

MONITORING TEMPERATURES...

PRESERVING PRODUCTS...



ALTERNATIVES

COLD CHAIN COMPLIANCE
FOR PRODUCT INTEGRITY



Challenges of Cold Supply Chain

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*An excerpt from "A Compliant Cold Chain Management for
the Integrity of Biological Products"*

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ALTERNATIVES

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OUR FUTURE

Biopharmaceuticals/Biosimilars:

- Within the next couple of years, more than 50% of newly approved medicines will be **Biopharmaceuticals**.
- Beginning in 2010, a number of major biotech medicines have come off patent and are technically facing **biosimilar** competition.
- Biopharmaceuticals have a fragile nature: they are potentially very sensitive to enzymatic action in the manufacturing process and formulation and they are highly complex protein molecules. The biological activity of which depends on their structural integrity.
- Both chemical and physical instability may contribute to a loss of activity.
- Chemical instability arises from the modification of covalent bonds, whereas physical instability arises when the non-covalent forces maintaining the secondary or tertiary structure of the protein are disrupted. Physical instability can be minimised **by careful attention to storage and handling**.
- One of the major factors in maintaining the quality and integrity of Biopharmaceuticals/Biosimilars is **control of storage and transportation temperatures**.



COLD CHAIN PRODUCTS

Areas of Responsibility:

- Manufacturers of Cold Chain Products e.g. biopharmaceuticals have direct responsibility for, and control over, the correct storage and handling of their products from the start of production, through dispatch from their main supply warehouse, until the products reach the first point of shipment, which maybe a local operating company, wholesaler or a hospital.

Zone of Strict Guidelines Compliance

- Beyond that point, however, they can have only an indirect influence, by indicating to other distributors and users of the products how they should be stored and handled based on the evidence from preclinical studies and basic knowledge about therapeutic proteins.

Zone of Influence



COLD CHAIN REGULATIONS & GUIDELINES

- **Health Canada (HPFB Inspectorate):**

«Guide 069, Guidelines for temperature Control of Drug Products during Storage and Transportation »; 2005.

- **US Pharmaceopaedia:**

Chapter <1079>: « Good Storage & Shipping Practices »; Updates: « Good Storage and Transportation Practices for Drug Products » (2010).

- **Parenteral Drug Association (PDA):**

PDA Technical Report No39, revised 27: « Guidance for temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-sensitive medicinal Products through the Transportation Environment » (Suppl., vol. 61, no S-2)

- **Food and Drug Administration (FDA):**

« Draft Guidance for Industry, Stability Testing of Drug Substances and Drug Products » June 1998; International Conference on Harmonization (ICH), « Guidance for Industry, Q1A(R2): Stability Testing of New Drug Substances and Products », November 2003.

- **Health Distribution Management Association (HDMA):**

« Guidelines for Managing Cold Chain & Temperature Sensitive Products » (2009).

- **EU 'Guidelines on Good Distribution Practice of Medicinal Products for Human Use' (94/C 63/03) (1992) (Official basis for inspections)**



COLD CHAIN REGULATIONS & GUIDELINES

- **International Air Transport Association (IATA)**

Time and Temperature Task Force (TTTF); « The Perishable Cargo Regulations manual »

- **International Safe Transit Association (ISTA)**

- Test Procedure 5B : Focused simulation guide for thermal performance testing of temperature controlled transport packaging.

- Test procedure 7D: Thermal controlled transport packaging for parcel delivery system shipment.

- **American Society for Testing and Material (ASTM)**

Standard Test Method D 3103-99: Thermal insulation quality of packages.

- **British Association of Pharmaceutical Wholesalers**

Protocol for the control of storage temperatures of medicinal products: May 1999.

- **International Conference on Harmonization (ICH)**

Note for guidance on stability testing: stability testing of drug substances and products (ICH): CPMP/ICH/2736/99 (revision of ICH/380/95).



COLD CHAIN REGULATIONS & GUIDELINES

Health Canada, Health Products and Food Branch Inspectorate Guide-0069
“Guidelines for Temperature Control of Drug Products during Storage and Transportation”:

- Drug products must be shipped and stored in a manner that **does not risk exposure to temperatures outside of their *recommended storage conditions***; potentially impacting the safety and effectiveness of the drug product. Section 11 of the *Food and Drugs Act*, read together with the definition “unsanitary conditions” in Section 2 of the *Food and Drugs Act*, prohibits any person from:

“...packag[ing] or stor[ing] for sale any drug under ...such conditions or circumstances as might....render [a drug] injurious to health”.

- Fabricators, packagers/labellers, distributors, importers and wholesalers are additionally responsible for the appropriate handling, storage and distribution of drugs according to C.02.015 of the *Food and Drug Regulations*. These requirements are in place to maintain the quality of the drugs. Every activity in the distribution of drugs should be carried out according to requirements of the *Food and Drugs Act*, the principles of Good Manufacturing Practices (GMP), good storage and good distribution practices.



COLD CHAIN REGULATIONS & GUIDELINES

US FDA: Adulterated Drug Products, FD & C Act Chapter V, sec.501.

- Sub-chapter A, (2)(B) states:

*"A drug or device shall be deemed adulterated - if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, **or holding** do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess."*

- The use of the term *holding* is an interesting one. "**Holding**" of a drug occurs when the drug is being distributed, transported, warehoused or stored.
- "Storage (holding) of a drug at appropriate temperatures and under appropriate conditions is a requirement" within current Good Manufacturing Practices (cGMP). Code of Federal Regulations Title 21, Sub-chapter C, Part 205 Sec. 205.50(c)



WHO IS INVOLVED

Health Canada (Guide-0069):

- All persons and companies involved in the storage and transportation of drug products.
- All persons and companies including **fabricators, packagers/labellers, distributors, importers, and wholesalers** share responsibility for ensuring that appropriate storage and transportation conditions are maintained from the point of manufacturing up to the delivery of the drug products to the *final distribution point*. (e.g. pharmacy, hospitals, clinics, retail stores, etc).

USP:

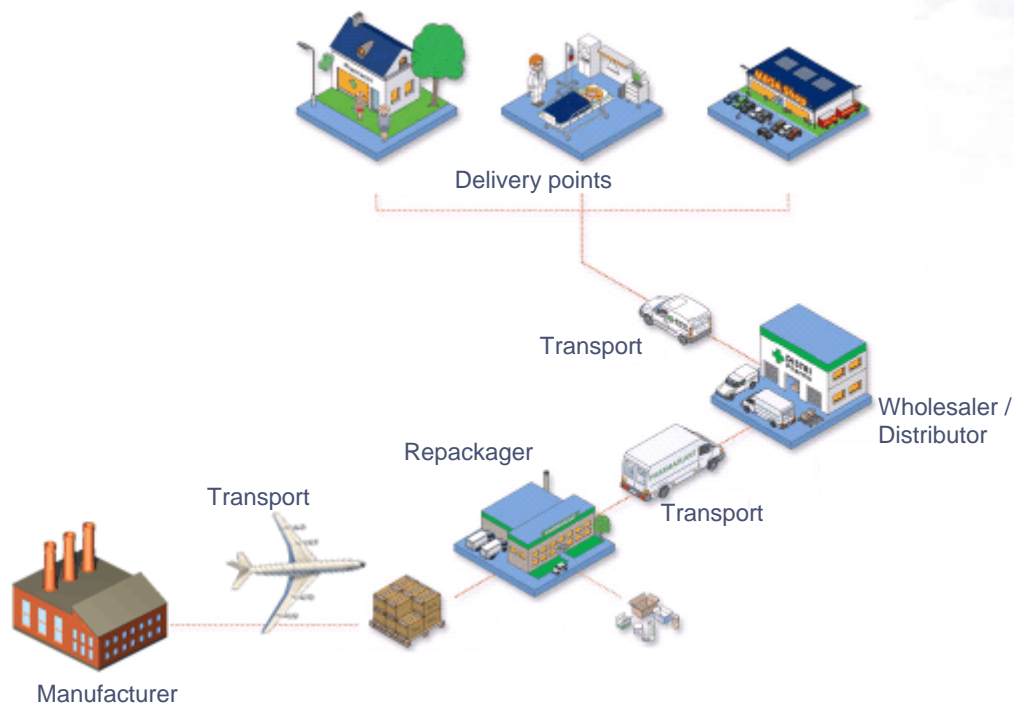
- All organizations and individuals involved in any aspects of the storage and transportation of drug products including: **manufacturers of legally marketed drug products (contractors included), packagers, repackagers, laboratories, brokers, exporters and importers, wholesale distributors, transportation companies, 3PL providers, mail distributors, pharmacies, hospitals, physician offices, end-user home.**



COLD SUPPLY CHAIN

Challenges in the Cold Supply Chain:

- Preserve the adequate Storage & Handling Conditions (temperature) throughout the Cold Supply Chain.
- Document the Storage Conditions (temperature) throughout the Cold Supply Chain.
- Maintain the Product Safety throughout the Supply Chain (temperature, counterfeiting).



COLD CHAIN COMPLIANCE FOR PRODUCT INTEGRITY



PRINCIPLES

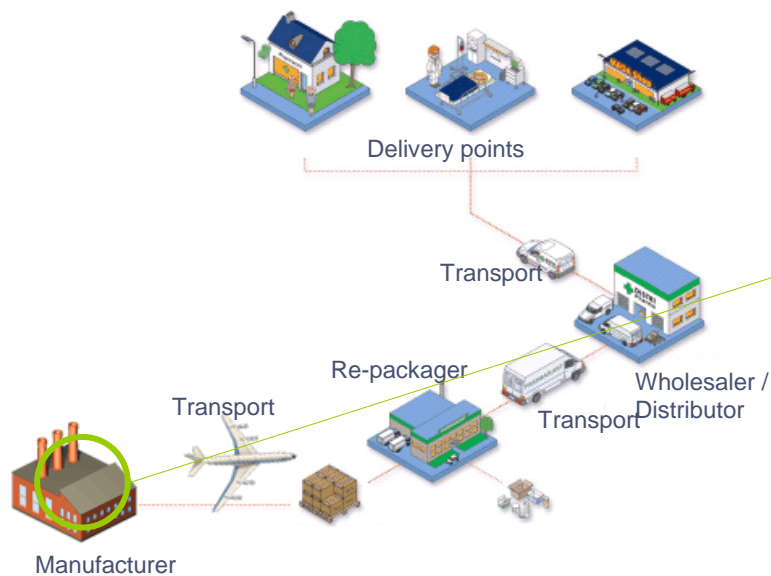
General Principles:

- The good quality of Cold Chain Products must be maintained throughout distribution networks.
- The Quality Control/Assurance service must make sure that conditions of storage are observed at any moment, including transport.
- Standardized Operation Procedures (SOPs) should describe all operations likely to affect the quality of Cold Chain Products or the distribution, including the reception of deliveries, storage and recording of storage conditions.
- Instruments and equipments used should be adequate to ensure a good conservation and distribution of Cold Chain Products



STABILITY / EXCURSIONS

- Everything starts at the Stability tests/Temperature excursion tests
- Stability tests:
 - Stability tests (normal, accelerated)
 - Temperature Excursion tests
- Will define the storage conditions (label) throughout the supply chain
- Will be used as reference in case of temperature excursions



Product Owner/Developer

Stability Test and Data: Perform complete stability tests and temperature excursions test (it helps the logistics)...



HOW TO REACH COLD CHAIN COMPLIANCE

What has been done to reach Cold Chain Compliance...

- Regulatory Gap Analysis
- Personnel Training
- Review and Writing of SOPs (related to Cold Chain, Storage & Shipping) and Documentation
- Temperature Mapping of Warehouse and Storage areas
- Qualification of Storage Equipment (Refrigerators/Freezers)
- Temperature Profile Studies in Transport (for uncontrolled transports)
- Test, Design and Qualification of Cold Chain Packaging Systems (outermost)
- Monitoring Solutions for Storage Conditions of Cold Chain Products
- Maintenance of Cold Chain Management and Compliance.

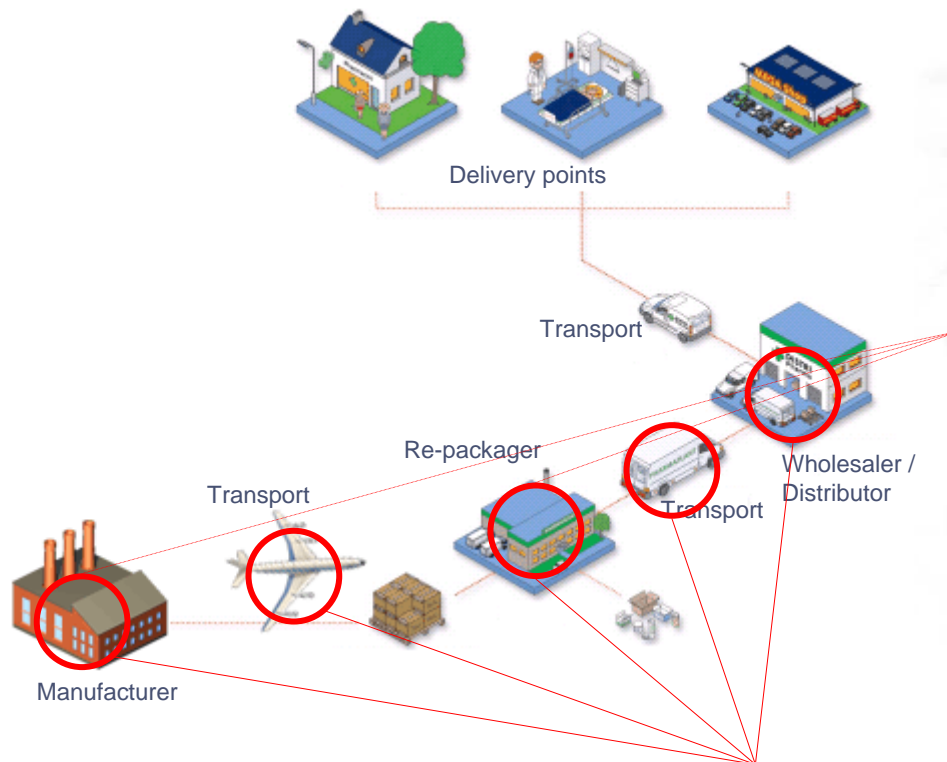


REGULATORY GAP ANALYSIS

- The purpose of the cold chain gap analysis and its documentation is to verify and establish the pertinence of the cold chain regulations to the audited facility.
- Verifications are made through a close collaboration of the Logistics, Quality Assurance, Quality Control and Shipping/Receiving depts.
 - Human Resources (Personnel)
 - Documentation
 - Procedures (SOPs)
 - Warehousing & Storage Area
 - Shipping and packaging methods
 - Monitoring & Environmental Controls
 - Quality Agreements (e.g. Transportation Contractual Agreements)



COLD CHAIN MANAGEMENT / COMPLIANCE



Storage/holding

Facilities: adequately installed, segregated and managed for drug products.

Receiving/shipping: protected, secured, separated from storage, monitored (not mapped).

Intransit: maintain at appropriate storage conditions...

Storage (ambient): secured, segregated, controls over environmental conditions, mapping studies, continuously monitored with alarms (temperature/RH)...

Storage (frozen/refrigerated): secured, exclusive & identified, performant, qualified (IQ/OQ), continuously monitored with alarms (temperature/RH)

Personnel: trained for Cold Chain and temperature-sensitive products

Procedures: SOPs for Cold Chain, Warehousing/Storage, Excursions

Documentation: receiving, shipping, storage conditions...

Quality Agreements: with specific Cold Chain aspects, responsibilities, interruptions...



PERSONNEL TRAINING

- Training on GMP and Cold Chain aspects, handling and storage of drug products
- Trainings should be ensured by qualified people
- Trainings should be in conformity with a written established program and training activities should be consigned in files
- The effectiveness of the continuous training should be evaluated periodically
- Staff working in areas where active, toxic, infectious or sensitizing products are handled, should receive a specific training for this purpose
- Formation of contractor's personnel (transporters...)



QUALITY AGREEMENT

- Quality agreements should be in place among organizations involved in the Drug supply chain;
- Should ensure clarity and transparency about the responsibilities of each organization;
- Take care of holidays, weekends and other interruptions, and of custom inspections;
- Should reflect the responsibilities of all organizations and the commitment to Cold Chain Quality
- Quality Agreements:
 - Manufacturer-Wholesaler
 - Manufacturer-Transporter
 - Manufacturer-Contractor
 - Wholesaler-Transporter



SOPs

Standard Operating Procedures (SOPs):

Standard Operating Procedures (SOPs) specific to receiving/storing, transportation and cold chain quality aspects should be in place and effective:

- Changes verification;
- Receiving and verification of drugs products;
- Methods of Storage and Holding Drugs;
- Cleaning and maintenance of Storage areas;
- Use and Maintenance of Storage equipment
- Policy of labelling (temperature-sensitive);
- Orders preparation and shipping of Drugs;
- Checking of delivery and shipping receipts;
- Environmental Controls and Monitoring;**
- Calibration/maintenance of measuring instruments;**
- Inventory control;**
- Management of stocks having reached the scratch date;
- Management of temperature excursions and other environmental condition excursions;**
- Corrective actions in case of problems during the transport of Drugs;**
- Management of damaged stocks, quarantined Drugs and returned products;
- The Safety of Stocks (theft, counterfeiting)...



DOCUMENTATION

- Transport and storage documentation (including precautions and/or warnings for the products shipping)
- Approved shipping documentation for the products forwarding
- Evidences demonstrating that shipping requirements were respected (temperature)
- Drugs production documentation
- Documentation attesting that drug manufacturing, packaging, labelling, analyze and **storage conditions** are in conformity with GMP requirements
- Documentation attesting that the duration during which the drug, placed in the container in which it is sold, will remain in conformity with the specifications
- Files on each Drug batch sale or manufacturing should be kept
- In Reception/Shipping documentation are described following information:
Drugs description, Quantity, Name and addresses of the recipient, Name and Addresses of the shipper, Batch number, Drug scratch date, **Shipping date**.



WAREHOUSING / STORAGE

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- Storage area with adequate airflow and temperature controls. Systems to mitigate risks (fire, water) should be in place.
- Temperature distribution in storage areas determined by mapping for 7 days in Winter and Summer. Reports were issued taking into account the different temperature ranges of drugs in the warehouses (hot and cold spots)



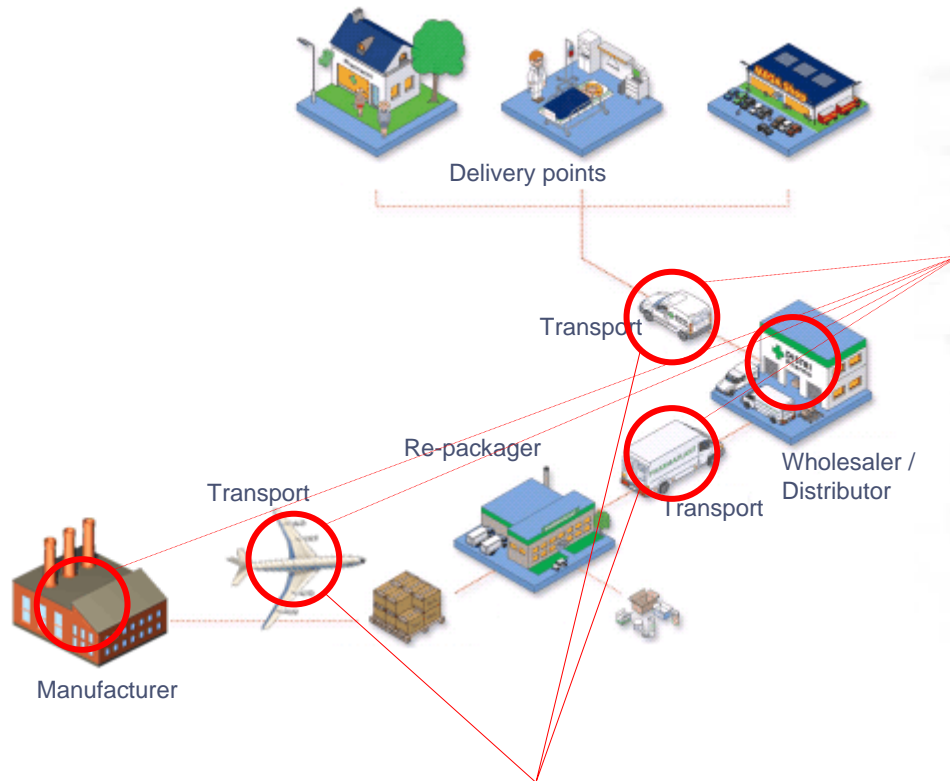
STORAGE EQUIPMENT

Storage Equipment (Refrigerator, Freezer)

- Storage equipments (refrigerators/freezers) should provide sufficient space to permit airflow
- Storage equipments should be able to maintain the required temperature limits: e.g. 2-8°C for refrigerators
- Storage equipments should be positioned in the facility so that they are not exposed to extreme environmental temperatures
- Storage equipments should be qualified (Installation/Operational) by following an approved protocol.



COLD CHAIN MANAGEMENT / COMPLIANCE



Transportation

Not-controlled: use of temperature-controlled packages or containers to maintain adequate temperature ranges during transports.

- Know/define your logistics
- Define external temperature profiles (seasonal)
- Develop protective cold chain packaging methods
- Qualify cold chain packaging methods

Transportation/Labeling

Labeling: labelling information about product characteristics and storage conditions (outermost)

Transportation

Temperature-controlled: qualified (IQ/OQ/PQ), continuously monitored with alarms (temperature/RH)...

Transporters: personnel training, Quality Agreement (transporters), Management of excursions...



TEMPERATURE PROFILES

- Temperature Profile Studies should be performed for temperature-uncontrolled transportation modes: to determine the temperature distribution profiles that apply onto its sensitive products along all the distribution and transportation processes during warm and cold weather conditions.
- Temperature Profile Studies are seasonal: 2 seasons (winter/summer), 3 seasons (winter/summer/intermediate), 4 seasons
- Temperature Profile Studies performed on « Worst-case destinations » and « Standard destinations »
- Temperature Profiles in Transport support the development of cold chain packaging methods (for temperature-uncontrolled transports)
- The packing used during the transportation of drug products should ensure the temperature uniformity in the container (in all seasons)
- Do not apply onto temperature-controlled transports



COLD CHAIN PACKAGING METHODS

For Temperature uncontrolled transports:

- Design and use insulated containers, conditioning materials and methods for shipments and storage, that are proven to maintain an internal temperature compliant with products labelling, during all transportation or storage process (including receiving) until product is packed-out and stored in the range of temperature applied
- Packaging and shipping methods shall be consistent with the temperature profiles and shall be qualified (Operational, Performance)
- Design of Logistics/Temperature Profiles/Packaging Methods may be complex



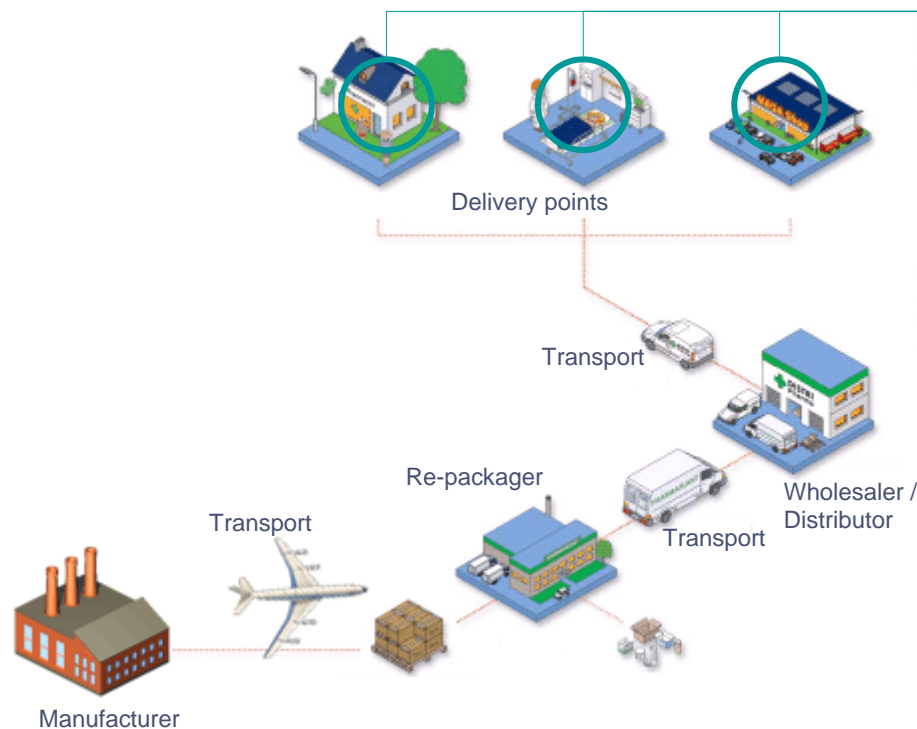
MONITORING

- Environmental conditions such as temperature, relative humidity, and light, should be monitored in all receiving, transferring, storing and holding areas.
- Should also apply onto temperature-controlled transports (and ideally onto all transports)
- Monitoring system should enable temperature (excursion) alarming, day and night
- Data should be stored securely. Temperature data should be available and check out regularly
- Alarms used to monitor the temperatures of storage enclosures should be checked out regularly
- Instruments used to supervise and control the temperature of products in stock should be calibrated at least once a year and should be placed in a preventive maintenance program
- Measuring instruments in place (Monitoring) should be qualified. Monitoring software should be secured and compliant



DELIVERY POINTS (INFLUENCE)

- Storage and Delivery conditions (temperature) should be controlled and maintained at delivery points.
- Special attention: Storage equipment (refrigerated), Monitoring, Delivery Packaging



Delivery points

Documentation: information about product characteristics and storage conditions....

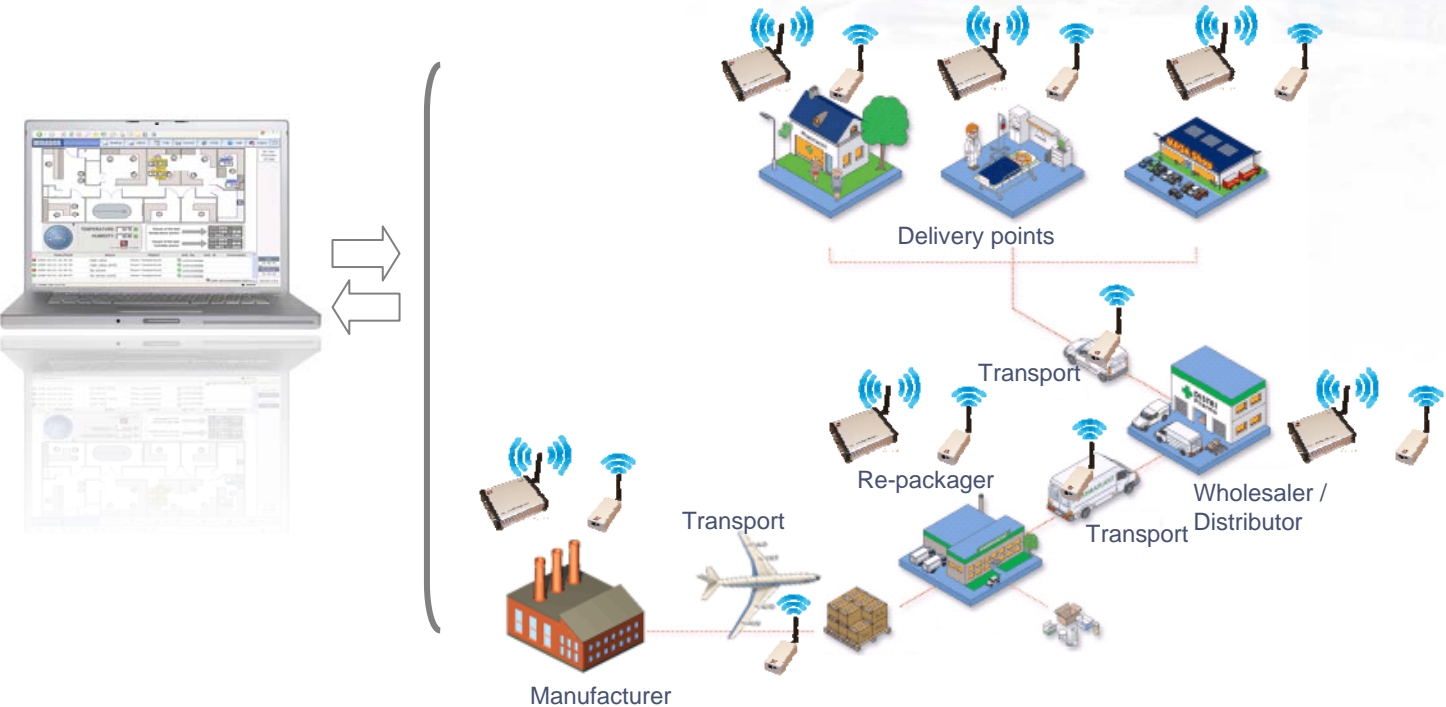
Storage: exclusive, continuously monitored with alarms (temperature)

Delivery: special packaging for temperature-controlled delivery, notice to end-users...



MONITORING THE COLD SUPPLY CHAIN

- Today, ensuring Cold Chain Products are continuously stored, handled and transported under adequate environmental conditions (temperature) is crucial.
- Automated Monitoring Systems now enable to monitor and track storage and transport conditions throughout the Supply Chain up to the end-users.



COLD CHAIN COMPLIANCE FOR PRODUCT INTEGRITY

MONITORING THE COLD SUPPLY CHAIN

- Next generation automated monitoring systems can provide a controlled supply chain environment:
 - Automated and paperless, User-friendly
 - Sensors with memory and data logger capabilities
 - Self-healing Mesh Networks of Wireless Sensors/Readers
 - Self-detection of incoming Sensors
 - Secured Web Environment
 - Complete alarming management and capabilities
 - Management system for sites, routes, shipments...
 - Remote Monitoring Capabilities...
- It provides
 - Real-time continuous wireless monitoring of storage areas and facilities: laboratories warehouses, storage areas, pharmacies, hospitals...
 - Real-time continuous wireless monitoring of temperature-controlled transportation modes: trailers, vans, containers...
 - Continuous wireless monitoring and tracking of shipments and products (pallets, boxes...)



CONCLUSION

- Ensuring an efficient Cold Chain Regulatory Compliance program is a crucial step for the commercialization and distribution of Cold Chain Products. Throughout the supply chain, a special attention should be put on:
 - Training:** Train your staff and personnel about Cold Chain aspects and SOPs.
 - SOPs:** on Cold Chain processes.
 - Documentation:** be sure documentation on product storage conditions are maintained and available.
 - Quality Agreements:** with third-parties and suppliers.
 - Storage Conditions:** in Warehouses and Equipments (Control Change).
 - Monitoring:** ensure an efficient monitoring of your storage areas and transports.
 - Temperature Profiles** and **Qualified Packaging Methods:** to be periodically controlled and updated (Cold Chain Maintenance).

