

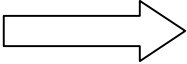
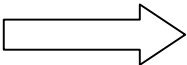


SHEDDING STUDIES

INTRODUCTION

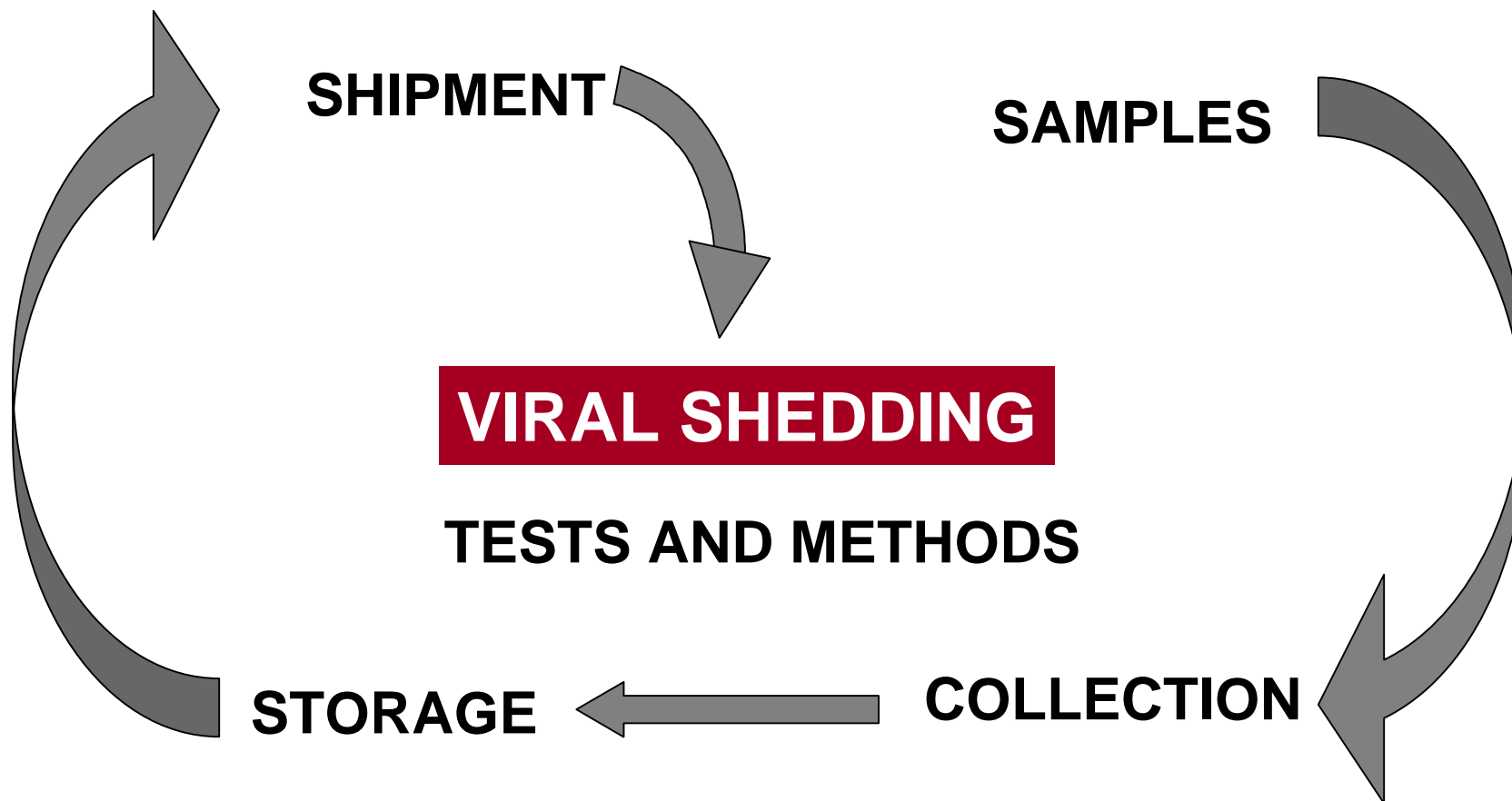
- Viral shedding is crucial for Gene Therapy Products
- Safety linked with shedding data
 - For the patient
 - For families and friends
 - For the environment
- No treatment possible without good safety results
- Shedding studies must be conducted properly

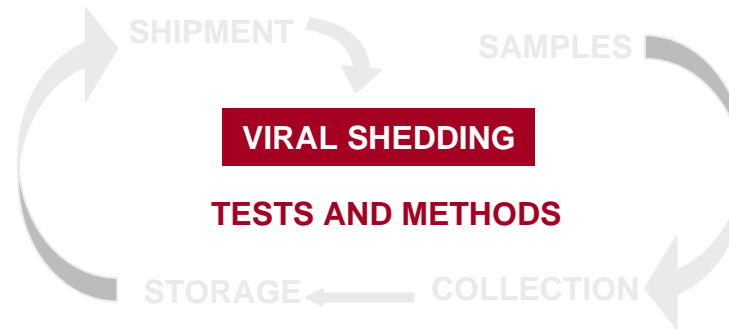
THE STRATEGY

- Viral shedding must be evaluated early in Phase I and through all phases
- Launch requires strong data
- Viral shedding evaluation is mandatory and costly
-  What is the best approach?
-  A clinical trial dedicated to viral shedding evaluation?

VIRAL SHEDDING EVALUATION

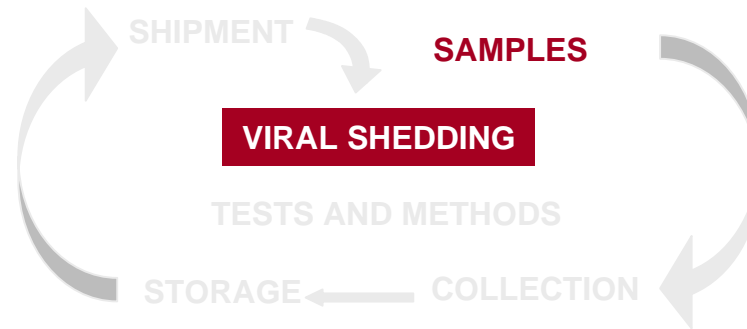
- Test selection is very complex
- Multiple parameters have to be considered to obtain strong data
 - Sample type
 - Sampling times
 - Logistical issues
 - Analysis and method validation



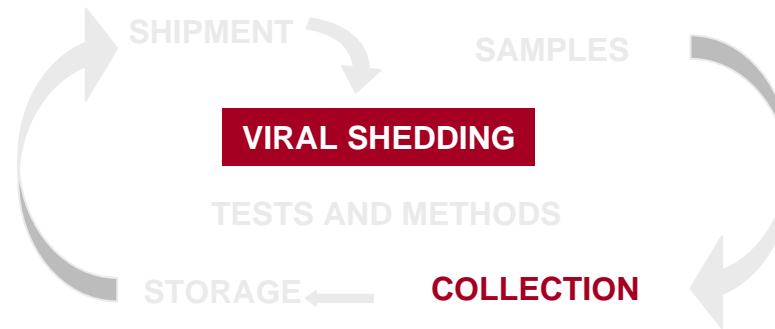


- No routine testing
- Methods developed according to viral construct
- Very sensitive tests using cellular and molecular methods
- Test validation is crucial
- Lab selection based on strong partnership

SAMPLING



- Multiple sample types for full evaluation
- Multiple sampling points requested
- Test results depend on the quality of the samples
- Sample collection process is crucial



- Collection procedures
- Clinical site training
- Sampling kits
- Clinical site monitoring
- Labeling

EXAMPLES

- Collection procedure
- Sampling kits

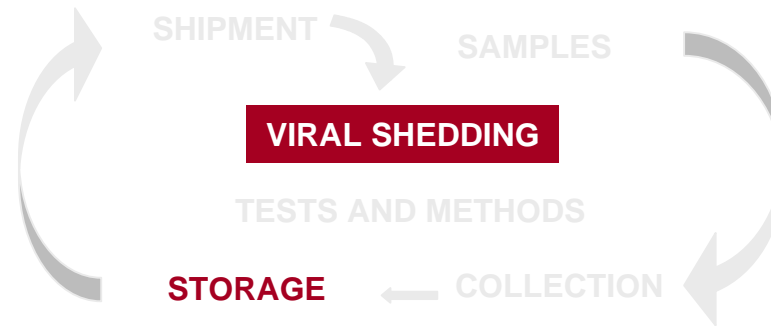


- Issues
 - Preparation issues
 - Labeling issues
 - Mix up between patient and household member
 - Tubes not labeled
 - Timing issues
 - Tubes not collected at baseline but after treatment
 - Tubes not collected

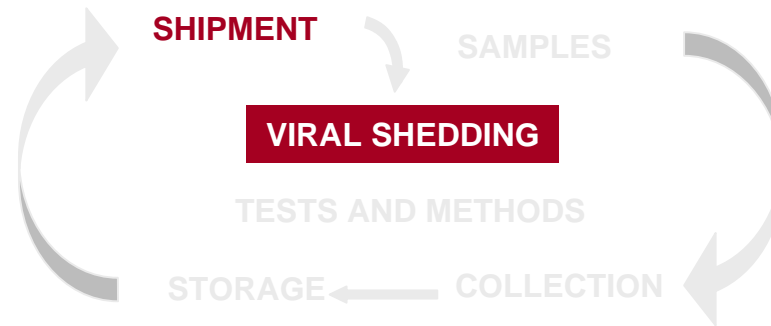
COLLECTION PROCEDURE

- Draw blood slowly, using a syringe if possible, and the largest-bore catheter that is feasible for the patient.
- Transfer blood to a CTAD vacutainer tube (Hemogard, sedimentation rate determination 4.5 mL tubes), being careful to minimize agitation of the sample.
- Gently mix tube by inverting 4 times
- Centrifuge at 2000 X g for 15 minutes at room temperature within 1 hour of blood draw. Within 30 minutes after centrifugation, draw off plasma very slowly with transfer pipette to within 0.5 cm of the buffy coat, taking great care not to disturb the buffy coat (any contamination may invalidate the assay).
- Pipette the plasma specimen into two separate plastic cryovials.
- Complete corresponding lines for each blood draw on the shipping log. Include patient identification number, initials, and date of specimen collection.
- All specimens must be stored frozen at -20°C (or colder) in a freezer
- The Specimen Log Sheets must be completed and included along with all shipments
- Only the primary samples of each patient should be sent with the first shipment to ensure that duplicates are available at the site for backup in case of damage during shipment.

STORAGE



- Qualified Freezer / Refrigerator
- Restricted area
- Monitored temperature equipment
- Storage documentation requirements



- Select the best shipping temperature
- Courier selection
- Cold chain management
- Shipping materials
- Shipping requirements
- Shipping issues

SHIPMENT - SELECT THE BEST SHIPPING TEMPERATURE

Select the
best
shipping
temperature



Courier
selection



Cold chain
Management



Shipping
Materials



Shipping
Requirements



Shipping
issues

● Depends on the stability of the viral construct

- The best but also the easiest to manage
 - -20°C versus dry ice
- Viral construct is temperature sensitive
 - Impact of Thawing / Freezing issues

SHIPMENT – COURIER SELECTION

Select the
best
shipping
temperature



**Courier
selection**



Cold chain
Management



Shipping
Materials



Shipping
Requirements



Shipping
issues

- Some parameters will impact the selection
 - The nature of the samples
 - The clinical site and testing lab locations
 - The level of internal expertise
 - The QA requirements
 - The budget
- Different courier types for different needs
 - Support
 - Training

SHIPMENT – COLD CHAIN MANAGEMENT

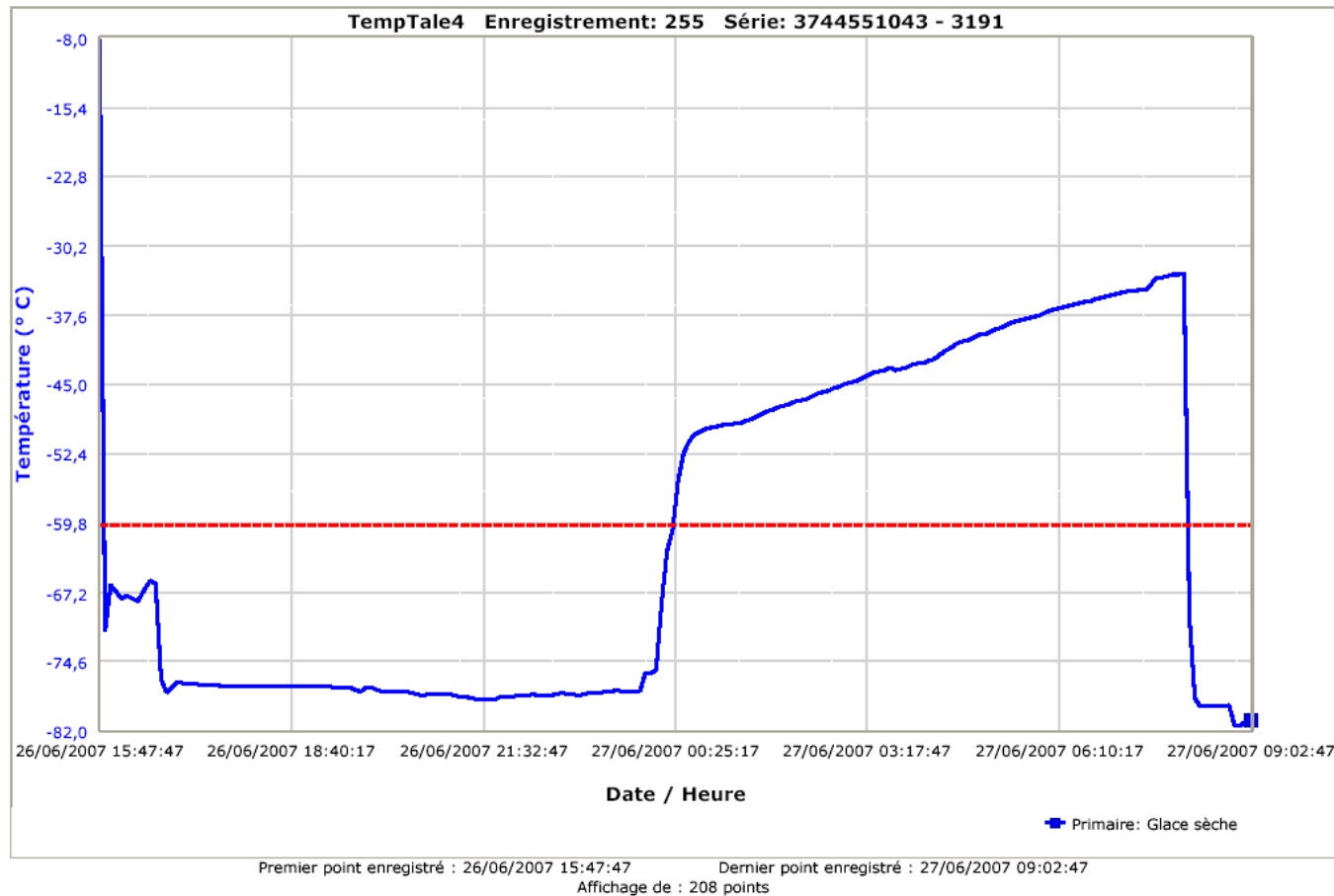


- Viral products are temperature sensitive
- Most of the time, frozen shipment under dry ice, or at +2°C+8°C with gel packs
 - Cold chain must be well managed
 - Packaging selection is crucial
 - Temperature probe
 - Strong partnership with a courier

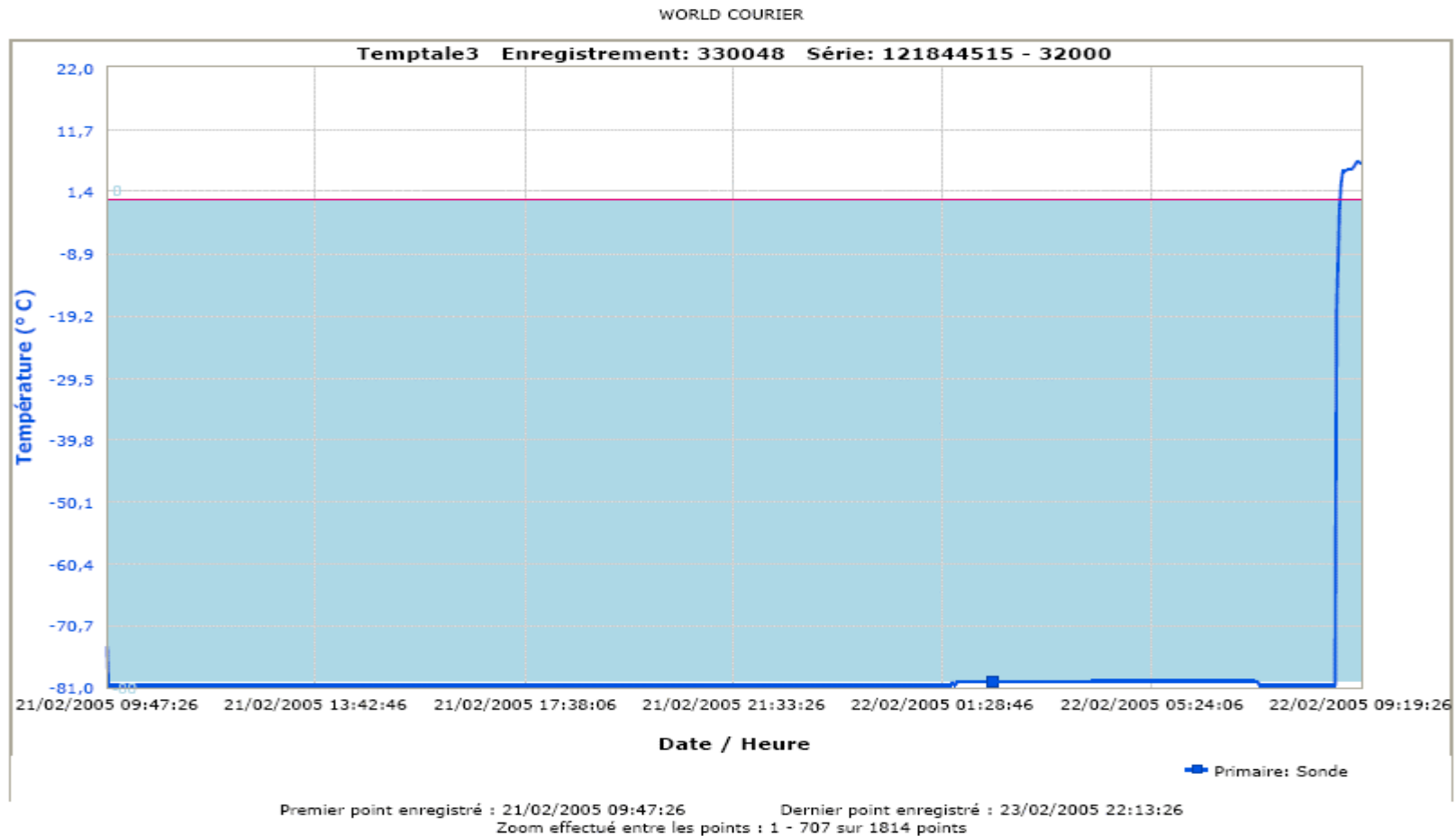
EXAMPLE: Temperature impact

- Shipment under dry ice
- Biological samples containing adenoviral construct
- Lack of cold chain management
- Freeze / Thaw accident
 - Decrease in viral concentration
 - False negative shedding results

Shipment of biological samples: -80°C



Shipment of biological samples: -80°C



Commentaires :

CONFIDENTIAL

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SHIPMENT – SHIPPING MATERIAL

Packaging validation

Select the
best
shipping
temperature

Courier
selection

Cold chain
Management

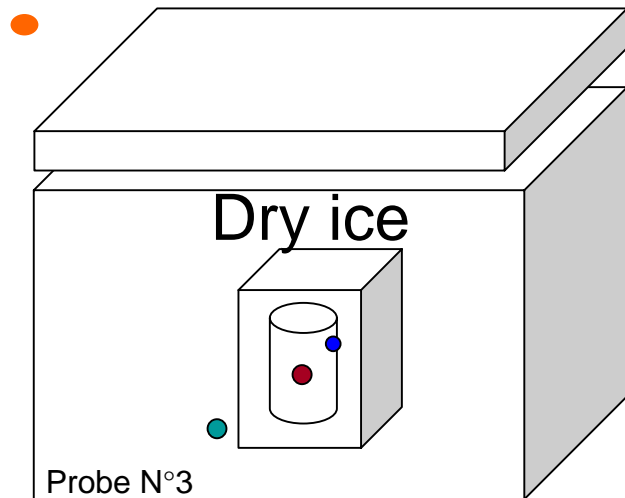
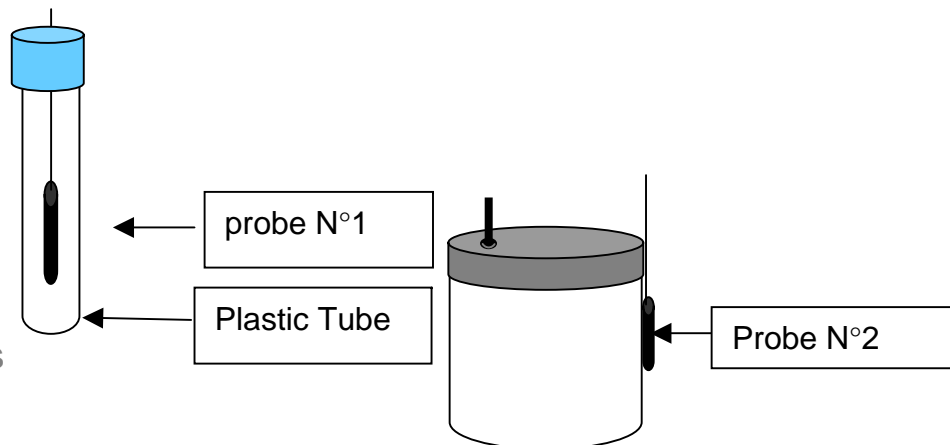
**Shipping
Materials**

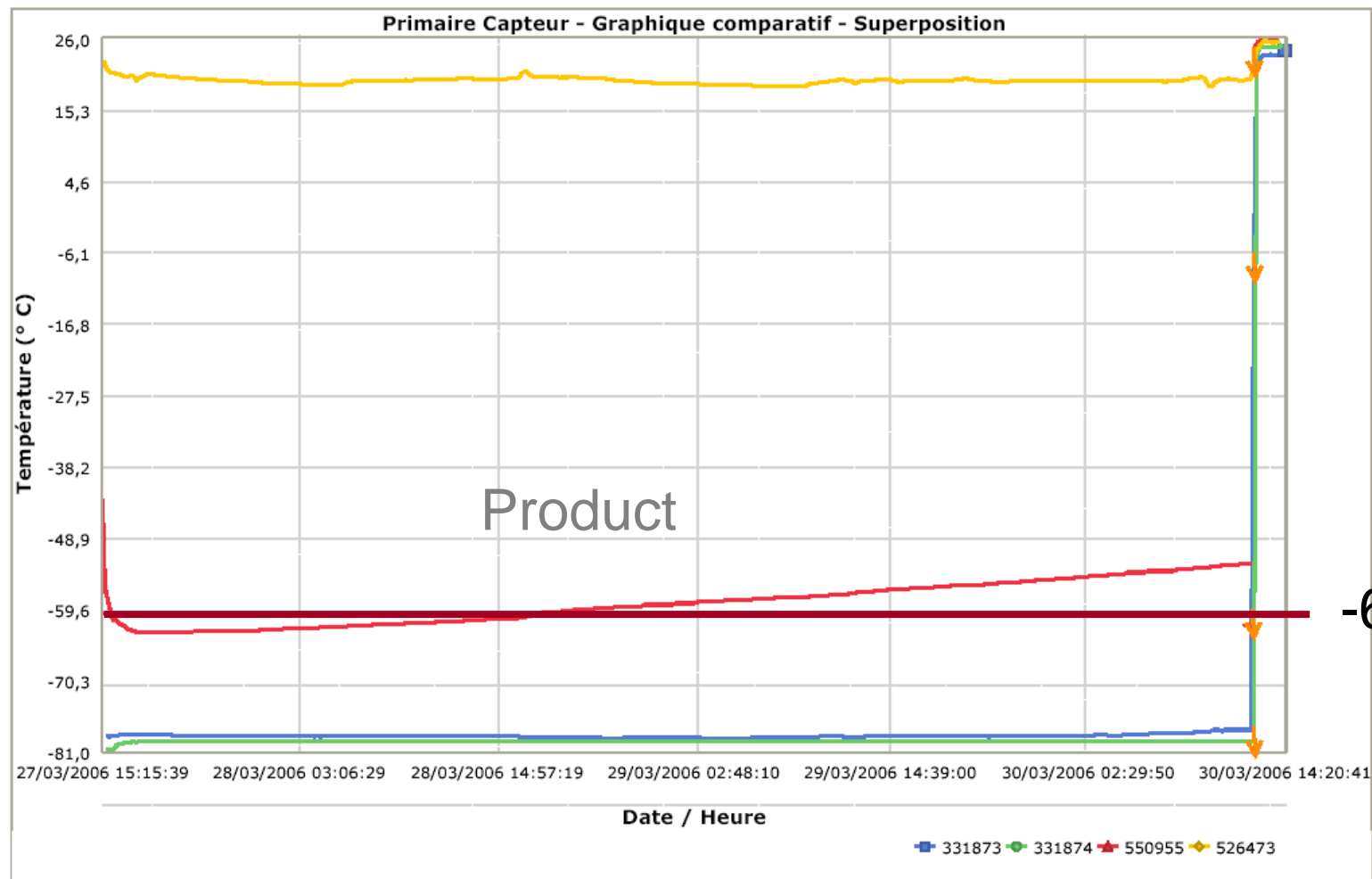
Shipping
Requirements

Shipping
issues



Ambient temperature





Premier point enregistré : 15/06/2006 15:43:19

Dernier point enregistré : 21/06/2006 15:33:23

CONFIDENTIEL

SOLUTIONS

ALL PACKED IN ONE

Select the
best
shipping
temperature



Courier
selection



Cold chain
Management



**Shipping
Materials**



Shipping
Requirements



Shipping
issues



SHIPMENT – SHIPPING REQUIREMENTS

Select the
best
shipping
temperature

Courier
selection

Cold chain
Management

Shipping
Materials

**Shipping
Requirements**

Shipping
issues

Customs, documents,
classification of the viral construct

CDC Permit, others...

SHIPMENT – SHIPPING ISSUES

Select the
best
shipping
temperature



Courier
selection



Cold chain
Management



Shipping
Materials



Shipping
Requirements



**Shipping
issues**

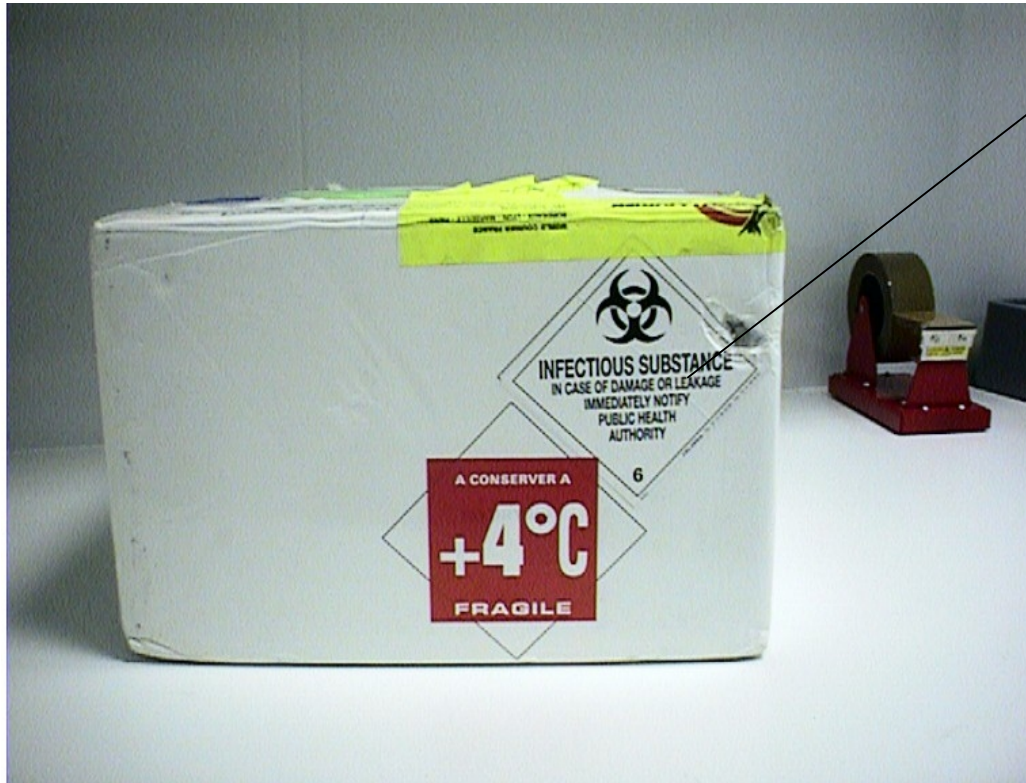
● Packaging

● Packaging instructions

● Initial sample temperature

● Replenishment of refrigerant

Packaging



Perforation
occurred during
shipment

Packaging Refused by
airline company

Samples blocked

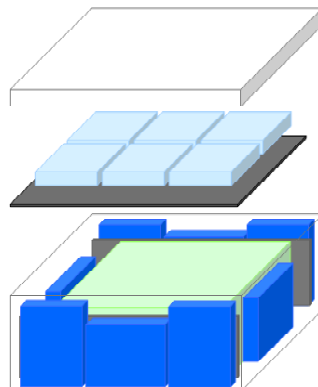
Selected option: Replace the shipping box

QUESTION:

- > • HOW to find a certified company?
- > • HOW to transfer the responsibility of the shipment?
- > • HOW to verify that everything is properly done?
- > • HOW to be sure that the cold chain will be maintain

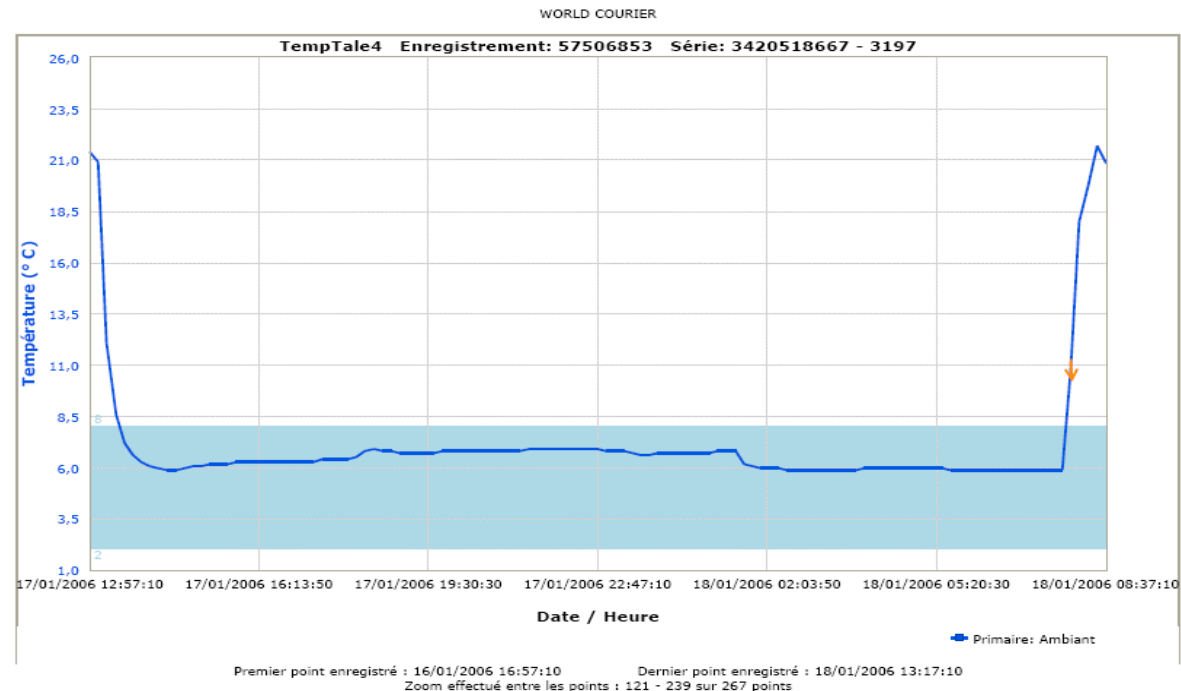


SHIPMENT – SHIPPING ISSUES



- Foam separator
- Refrigerated gel pack
- Frozen gel pack
- Product

Packing instructions have been followed



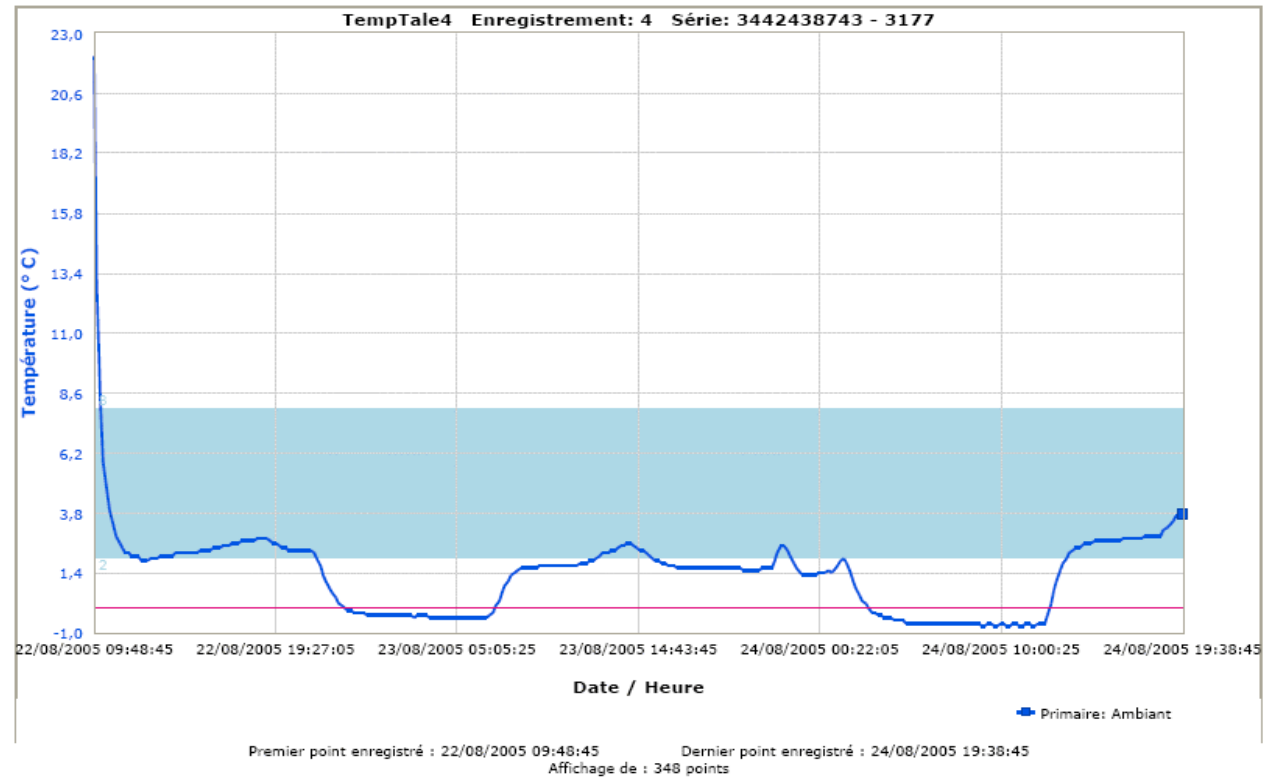
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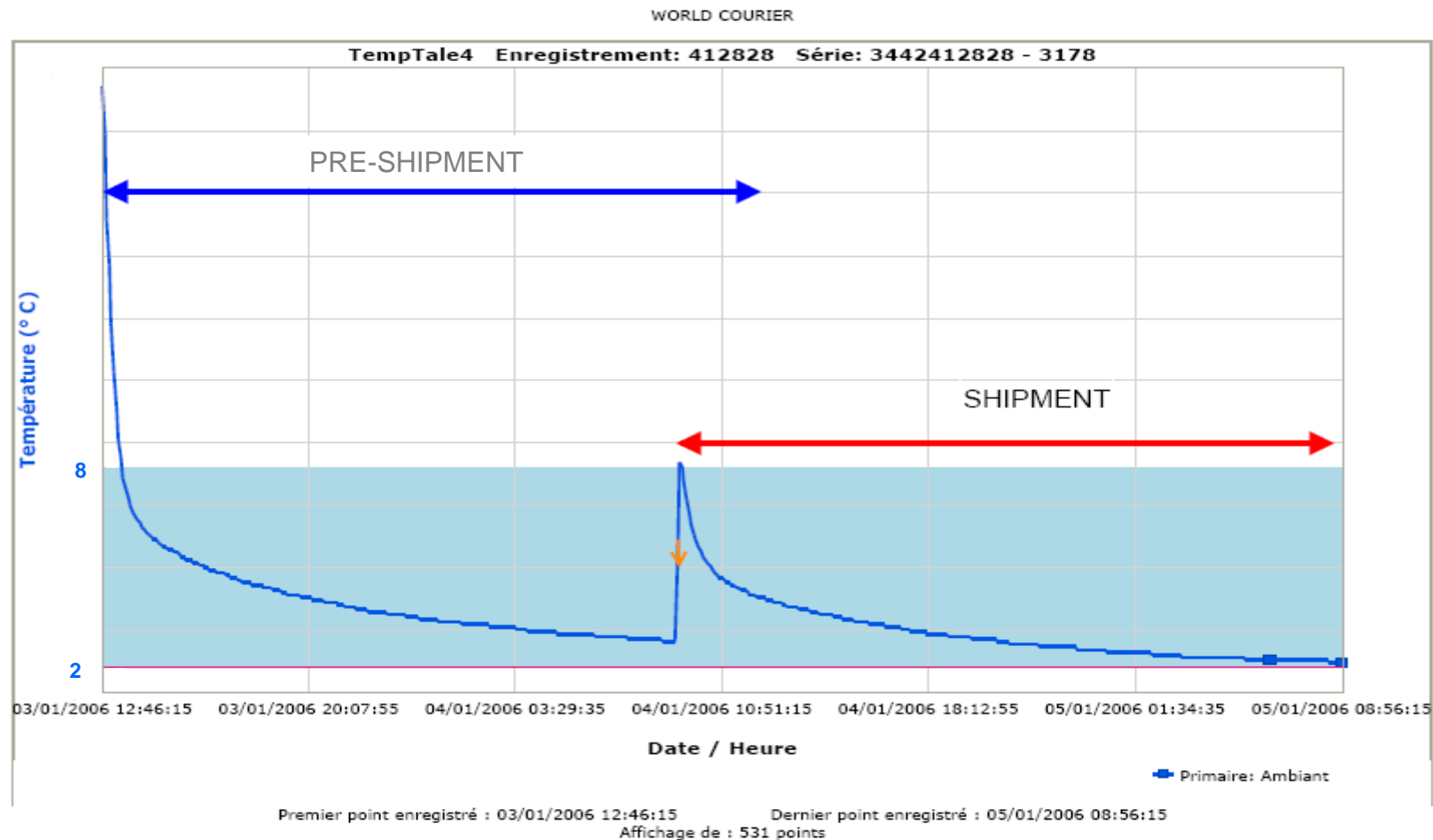
SHIPMENT – SHIPPING ISSUE

Packing instructions
have not been followed



SHIPMENT – SHIPPING ISSUE

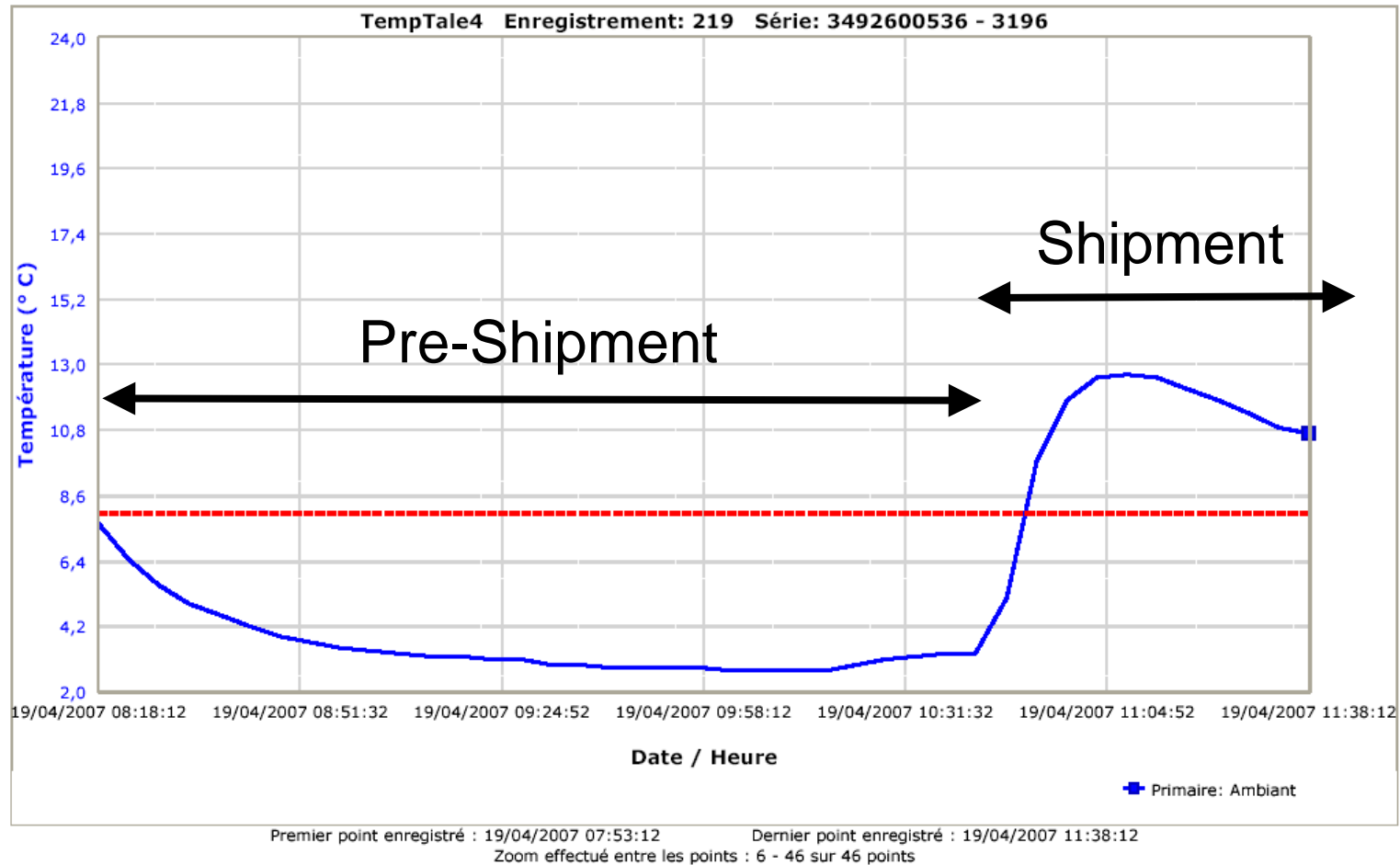
Initial product temperature: same as shipping temperature



Commentaires :

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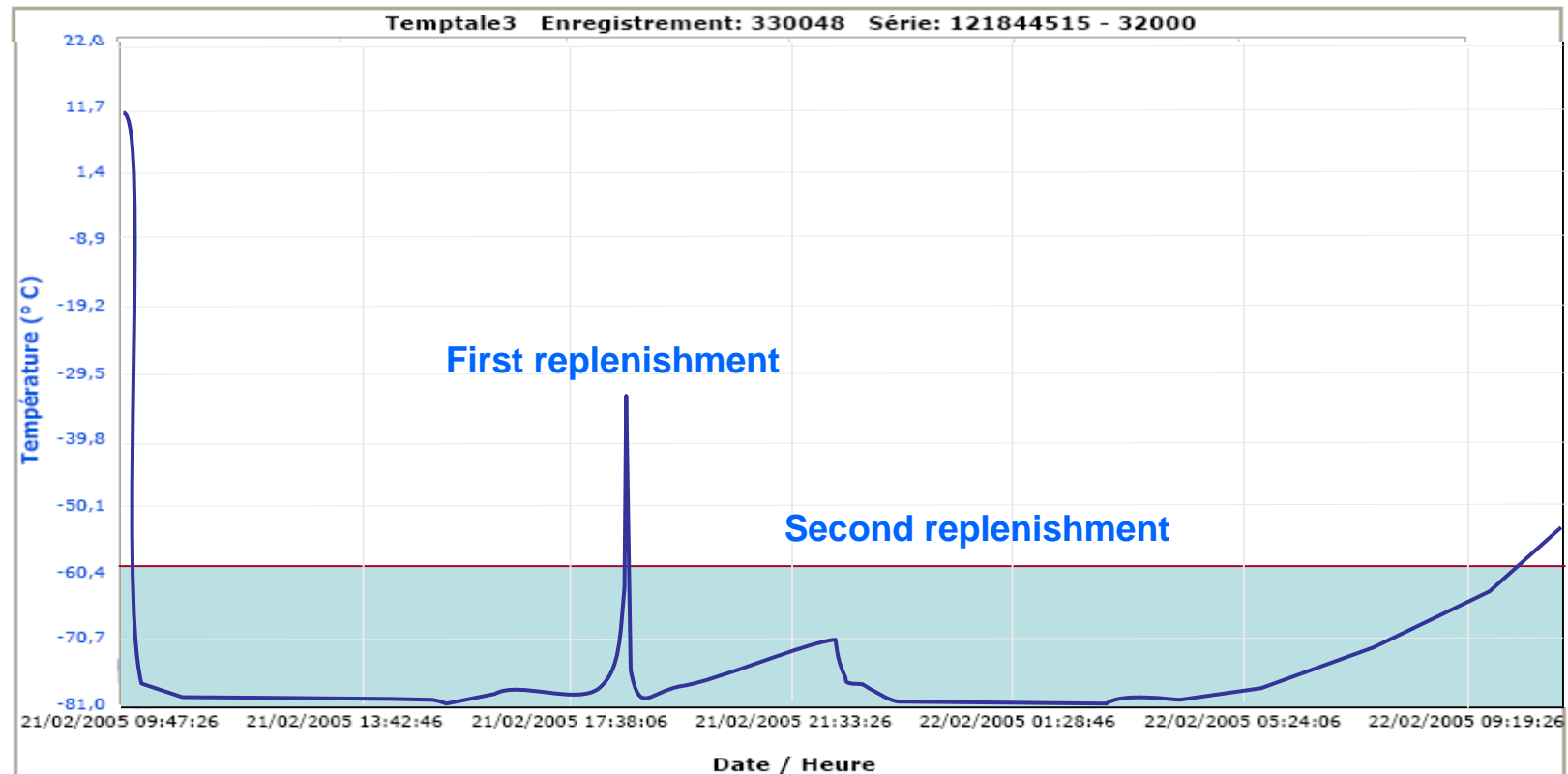
SHIPMENT – SHIPPING ISSUE



Initial product temperature: different as shipping temperature :
The samples have been collected few minutes before the pick-up

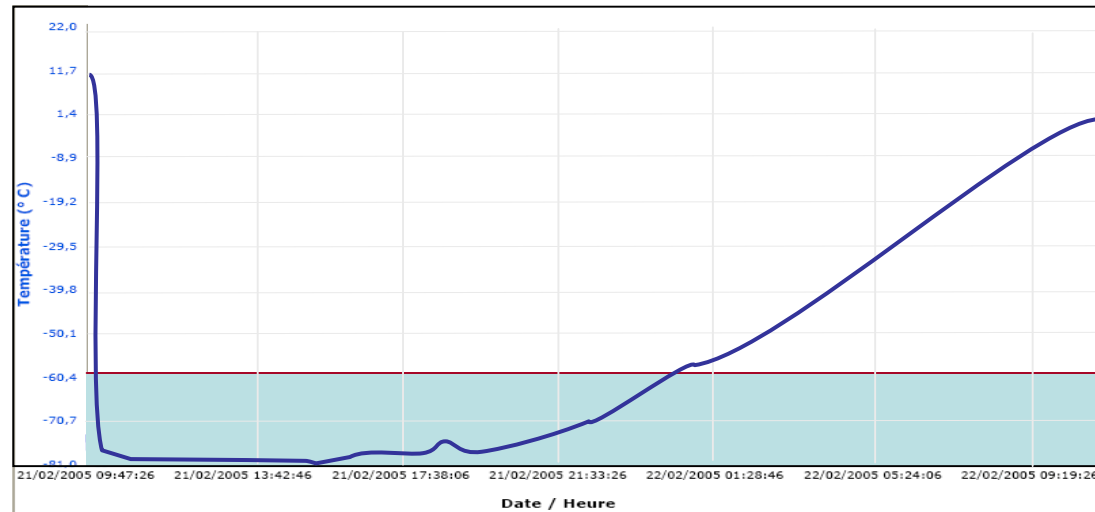
SHIPMENT – SHIPPING ISSUE

Appropriate replenishment

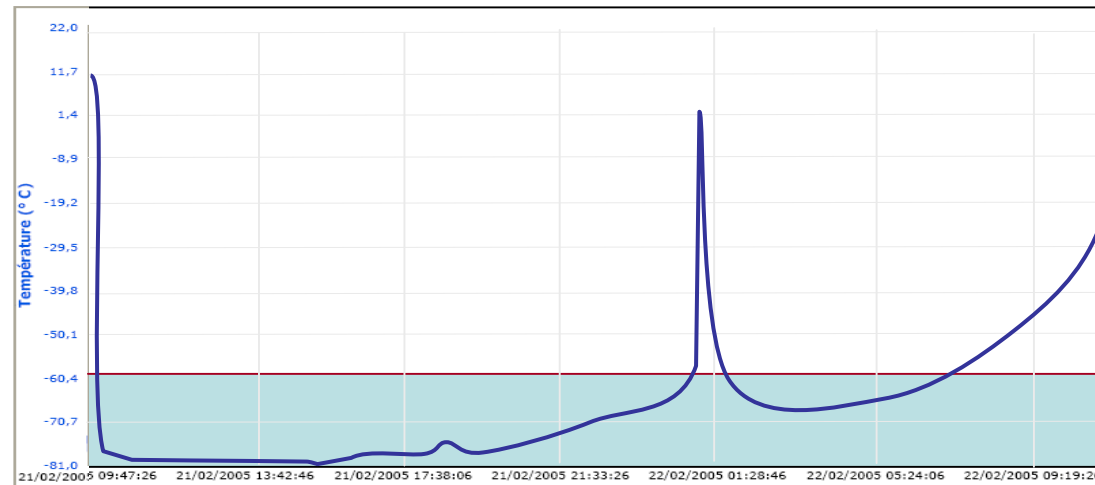


SHIPMENT – SHIPPING ISSUE

Without
replenishment



Not sufficient or too late
replenishment



CONCLUSION

- Multiple parameters could interfere in the viral shedding evaluation
- Strong expertise requires in all fields
- Harmonization through the process
- How to reduce shedding evaluation costs
 - Could we use the data through different constructs / indications
 - Specific guidelines needed