Cold Chain Custody Quality Aspects

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Associate Director Validation – 16 Feb, 2015

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Agenda

- Introduction to Adelaide site South Australia
- Cold Chain Custody Quality Aspects
- Case study frozen shipments Australia to Europe
- Questions and Answers

ADELAIDE

- **Part of Biologics in the Pfizer network**
- **Headcount: @100**

Technology

Microbial Drug Substance Production

- Microbial fermentation (500L scale)
- Mid-stream harvest and cell breakage
- Refold (2,900L scale)
- Down-stream purification
- Final fill
- Frozen international shipments

Default Role

- More than 25 years experience in the field of E.coli based process development.
- Expressed over 50 different proteins including Antibody fragments, Growth hormones, Elastin and Multimer peptide repeat vaccine candidates.
- Produced numerous proteins for Phase I - III clinical trials for customers.
- Preparing for Commercial Manufacture.

EHS

The Adelaide site operates at Physical Containment Level 2 Large Scale (Office of the Gene Technology Regulator) and is equivalent to Bio Safety Level 2+ (Large Scale).
The site is ISO 14001 and OHSAS 18001 certified.

Quality

- Certified by Therapeutic Goods Administration (TGA) and produced clinical products for Australia, EU and USA
- Quality Control Analytical Testing - cGMP testing facilities, analytical assay transfer and validation experience

Cold Chain Shipments Quality aspects

- It sounds easy enough but what does it actually mean?
- What guidance is there apart from the regulatory observations?

Technical Report 39 (TR39 cold chain management),
Technical Report 72 (TR72 Passive Thermal Protection Systems for Global Distribution: Qualification and Operational Guidance)
Technical Report 64 (TR 64) active temperature control from the Parental Drug Association (PDA) well that was easy Don't forget the others

The current Good Manufacturing Practices (cGMP) as required by the FD&C Act: The Federal Food, Drug, and Cosmetic Act. Documented in the Code of Federal Regulations (CFRs) and regulated by the Food and Drug Administration (FDA) in the United States of America.
EudraLex – Volume 4 Good Manufacturing Practice Guidelines. The rules governing medicinal products in the European Union" contains guidance for the interpretation of the principles and guidelines of good manufacturing practices for medicinal products for human and veterinary use laid down in Commission Directives 91/356/EEC, as amended by Directive 2003/94/EC, and 91/412/EEC respectively

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Factors With Potential to Impact Shipment

- Temperature conditions at origin and destination.
- Seasonal temperature (winter versus summer).
- Load configuration.
- Transport routes and modes (Overnight air, ground, international etc.)
- Total duration of transit.
- Duration and location of handling and stop over points.
- Product handling.
- Custom /Quarantine requirements

Quality helpers

- Know the Process
- Walk the Process
- Own the Process

Quality helpers

- 1) Know what your markets requirements are
- 2) Know the routes where your products are shipped through. It might not be the way you think it is
- 3) Know the limitations of your shipping container
- 4) Know the limitation of your cold chain
- 5) Know what you need to do if things go wrong
- Risk management plays a big part but remember we love paper so it is evidence led and I am sure the patients won't thank you for taking short cuts if their life saving product does not get to them in one piece and is not fit to use!

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Where to Start

A Validation Master Plan (VMP) is a good start.

It is the basics of your control of the whole process

URS

User Requirement Statement

DQ

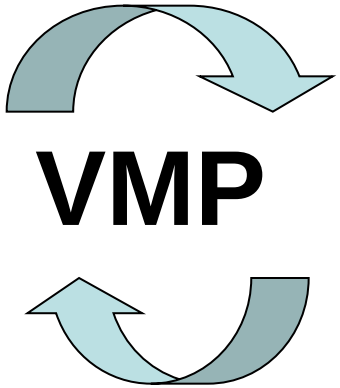
Design Qualification

VR

Validation Report

ITP

Investigation Test Procedure



PQ

Performance Qualification

IQ

Installation Qualification

OQ

Operation Qualification

IQ /OQ

Installation / Operational Qualification

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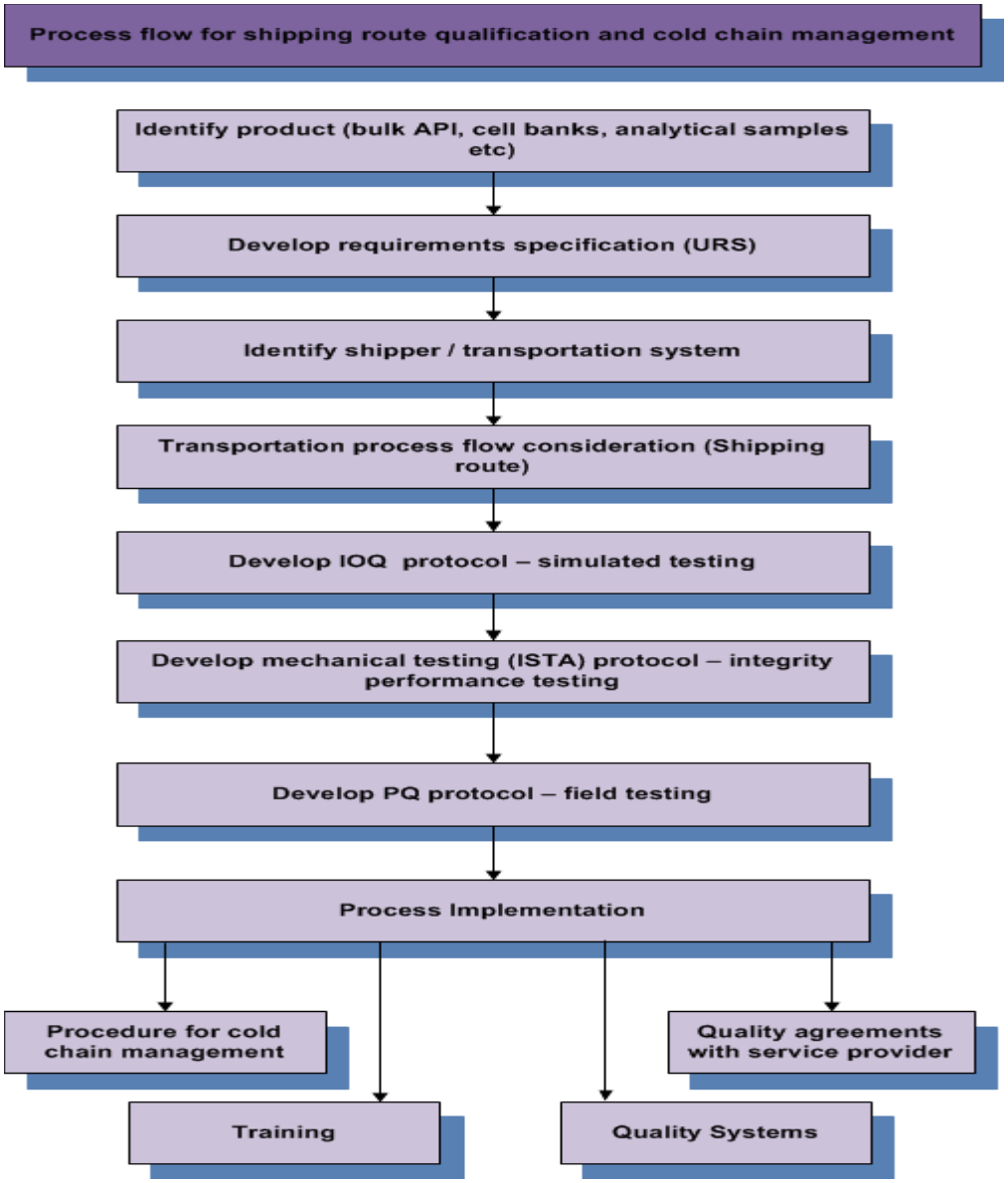
Validation Implementation Process Flow



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Decide on your storage/transport conditions for your shipping solution

Frozen	≤ -140°C Liquid Nitrogen	≤ -60°C Carbon Dioxide	-20°C± 5°C Frozen Water	≤ 0°C Frozen Water
Chilled	+0°C to +10°C			
Refrigerated	+2°C to +8°C			
Temperate	+8°C to ≤ +45°C	+15°C ± 5°C	+20°C ± 10°C	

PDA has nice technical report describing the storage/transport conditions (TR39)

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Can you spot anything wrong?

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Things do go wrong

It is better to go wrong in the testing than in actual shipments.

Outcome:

Back to the supplier for redesign.

Root Cause was the box mould was not rounded in the corners they were a straight 90°Joint.

Other shipping systems and monitors are available

See your show representative here today!

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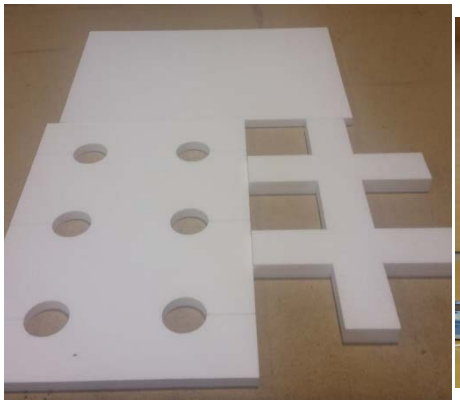
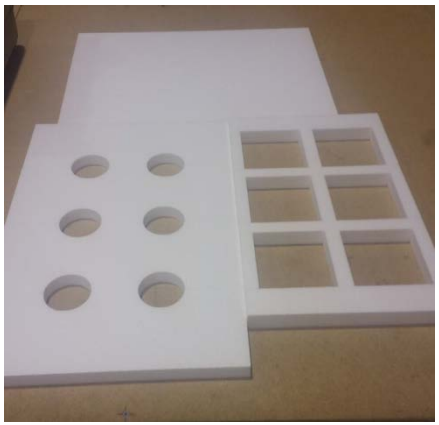
Choosing the templates to best fit the shipping lanes

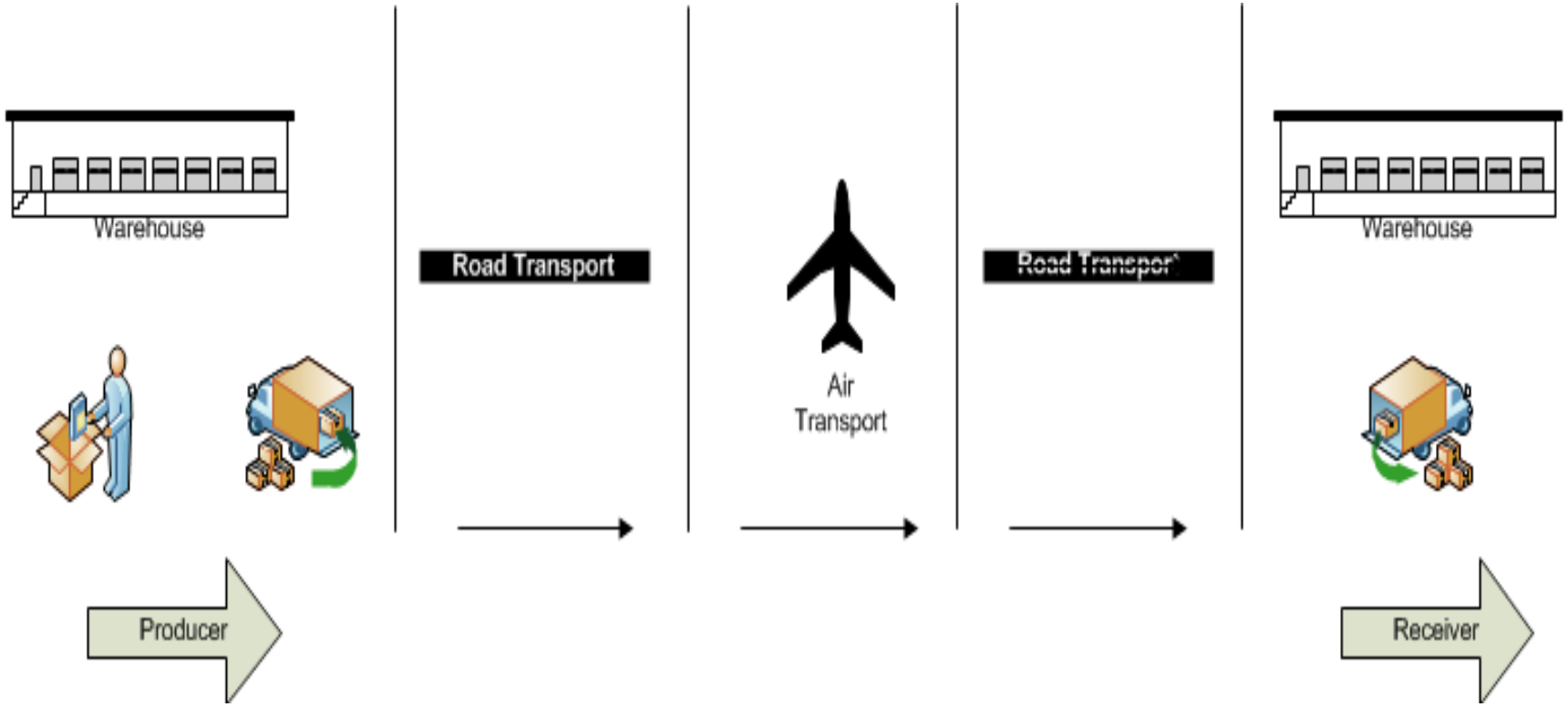




Full
Partial

Think which template would be best and which one is/are less suited for duration.
Or perhaps they all do the same time

Walk the Process



Walk the Process

- Road transfer from Hospira Adelaide to Adelaide airport
- The cut off for receipt of cargo is 17:30 hours on day of flight.

Flight departures 21:50 hours same day.

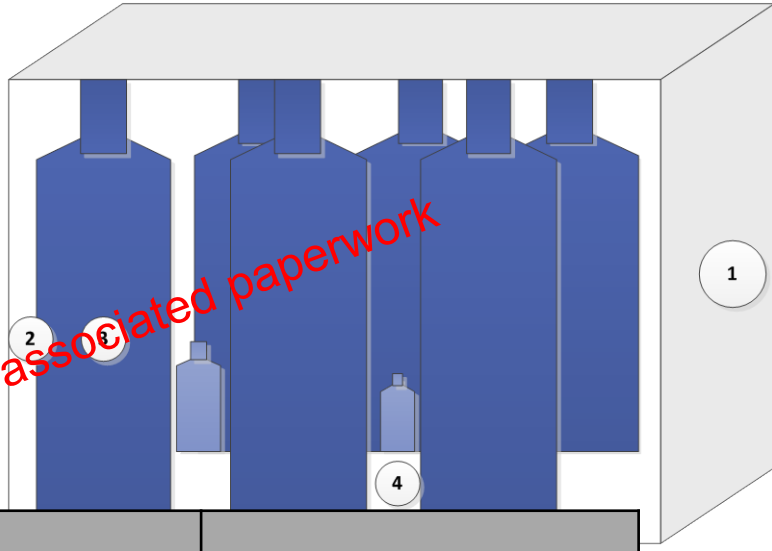
- Air transfer from Adelaide to Dubai
- Flight (12 hours but total transit time 13 hours 15 minutes)
- Stopover in Dubai
- Product is held in 3rd party cold store facility total stop over time is 2hr 30 minutes
- Air transfer from Dubai to London
- Flight total transit time is 7 hours 30 minutes.
- Stopover in London
- Airline release in London is 2 hr and transfer from Heathrow to 3rd party hauler cold store is @40 minutes.
- Package Held at 3rd party Hauler Store
- Product is held in cold store at 3rd party hauler not re-iced on arrival.

Walk the Process

- Dry ice added prior to departure
- Product is re-iced in cold store, delivered to carrier 19:00 hours the night before departure the product will remain in cold store until flight departure.
- Air transfer from London to closest airport to European destination
- Flight departs 06:00 hours local time. Transfer time is 2 hours 20 minutes arrives local time 09:20 hours.
- Stop over time to departure is 4 hr 40 minutes
- Air transfer from European airport to final destination
- Flight departs 13:00 hours local time. Transit time is 55 minutes arrives local time 13:55 hours.
- Road transfer from Airport to Receiving Site
- Product takes around 2 hours to retrieve from airline and 1 hour to deliver

Packing the shipping container

What have we forgotten?



VALIDATED Shipping solution includes all the associated paperwork

Item	Description	Quantity required
Shipper (Polystyrene box, one bottom insert and two top inserts)	Shipper Identification	1
Dry ice	Cylindrical dry ice pellets	20 kg
Bottle (MS635A)	30 mL PETG bottle	1
Bottle (MS635C)	125 mL PETG bottle	1
Bottles (MS635G)	2 L PETG bottles	6
Data loggers including certs and configurations	Data loggers	4
Shipping paperwork	Shipping paperwork	1
Security tags	Security tags	1
Taper evident tape	Tamper evident tape	1

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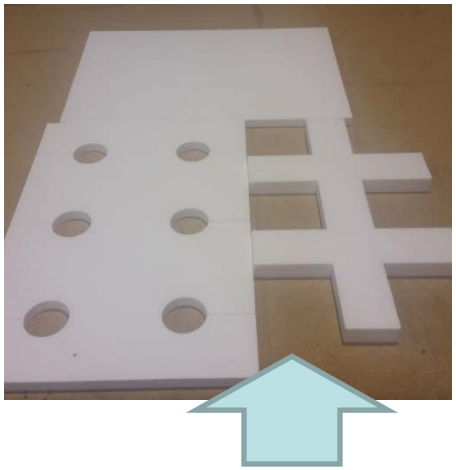
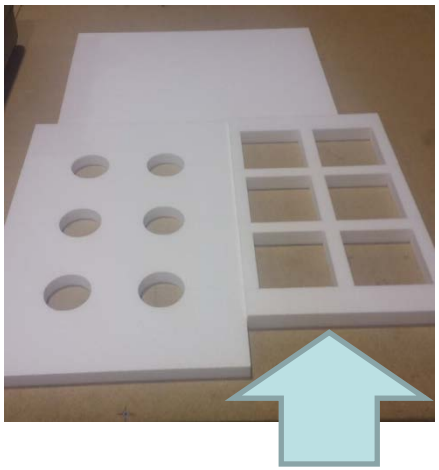
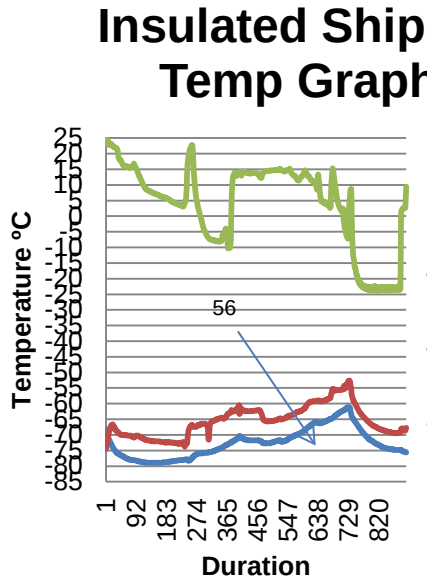
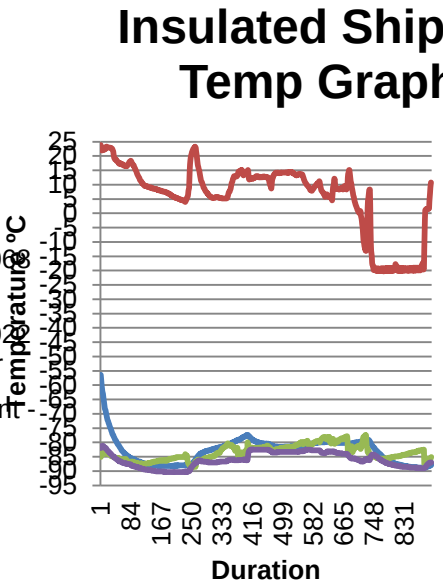
Examine the data from the shipping lanes

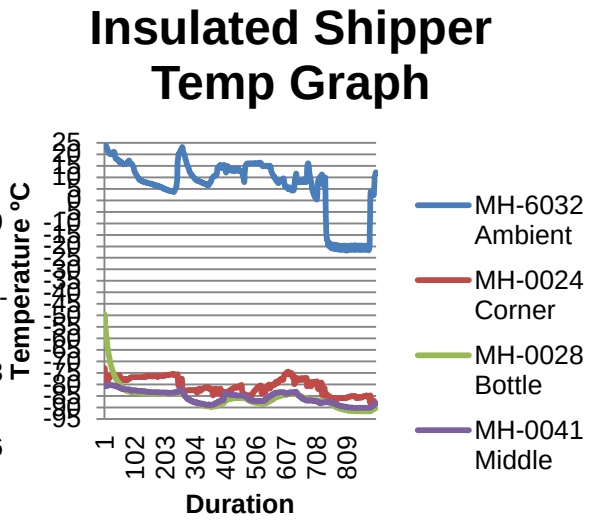




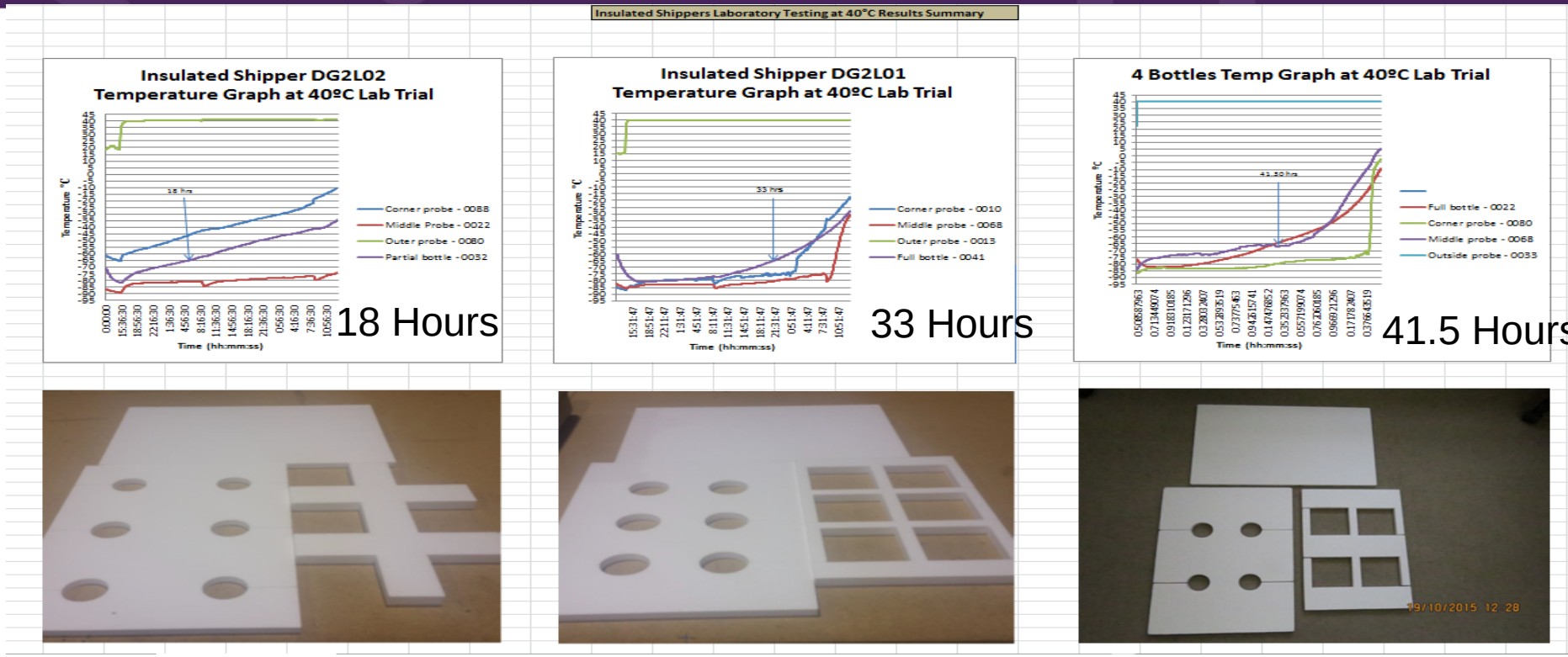
Who would have thought adding an extra strip increases the duration of the shipment !







Worse Case trials



Push the shipping container to the maximum in a controlled environment.
Remember this will be your product and any excursion to the shipping temperature will result in time and investigations.
It is better to know what can be tolerated up front than having to find out when it does happen!

In our case we were only concerned with heat but your product might to susceptible to cold

Own the Process

- Validated transportation takes @72 hours for door to door delivery.
- Every touch point is tracked. Hand over/shipping logs/captains logs supplied as part of the shipping package checked to ensure there has been no delays.
- Shipping containers checked for integrity at touch points. Each container is checked for damage so if there is damage it reduces the time of discovery and time can be spent to identify what went wrong or why there was damage.
- Security tags and tamper evident tape checked and recorded.

  If the containers are inspected full traceability/integrity is maintained
- Any delay is recorded and communicated to the **sending site**.

  It is their responsibility to ensure shipment reaches the destination

  as it is their ‘Validated’ shipping process !

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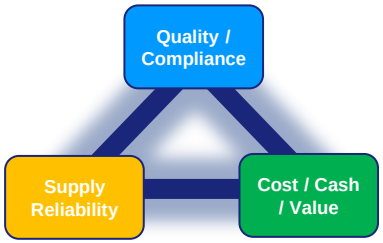
And Finally

- Thank you for your time
- I will open the floor for Questions



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Bibliography

- Nigel Bleakley
- Nigel has over 20 years' experience in the field of Validation.
- He is currently working as Associate Director of Validation with Hospira, a Pfizer company responsible for the site Validation program to support Biologics and Bio similar's.
- As part of this role overseeing the cold chain custody for the site products with shipments around Australia, Europe and USA.
- Nigel has supported topics such as cold chain 'last mile' and process validation within Industry.