Pharmaceutical Supply Chain: Validation and Verification

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Outline

• What is meant by supply chain and supply chain management

• Risks in the supply chain and mitigating the risk
  – Where do the risks occur within the chain
  – Risk to the quality of the drug
  – Risk to the public
  – Mitigating the risks

• Regulatory references

• Verification of the Supply Chain
  – Plan the chain and define stakeholders
  – Know the risks and ensure appropriate actions are taken to mitigate them
  – Ensure GMP and Validation requirements of chain components are met

• Validation of the Supply Chain
  – Define the metrics and collect the data
  – Validate the chain

• The future
Supply Chain Management

Supply chain management (SCM) is the management of the flow of goods. It includes the movement and storage of raw materials, work-in-process inventory, and finished goods from point of origin to point of consumption.
Supply Chain Management

Supply Chain Management (SCM) is the integration and management of key business functions that promote the flow of products downstream from raw materials to the end consumer and the flow of information upstream from consumer to supplier.
Supply Chain Management: The Council of Supply Chain Management Professionals

"Supply Chain Management encompasses the planning and management of all activities involved in sourcing and procurement, conversion, and all logistics management activities. Importantly, it also includes coordination and collaboration with channel partners, which can be suppliers, intermediaries, third-party service providers, and customers. In essence, supply chain management integrates supply and demand management within and across companies.

Supply Chain Management is an integrating function with primary responsibility for linking major business functions and business processes within and across companies into a cohesive and high-performing business model. It includes all of the logistics management activities noted above, as well as manufacturing operations, and it drives coordination of processes and activities with and across marketing, sales, product design, finance and information technology."

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Drug Supply Chain Simplified Model
(Material Flow)

- Raw Materials/Intermediates
- Composite
- Pharmacies & mail order service
- API Manufacturing
- Finished
- Packaging
- Wholesaler
- GDP

* Transportation Step
@ Point of transmittal/Interface
(receiver responsible)

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Drug Supply Chain Simplified Model

(Information & Funds Flow)

Consumer & Physicians

Pharmacy

Wholesaler

GDP

Suppliers, Raw Material, intermediates, etc.

Drug Producer

Distributor

Funds, $

Information
Notes about the supply chain

• Final consumer/customer is an integral part of and drives the supply chain.
• Primary reason of the existence of any supply chain is to satisfy customer needs while generating profit for itself.
• Supply chains are dynamic and change all the time in response to customer demands and economic pressures among other reasons.
Notes about the supply chain

• Any and all of the steps shown can be done using contractors (i.e. these steps can be outsourced).

• Most supply chains are networks as opposed to being one point interface as suggested in the simplified model presented earlier.
Notes about the supply chain

• Supply chains have many stakeholders including in-house suppliers, external product suppliers, and external partners such as logistics managers, carriers, freight forwarders, airports, customs, warehouses, pharmacies, study coordinators, clinical investigators, depot managers, and others.
Notes about the supply chain

• Transportation steps as well as the transmittal/interface points offer opportunity of damage to the drug (both physical and to the quality), theft, introduction of expired, stolen, adulterated, counterfeit, and in general introduction of harmful drugs or components thereof into the chain.
Some of the Challenges facing a Global Supply Chain

• Drugs being made at far reaches of the world
• Inability to oversee all producers
• Language and cultural barriers
• Lengthy distances and hence time for shipping and receiving
• Uneven quality in transportation infrastructure (varied road quality, maintenance of vehicles, airports, etc.)
• Varied bureaucratic culture, rules, regulatory requirements and procedures
• Unplanned delays during transportation due to failures or weather related issues
• Unplanned delays in customs
Where do Problems Occur

Issues can occur anywhere within the chain:

• At compounder’s operation
• At contractor’s operation & facility
• At the points of transmittal (receiving and hand-off)
• During shipping and transportation
• While in storage
• At wholesaler
• At Pharmacy benefits manager
• At the pharmacy and on the shelves (OTC)
The Problems

- Contamination during transportation & storage, at compounders, etc.
- Production non-GMP compliant drug/intermediates by contractors
- Economically Motivated Adulteration (EMA) by contract producer
- Economically Motivated Adulteration (EMA) within the chain
  - Counterfeit drugs introduced in the chain
  - Adulterated drugs introduced in the chain
  - Rejected drugs introduced in the chain
  - Drugs being stolen during transport and storage
  - Stolen drugs being reintroduced into the chain
The Problems

• Drug suffering climate issues during transportation or storage
• Delivery of questionable drug or product
• Delayed, wrong, or non delivery causing drug shortages
• Deterioration of the drug due to lengthy dwelling in the supply chain
• Issues with contractors, suppliers, transporters, etc.
Regulatory References

- 21 CFR 210 & 211 requires manufacturers, processors, packagers, or holders of drug products to comply with GMP.
- Title VII of the Food and Drug Administration Safety and Innovation Act (FDASIA)-July 9, 2012 gives FDA authority to ensure the safety of the Pharmaceutical supply chain
- Drug Quality and Security Act (DQSA) – November 27, 2013 defines the requirements that entities in the supply chain must satisfy to ensure drug safety within the distribution chain.
Regulatory References

• Drug Supply Chain Security Act (DSCSA)
  – Title II of the Drug Quality and Security Act of 2013
  – Outlines critical steps to build an electronic, interoperable system to identify and trace certain prescription drugs as they are distributed in the United States.

• FDA Secure Supply Chain Pilot Program
  – Voluntary program, which enables qualified firms to expedite the importation of active pharmaceutical ingredients and finished drug products into the United States.
  – Program-The goal of the program is to enable FDA to focus its imports surveillance resources on preventing the entry of high-risk drugs that are the most likely to compromise the quality and safety of the U.S. drug supply.
  – Jointly administered by FDA’s Center for Drug Evaluation and Research (CDER) and Office of Regulatory Affairs (ORA).
Regulatory References

• Falsified Medicine Directive (EU) – 2011
  – How to certify GMP for 3rd world countries
  – GDP requirements

• EU GDP Regulations: Principle

• WHO GDP Guidance
FDASIA

Gives FDA the authority to:

• Collect and analyze data to make risk-informed decisions,
• Advance its risk-based approach to facility oversight
• Strengthen its partnerships with foreign regulators
• Drive safety and quality throughout the supply chain through strengthened tools.
DQSA

• Requires all entities to comply with GMP requirements
• Requires all entities to ensure that the drugs in the chain are not adulterated.
• Requires every transfer of ownership within the chain to provide documentation as to origin and previous owner.
• Prevents any entity from accepting transfer without such documentation.
• All entities involved must maintain such documentation for at least six years.
Adulterated Drug

• FDCA (passed by Congress in 1938) indicate:
  – Drug is adulterated if the manufacturing operation, the facility, and the controls used to produce it are not in conformance with CGMP to ensure the drug meets safety, identity, strength, quality, and purity characteristics
  – GMP includes implementation of quality oversight and control over the manufacturing of the drug
Adulterated Drug

• In addition, the following are adulterated drugs:
  – Contaminated drugs whether microbial or not
  – Drugs with reduced or no activity
  – Drugs that are altered due to exposure to adverse environmental condition (unintentional)
  – Drugs that are altered intentionally
  – What else?
Some Risks Associated with Supply Chain

• Steeling may cause drug shortages and unavailability of therapy for patients
• Adulterated and rejected drugs may cause harm to patients
• Drugs losing effectiveness due to lengthy storage or adverse storage conditions may cause harm to patients
• Counterfeit drugs in the chain have been shown to cause harm to the patient.
Some Risks Associated with Supply Chain

• Drug stability profile may dictate method of and time allowed for shipping
  – Half life
  – Effect of temperature
  – Effect of humidity

• Cost and sales volume of drug
  – Expensive drugs are more apt to be stolen
  – Drugs in high demand with large sales volume are more apt to be counterfeit
Some Risks Associated with Supply Chain

• Delivery Route
  – How long is the trip
  – What is the means of transportation to be used
  – What are the temperature extremes that maybe encountered and for how long
  – Will intermediate storage (including storage at customs) be required? For how long? and at what conditions? Are they secure?
  – Security along route and known problem spots
Some Risks Associated with Supply Chain

• Wholesaler
  – Storage security
  – Storage conditions
  – Systems to ensure no problems in distribution (Computerized systems)
  – Systems to ensure inventory control, and that no adulterated, counterfeit, or stolen drugs are introduced
Some Risks Associated with Supply Chain

• The package (Insulated, thermal bricks?, phase change material?)
  – Strength and ability to withstand handling
  – Insulation capability
  – Temperature maintenance capability
  – Leaking of dry ice
  – Qualification of packaging
Some Risks Associated with Supply Chain

• Shipping container
  – Insulation
  – Temperature control ability
  – Cleanliness
  – Security
  – Validation status of the container
How to Mitigate the Risks

• Insure GMP Compliance by all involved
• Insure all involved have a quality system in place
• Audit all of your subcontractors
• Plan transportation routes carefully
  – Carefully map the supply chain and identify all stakeholders
• Ensure computerized systems (for tracking, maintaining records, etc.) are part 11 compliant and validated.
• Recognize the signs (drugs in shortage, cheaper production routes, etc.)
How to Mitigate the Risks

• Good analytical techniques for products and intermediates and understand how your method can be duped.
• Global Positioning Systems (GPS) ability to recognize location of delays (RFID) combined with temperature and humidity data at the location.
• Ensure storage areas are secured (audit)
• Alarmed containers with good, secure, and tamper evident locking mechanisms
How to Mitigate the Risks

• Based on knowledge of product stability
  – Use of insulated packaging
  – Use of temperature monitoring at the container level – data loggers/transmitters/alarms
  – Use temperature monitoring at the package level - data loggers/transmitters/alarms
  – Real time transmittal of info via web access, email and smart phones
The Responsibilities

• Ultimate responsibility lies with license holder
• All entities involved in manufacture, processing, packaging, and holding must comply with GMP requirements. As such they are responsible to ensure drug products are not adulterated within the supply chain.
The Responsibilities

• Supplier, whole sale and distributor to protect drug against breakage, adulteration & theft

• Regardless of the mode of transportation demonstrate drug has not been exposed to conditions that may compromise its quality

• Use risk assessment of delivery routes to determine where temperature controls are required
Verification of the Supply Chain

1. Plan your supply chain and identify all of its stakeholders
   - Who are your raw material, intermediate, and final product supplier
   - Who will package the product
   - Who will transport the various materials
   - Who will store, sell and distribute your product

2. Define the risk associated with each step in the chain and prioritize as well as define the extent of the effort you must expend to secure each step.
Verification of the Supply Chain

3. Audit your manufacturers to confirm:
   - Quality – Product, systems, personnel
   - Technical – Capability of operation & personnel
   - Timing – Capacity and rates of production
   - Cost - Cost of goods
   - Reliability and financial stability

4. Audit your supply chain logistics suppliers:
   - Verify and audit your transporter
   - Verify, audit, and learn about the route
   - Audit transportation equipment or packages manufacturer, storage areas etc. for suitability, security and reliability of product
   - Expediters, agents, brokers, security service providers, and other logistics suppliers
Verification of the Supply Chain

5. Establish a Quality Agreement with your partners throughout the supply chain

6. Establish good communication systems

7. Use Digital technology to improve your supply chain visibility – Serialization (track & Trace)
   - know where your supply is at all times
   - Know if problems occur
   - Know about delays
   - Know about adverse conditions
Verification of the Supply Chain

8. Verify that your wholesaler is licensed
   – Do not use unlicensed wholesalers
   – Consult with FDA and the states

9. Ensure your logistics providers are licensed

10. Ensure all personnel involved in the supply chain, especially in the logistics portions, are well trained and understand their role in securing the chain
Verification of the Supply Chain

11. Confirm honesty and high business ethics of the stakeholders

12. Validate Supply Chain components and systems as appropriate and necessary

13. Cold Chain Validation (End-2-End Temperature Management)
Verification of the Supply Chain

14. Audit and test your supply chain prior to using it (validate it)
Tracking and Traceability

• Tracking and Traceability of the supply chain (Serialization) - as defined in DQSA
  – Recording transfers
  – Ensuring products in custody are legitimate and known at all times
  – Entities must report and not accept suspect drug products, components, intermediates, etc.
  – The entire chain of custody must be GMP compliant and “certified” as such
  – Serial numbers to be assigned by manufacturer to the smallest possible unit and records maintained
Serialization Model
Track & Trace

Manufacturer assigns serial no.

Wholesaler receives drug

Distributor

Pharmacy

Patient

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GMP Aspects of Supply Chain

• Good documentation and communication
• Secure and proper storage of materials
• Validation of storage facilities and conditions
• Validation of shipping methods and conditions.
• Validation of packages and containers
GMP Aspects of Supply Chain

• Test incoming material. Make sure the methods are validated and specific to the material being tested.
• Audit your contractors and use quality agreements to define responsibilities.
• Know your supplier and insist on them providing the pedigree of their supply.
• Validate and secure your storage facilities.
GMP Aspects of Supply Chain

- **Validate** and Secure transport equipment
- Know and qualify your shippers.
- Plan long transport requirements so as not to delay in unsuitable conditions?
- Track and monitor your product throughout?
- Be alert to complaints.
Validation Requirements in Your Supply Chain

- Validation of all the manufacturing processes used in the chain
- Validation of transport packaging
- Validation of tests
- Validation of transport equipment
- Validation of storage facilities
- Validation of the computerized systems necessary for tracking and tracing of product
Good Distribution Practice (GDP) - EU

• Wholesale distributors must maintain a quality system setting out responsibilities, processes, and risk management principles in relation to their activities.

• The quality system is the responsibility of the organization's management and requires their leadership and active participation and should be supported by staff commitment.
Good Distribution Practice (GDP) - EU

• All activities should be clearly defined and systematically reviewed
• All critical steps of distribution processes and significant changes should be justified and where relevant validated
Validation of Supply Chain
Validation of Supply Chain

• Define the metrics — What you will test against
  – On time delivery and availability to the patient
  – Delivery of quality product to the patient
  – Undamaged and clean packaging reaching patient
  – Delivery of product at appropriate price
  – Meeting patient demands, requirements and needs
  – What else?
Validation of Supply Chain

• Define the data to measure
  – Satisfaction level of patient (happy about the appearance, quality, timing, meeting their needs, etc.)
  – Timing at various points within the chain
  – Environmental conditions at the various points within the chain
  – Storage security and quality related data (warehouse break-ins, storage rodent/pest control data, etc.)
  – Inventory data within the chain and backorder levels
  – Pricing data at the various points within the chain
  – Information about your supply chain partners (references, complaints, regulatory actions, etc.)
Validation of Supply Chain

• Confirm/Validate that the metrics are met by the supply chain
  – Confirm drug delivered to patient is of appropriate quality, safety, and efficacy
  – Confirm meeting patient needs and requirements
  – Confirm the whereabouts of the product at all times
  – Confirm the appropriateness of the timing and residence time at the various points
  – Confirm the acceptability of environmental conditions throughout the chain as well as rodent and pest control
  – Confirm appropriate inventory at various distribution points-No shortages occur due to delays, theft, adulteration, etc.
Validation of Supply Chain

• Confirm/Validate that the metrics are met by the supply chain
  – Information flow from patient to you (all stakeholders having appropriate communication channels)
  – Confirm price is maintained
  – Confirm stakeholders are committed to the security of the supply chain
  – Confirm suppliers are honest, ethical, have good references, no regulatory actions pending, etc.
The Future: Some Thoughts

• The supply chain to change from stock-based to order-based.
• Most likely will bypass wholesaler and ship direct to consumer or pharmacist.
• Drug pedigree to be well known at all time
The future:
Regulatory Requirements

• All drugs to have a unique identifier (National Drug Code – NDC) by the end of 2017
• All wholesalers, distributors and dispensers to only trade products that have the NDC by the end of 2019
• By the end of 2023 all drugs will have an electronic interoperable system to track drugs at the individual package level. (monitoring)
Entities Governed

• Manufacturers
• Dispensers
• Packagers and re-packagers
• Distributors
• Third party logistics providers
Requirements

• Require an entity to provide documentation to the regulator within 24 hours in case of investigational request.

• Quarantine suspect products; investigate illegitimate products; have a numerical identifier at the package level (for manufacturers).
Requirements

• Entities not to accept products without numerical identifier, which are deemed misbranded.

• If product determined to be illegitimate must 1) quarantine product; 2) remove from distribution chain; 3) assist partners in removing from chain; 4) retain samples to aide investigations; 5) notify authorities and trading partners within 24 hours.
Requirements

• Most of these requirements also apply to third party logistics providers. Such organization must be licensed by regulators

• Third party logistics providers:
  – To have state licensed facilities
  – If state does not have license requirements, then regulator must license
  – To provide annual reports to regulators
Summary

- Pharmaceutical supply chain poses a great risk to the quality of the drug and hence to the patient
- Governments, and regulators have become concerned and issued laws and guidance to help reduce the risks associated with the supply chain
- The greatest risk to drug quality occurs during transport, storage, and hand-off
- Transparency of the supply chain is the most important tool to mitigate the risks associated with it.
- Planning your route, knowing the risks associated with it is and knowing your stakeholders is a must for protecting your drug
- Knowing the proper metrics and collecting the right data are essential requirements to validate your supply chain