power back and takes the receiver out
- A good solution but only if receiver doesn't have to do anything, i. e. press a button, no upload etc.

4.15 | Breakout Discussion B
Active to Passive as Part of a Risk Mitigation Strategy

Discussion led by **Ben VanderPlas** | Sonoco ThermoSafe

Ben led a discussion and presented a risk based approach to assess the most optimal solution, active or passive, dependent on the dynamics of a given shipping lane.

- From a packaging and logistics approach the shipper must understand and review the flow of materials. Working through a lane mapping exercise can help breakdown the process and allow for a step-by-step risk assessment to occur. Depending on the solution of choice, active or passive, decisions will be made differently. Ultimately the most optimal solution will be a balance of cost versus risk in order to maintain quality. Risk can be mitigated by appropriate packaging solution balanced with logistics service offerings.
- From a drug manufacturing perspective it is important to understand the risk of temperature excursions to any given product. Do you have sufficient stability data? Can you use the stability data for a given shipping lane? These dynamics will have a dramatic impact to the packaging solution and logistics service levels.
- Monitoring both internal and external temperatures is important. Internal is needed for product release for international shipments while external temperatures increase visibility as to how each shipment is handled. Tracking and trending this data will highlight where process is not followed and can allow you to optimize solutions based on common temperature exposure and shipping durations.
- The foundation to risk mitigation is a formal Quality Management system that will define qualification/validation, documentation control, training and development, deviation management and CAPA, internal and external audits, and KPI's and continuous improvement metrics. It is important to have SOP's in place with all partners and qualified vendors with quality agreements in place. Use GDP's as a guidance.
- Active and passive solutions both have their place in the temperature controlled supply chain. The most optimal solution will depend on many dynamics that must be assessed to appropriately mitigate risk.

4.15 | Breakout Discussion C
Direct to Patient (DTP) Distribution of Temperature Control Clinical & Commercial Products

Discussion led by **Mike Sweeny** | World Courier

World Courier has 13 mio shipments a year
(60 % are temperature controlled drug shipments)

- They provide pre-conditioned boxes with a temperature monitor in it
- Mostly clinical trial drugs but some are commercial
- Their excursion % is very low
- A controlled document needs to be signed off on when the product is delivered to the patient
- Much of the industry is moving towards home care nursing providers. Over 50 % of World Courier shipments are through in-home nursing companies
- World Courier has a qualified fridge to store meds on site in patient's homes. Data logger pulls data every 5–10 mins and sends it to the cloud
- They are moving to real-time monitoring – the nurse wants to be able to open an app and see what the last temperature reading was and where the product is so he/she knows whether to prep the patient or not

Thank you for joining the Patio Party and Dinner under the Stars

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