EU Supply Chain Requirements & Considerations for Temperature Sensitive Products

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Agenda

- EU Supply Chain
- Good Distribution Practice
- Falsified Medicine Directive
- Supply Chain Qualification

EU Supply Chain

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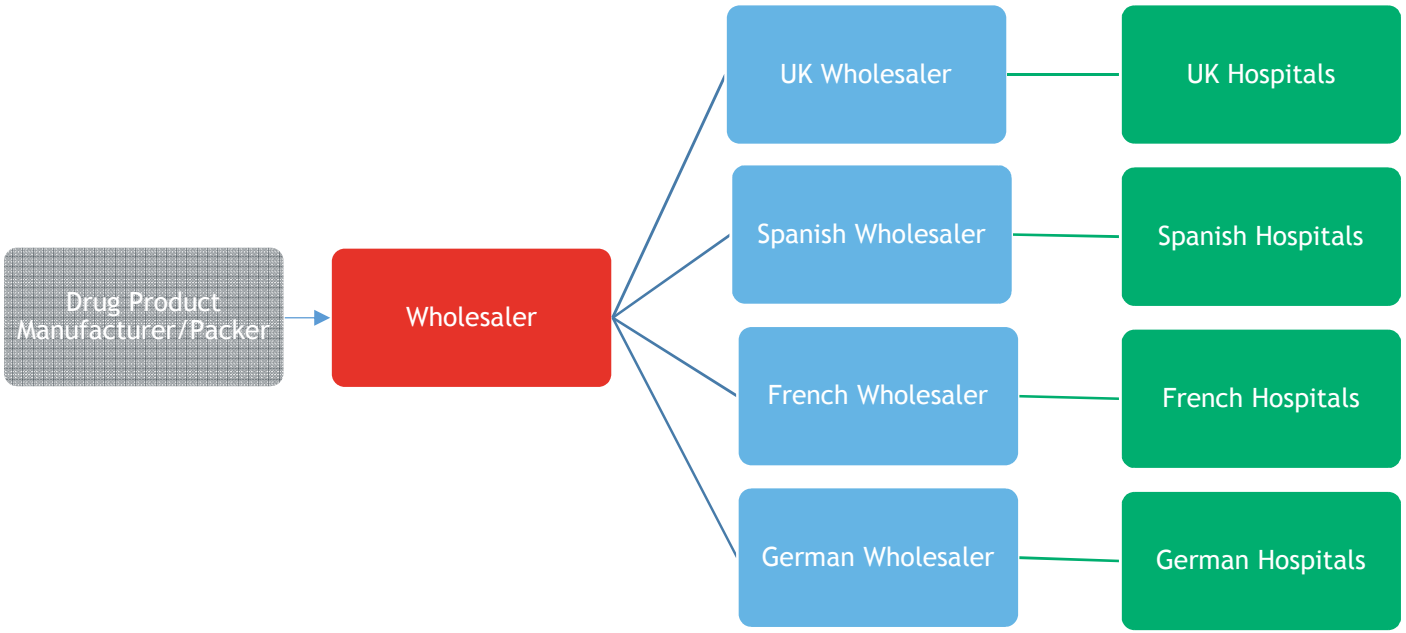
EU Supply Chain

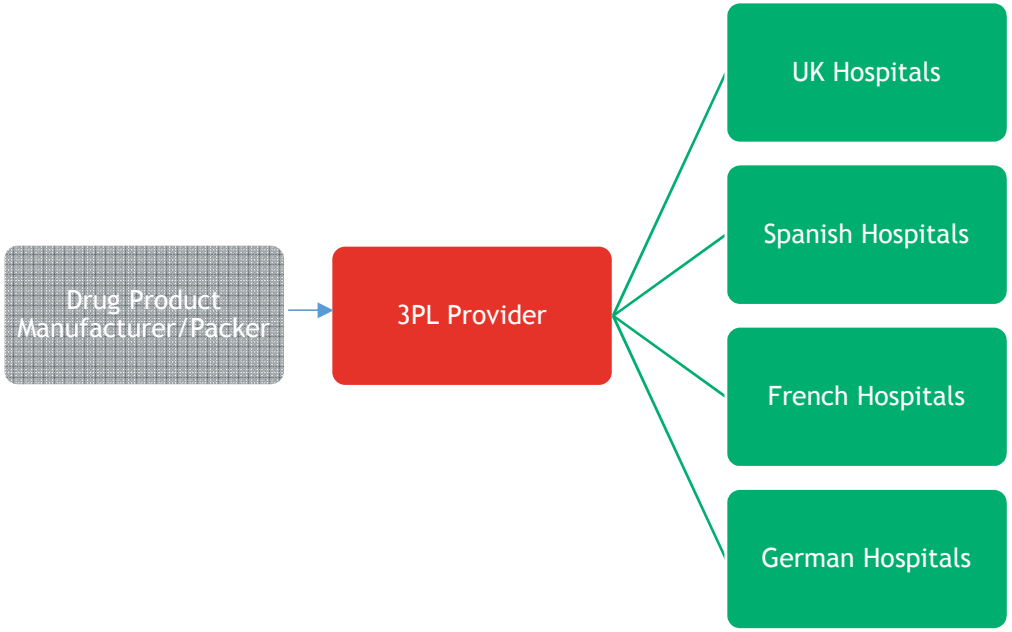
- Stock Holding
- Inventory Management
- Order Processing
- Invoicing

EU Supply Chain – Traditional Supply Chain



- Disadvantages for high value or orphan drugs
  - High stock holding & cash flow implications
  - Complex planning and contract management

EU Supply Chain – 3PL Supply Chain



- Advantages for high value or orphan drugs
  - Full supply chain management with one provider
  - One storage facility for stock

EU Supply Chain – Order Processing

- Utilising a 3PL supply chain there are 3 options for order placement:
  - Hospitals order direct with the 3PL provider
  - Hospitals order from Affiliates/Country Managers
  - Hospitals order through a central EU Sales Team

- Invoice management can be handled by:
  - 3PL Provider
  - Affiliates/Country Managers
  - EU Sales Team

GDP – Good Distribution Practice

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Good Distribution Practice (GDP)

- EU Guidelines (2013/C 343/01) on Good Distribution Practice of medicinal products for human use
  - Good Distribution Practice (GDP)

    "is that part of quality assurance which ensures that the quality of medicinal products is maintained throughout all stages of the supply chain, from the site of manufacture to the pharmacy or person authorised to supply medicinal products"

- USP 36 <1079> Good Storage and Distribution Practice for Drug products

Good Distribution Practice (GDP)

- Any person acting as a wholesale distributor has to hold a wholesale distribution authorisation and must comply with the principle of and guidelines for GDP

- Wholesale distribution of medicinal products is ***'all activities of procuring, holding, supplying or exporting medicinal products, apart from supplying medicinal products to the public'.***

  - **PROCURE** - Buy medicinal products
  - **HOLD** - Store medicinal products
  - **SUPPLY** - Sell medicinal products
  - **EXPORT** - Outside EEA (European Economic Area)

Good Distribution Practice (GDP)

EU Guidelines (2013/C 343/01) were published 5th November 2013

- Due to increasingly complex distribution networks the previous guidelines were inadequate

- Clarify the regulations so that the risk of counterfeit medicines entering the legal supply chain as well as any other negative impact of quality and integrity of the medicinal product, would be avoided.

Good Distribution Practice (GDP)

In the revised GDP regulation clear emphasis on the following items was introduced:

- **Quality Management** including Quality Risk Management (QRM)
- **Sufficient competent personnel** to carry out all the tasks for which the wholesale distributor is responsible
- **Adequate premises, installations and equipment** to ensure proper storage and distribution of medicinal products
- **Suitable documentation** that prevents errors from spoken communication
- **Qualification** of suppliers and customers – as well as brokers

Good Distribution Practice (GDP)

In the revised GDP regulation clear emphasis on the following items was introduced:

- Appropriate **management of complaints,** returns, suspected falsified medicinal products and recalls
- **Outsourced** activities correctly defined to avoid misunderstandings
- Specific rules for **transport** (in particular to protect medicinal products against breakage, adulteration and theft and to ensure that temperature conditions are maintained within acceptable limits during transport)
- Specific rules for **exporting**
- Specific rules for **brokers** (person involved in activities in relation to the sale or purchase of medicinal products)

Falsified Medicines Directive (FMD) 2011/62/EU

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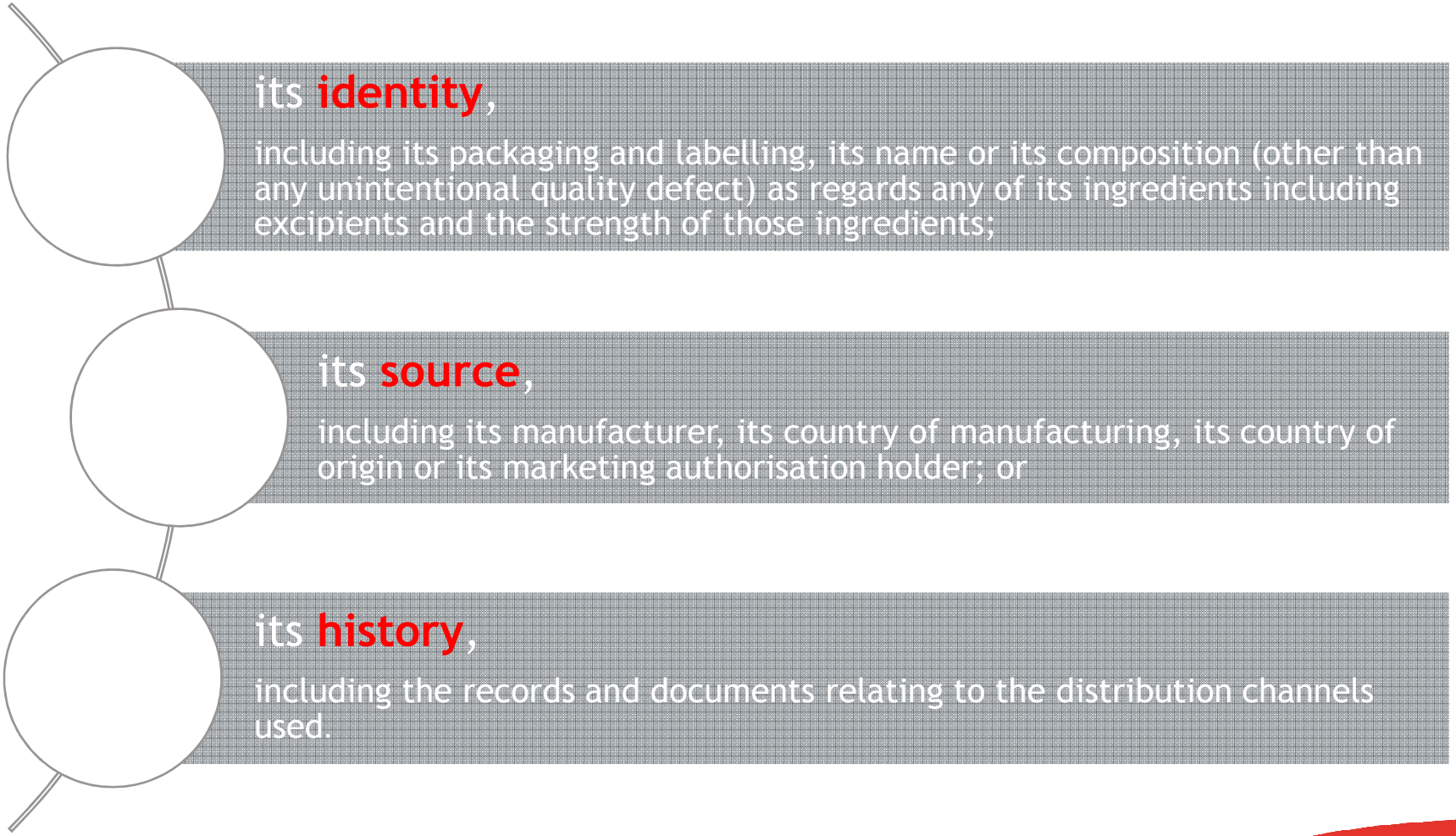
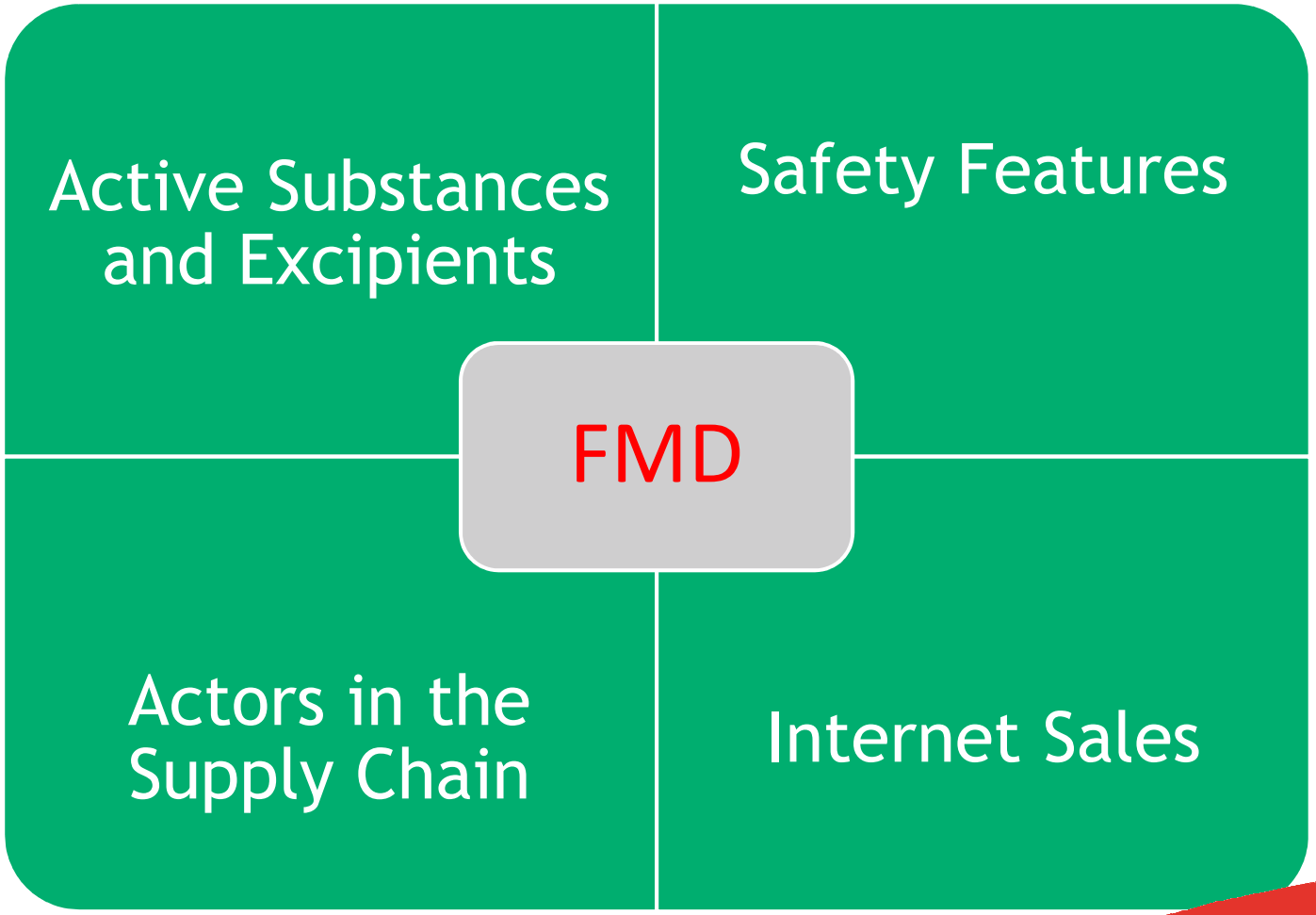
Falsified Medicines Directive

- Falsified Medicines Directive (FMD) 2011/62/EU published in 2011
  - US equivalent Drug Supply Chain Security Act (DSCSA)
- A ‘falsified medicinal product’ means any medicinal product with a false representation of:

Falsified Medicines Directive



Falsified Medicines Directive



Falsified Medicines Directive

MHRA provided the below example of counterfeit medicine within the EU wholesale supply chain.

- Suspected counterfeit batches of Herceptin were identified in Germany
  - Batch number of the primary and secondary packaging differed
  - The product was partially liquid although it was a lyophilised powder
  - Residue of product was on the outside of the vial
  - Some of the batch appeared to have been tampered with
- Further suspected counterfeit Herceptin was seized from UK wholesalers.
- All affected Herceptin batches had been procured from an Italian Wholesaler.
- Investigation in Italy suggested the Herceptin had been stolen from hospitals and refilled.

Falsified Medicines Directive

- As detailed in the Guidelines on Good Distribution Practise of Medicinal Products for Human Use (2013/C 343/01) Chapter 6.4:
  - 'Wholesale distributors must immediately inform the competent authority and the marketing authorisation holder of any medicinal products they identify as falsified or suspect to be falsified.
    - A procedure should be in place to this effect. It should be recorded with all the original details and investigated.
  - Any falsified medicinal products found in the supply chain should immediately be physically segregated and stored in a dedicated area away from other medicinal products.
    - All relevant activities in relation to such products should be documented and records retained.'

Supply Chain Qualification

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Supply Chain Qualification

Good Distribution Practice (2013/C 343/01)

- **GDP Chapter 9 - Transportation**
  - *'The required storage conditions for the medicinal products should be maintained during transportation within the defined limits as described by the manufacturers or on the outer packaging'*
  - *'Regardless of the mode of transport, it should be possible to demonstrate that the medicines have not been exposed to conditions that may compromise their quality and integrity. A risk-based approach should be utilised when planning transportation.'*

- **GDP Chapter 7 - Outsourced Activities**
  - *'Any activity covered by the GDP Guide that is outsourced should be clearly defined. There must be a written Contract between the Contract Giver and the Contract Acceptor which clearly establishes the duties of each party'*

Supply Chain Qualification

Almac utilise a two stage approach for supply chain qualifications

- Product Specific Risk Assessment
- Performance Qualification

Supply Chain Qualification – Risk Assessment

EMEA Guidelines on declaration of storage conditions

- This medicinal product does not require any special storage conditions
- Do not store above 30ºC/Store below 30ºC
- Do not store above 25ºC/Store below 25ºC
- Store in a refrigerator
- Store in a freezer

FDA Storage Temperature

- Controlled Room Temperature: 20ºC to 25ºC with allowable excursions between 15ºC and 30ºC
- Controlled Cold Temperature: 2ºC to 8ºC with allowable excursions between 0ºC and 15ºC

Supply Chain Qualification – Risk Assessment

Quality Critical Attributes

- Chemical stability
- Allowable temperature excursions
- Effect of moisture on the product
- Effect of light or X-Ray on the product

Product Configuration

- Primary, secondary & tertiary pack formats
- Typical shipment quantities
- Impact of vibration, altitude on the product

Supply Chain Qualification – Risk Assessment

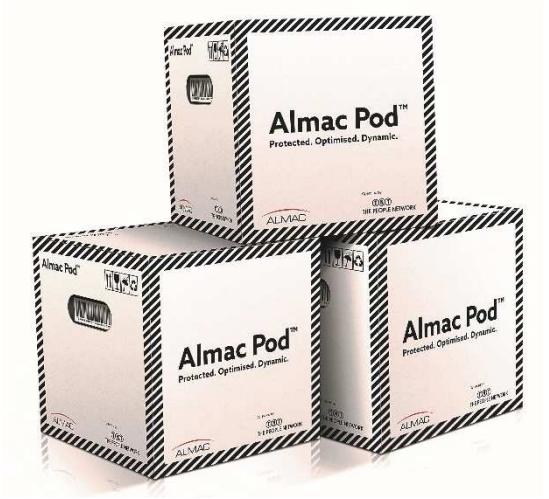
Physical Supply Chain

- Temperature conditions at origin, destination points, and throughout the complete route
- Seasonal temperatures (winter versus summer)
- Transport routes and modes
- Product handling at various transit points
- Import requirements at destination points
- Total duration of transit
- End Customer

Supply Chain Qualification – Risk Assessment

Temperature control in transit

- Passive Shipper range
- Active Shipper range



Temperature monitoring in transit

- Collect data about temperature sensitive products during transit
- Make more informed decisions if there are any delays during a shipment
- Select the appropriate temperature monitoring system
  - Alarm limits
  - Monitoring frequency
  - Position of monitors within shipment

Supply Chain Qualification – Risk Assessment

Selection of the correct transportation service provider

- **Freight companies (£)**
  - Road transport
  - Air & ocean freight
- **Express Couriers (££)**
  - Delivery to mainland Europe within 24hrs
  - 24 hour tracking facility
- **Premium Couriers (££££)**
  - Dedicated management of temperature sensitive shipments
  - Specialist handling for DG's and Controlled Substances
  - More suitable for difficult transit routes or customs clearance
  - 24 hour tracking facility & 24 hour customer service

Supply Chain Qualification – Risk Assessment

- Wholesale distribution of medicinal products is *'all activities of procuring, holding, supplying or exporting medicinal products, apart from supplying medicinal products to the public'.*
  - **HOLD - Store medicinal products**

- Storing medicinal products
  - Medicinal products are on site for a period of 36 hours or more
  - There is active refrigeration on site for the purpose of storing medicinal products
  - There is direct intervention with the shipment e.g. replenishing coolants

- Transport is defined as *'moving medicinal products between two locations without storing them for unjustified periods of time'*
  - Any activity covered by the GDP Guide that is outsourced should be clearly defined. There must be a written Contract between the Wholesale Distributor and the Transport provider which clearly establishes the duties of each party

Supply Chain Qualification – Performance Qualification

- Performance Qualification to qualify the supply chain to demonstrate it achieves the expected results.

- The Performance Qualification will typically:
  - include physical shipments of the product
    - utilise the minimum and maximum packout configurations
    - target the worst case destinations.

Supply Chain Qualification – Performance Qualification

The Performance Qualification enables you to challenge:

Documentation

Shipping System
Temperature control & Temperature monitoring

Pack-out
Robustness of packaging

Destinations
Customs clearance requirement

Transit Route
Number of steps in the transit route
Temperature extremes during transit

Time of Shipping
Winter & Summer configurations

Supply Chain Summary

- Select a Supply Chain Model
- Understand the Regulatory Requirements for your Supply Chain
- Qualify your Supply Chain

Thanks for Listening!