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Supplier Assurance Program



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Introduction

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Module Topics

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Current Regulatory Expectations

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Some Important Definitions

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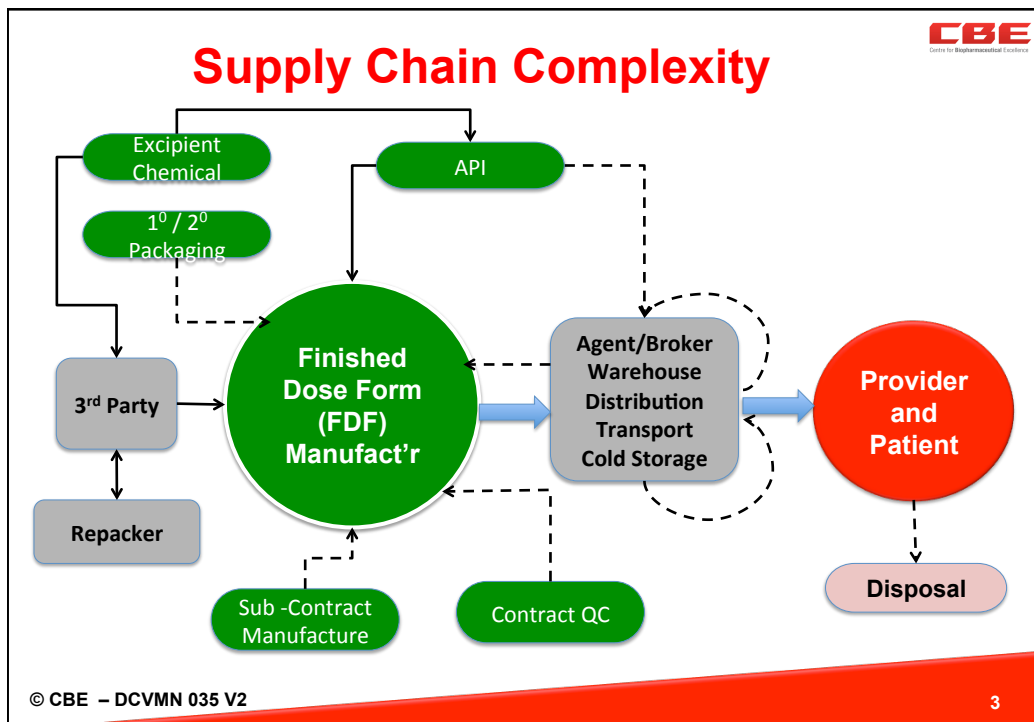
Risk Management Process

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Examples and modified FMEA

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Introduction



Starting Material Specifications and Receipt – 4.14, 4.23, 4.29

- 4.14 Specifications for starting and primary or printed packaging materials should include or provide reference to the approved suppliers and, if reasonable, the original producer of the material.
- 4.23 The records of the receipts should include Date of receipt and **supplier's** name and **manufacturer's** name;
- 4.29 There should be written policies, procedures, protocols, reports and the associated records of actions taken or conclusions reached for supplier audits

PICs and Starting Materials Controls

- 5.26. Starting materials should only be purchased from approved suppliers named in the relevant specification;
- 5.27. For each delivery, the containers should be checked for integrity of packaging and seal and for correspondence between the delivery note and the supplier's labels.

Why is the Supply Chain a challenge ?

- Diethylene glycol/glycerin excipient substitution
- Melamine in milk products
- Contaminated Heparin (over 80 deaths). OSCS issue re-surfaced in Ireland in 2009
- Contaminated paint in toys / pet food
- Asbestos in talc powder – Sth Korea 1200 products recalled
- Paracetamol tainted with Diethyl Glycol kills 25 children in Bangladesh
- Rampant counterfeiting occurring in distribution chain
- **Significant API and excipients substitution problems – Economically Motivated Contamination (EMC)**

This presentation will:

- Present the dimensions for supply chain risk assessment
- Provide classifications based on ICH Q9 / PICs Annex 20 quality risk management.
- Explain the risk categories for suppliers
- Present alternative risk mitigation options

PICs – Annex 20 Summary

- *“It is commonly understood that risk is defined as the combination of the probability of occurrence of harm and the severity of that harm.”*
- *“However, achieving a shared understanding of the application of risk management among diverse stakeholders is difficult because each stakeholder might perceive different potential harms, place a different probability on each harm occurring and attribute different severities to each harm.”*
- Suppliers are removed from patients so risk is likely to be viewed in terms of market or \$ loss, not patient consequences.

PICs – Annex 20 – Appendix II Application to Materials Management

11.5 Assessment and evaluation of suppliers and contract manufacturers.

- To provide a comprehensive evaluation of suppliers and contract manufacturers (e.g., auditing, supplier quality agreements).
- **Starting material:** To assess differences and possible quality risks associated with variability in starting materials (e.g., age, route of synthesis).
- **Storage, logistics and distribution conditions**
 - To assess the adequacy of arrangements to ensure maintenance of appropriate storage and transport conditions (e.g., temperature, humidity, container design)
 - To determine the effect on product quality of discrepancies in storage or transport conditions (e.g. cold chain management)

Control Strategies for Supply Chain

- Rigorous incoming sampling programs
- 100% identity testing common
- Focus on cGMP based Supplier Assurance programs
- GMPs for excipients mooted and being legislated
- FDA moved into China and India
- API barrier imports from non-regulated countries – evidence of a Q7 GMP Certificate
- QPs required to either audit or have a 3rd party audit of API supply into EU
- TGA license Rx API manufacturers – co-operative audits with EU and FDA

Selecting and evaluating a supplier

- Initiate with a change control
- Risk profile and assessment (more later)
- Documented evaluation of supplier profile (more later)

Recommended:

Representative samples (e.g. from 3 different batches) may be requested from the supplier and tested as part of the evaluation of a new supplier.

Approval of the supplier should not continue if the starting material does not meet specifications.

Considerations for Selecting and Evaluating a Supplier

- any relevant audits/inspections conducted in the last 3 years and available reports, responses and close-out;
- Drug Master File – submitted to a Regulatory Agency
- current cGMP certificates, if applicable;
- third party certificates (e.g. ISO 9001, etc.);
- any technical information, such as information received from Regulatory Affairs in the API

Considerations for Selecting and Evaluating a Supplier

- GMP agreement, if available;
- Site Master File, if available;
- Any testing history for related starting materials from the supplier already delivered on site;
- Any testing results provided by the potential supplier; and
- Changes, deviations or investigations communicated by the supplier.

Participants in Supplier Risk Analysis

This group should include:

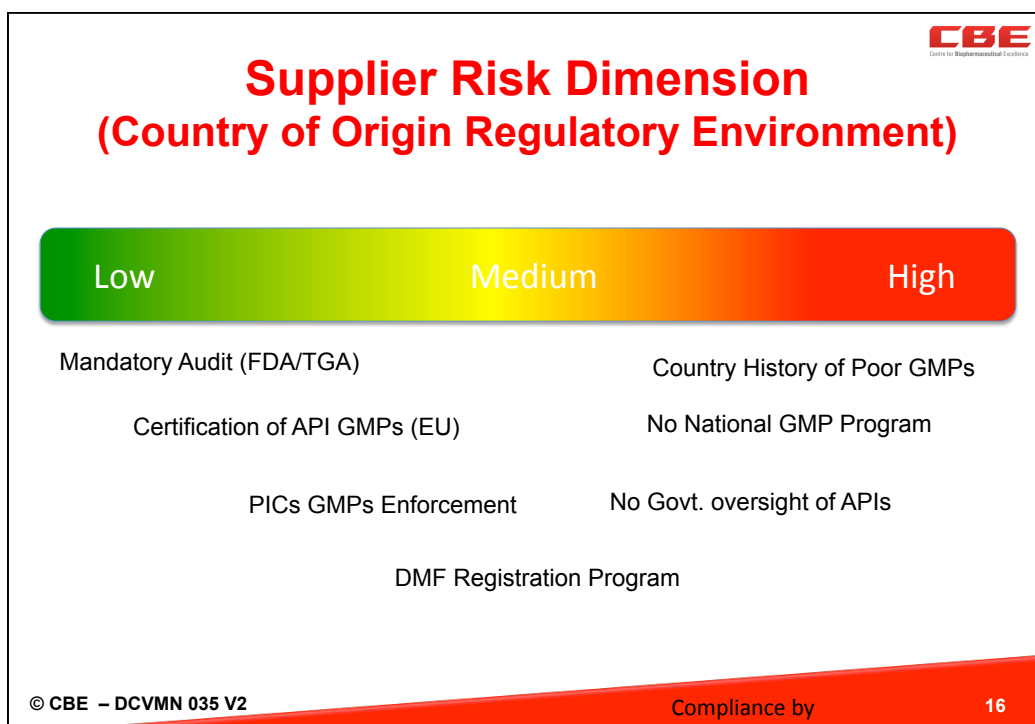
- Quality Assurance – to provide “SQulPP” related risks
- Purchasing Management – to provide profiles on supply chain
- Laboratory Management – to provide history on testing
- Independent facilitator(s) – to make sure all issues are raised
- Where possible API manufacturers
- Typically should focus on different supply chains separately e.g APIs by manufacturer, excipients, printed matter and components.

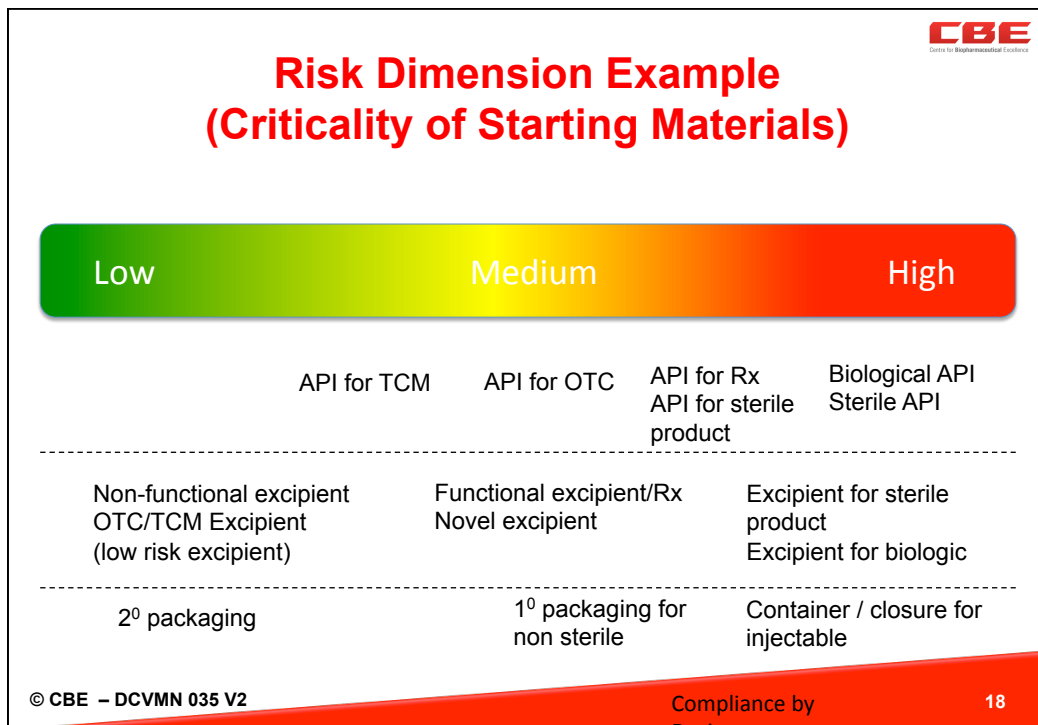
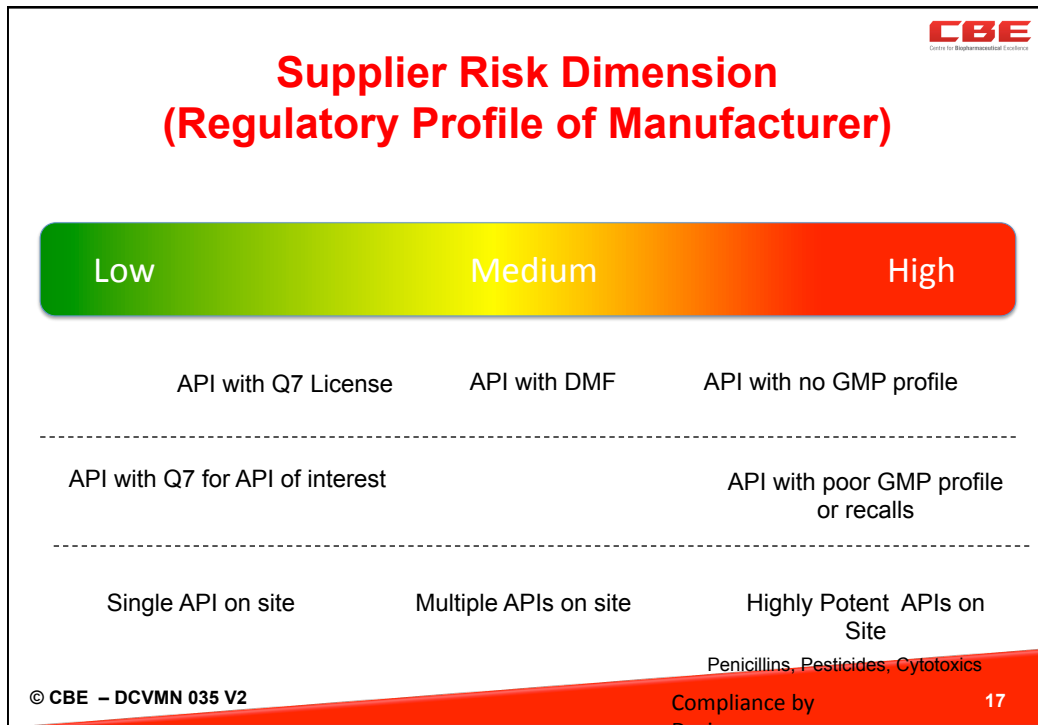
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Supplier Risk Classification

Category	Examples of Suppliers
1. Highest Risk	<ul style="list-style-type: none"> Manufacturers of APIs and excipients used in sterile preparations, or with known stability issues. Manufacturers of APIs in a country with poor or unknown GMP regulation. Brokers, distributors or agents where the supply chain from the manufacturer is complex, not fully known, or there is an increased possibility of counterfeit.
2 Moderate Risk	<ul style="list-style-type: none"> Manufacturers of APIs and excipients used in non-sterile pharmaceutical products. Brokers, distributors or agents handling APIs requiring cold chain management.
3. Low Risk	Manufacturers of excipients produced at a dedicated site (e.g. sugar).

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EU Recommendations for Risk Profiling – Criticality Considerations

- Transmissible Spongiform Encephalopathy (TSE potential)
- Potential for viral contamination
- Potential for microbiological or endotoxin contamination
- Potential, in general, for any impurity originating from the raw materials (e.g. aflatoxins, pesticides) or generated as part of the process and carried over (e.g. residual solvents, impurities and catalysts)
- Sterility assurance (for excipients claimed to be sterile)
- Use of dedicated or common equipment and/or facilities
- Environmental control and storage conditions

For functional excipients should also consider:

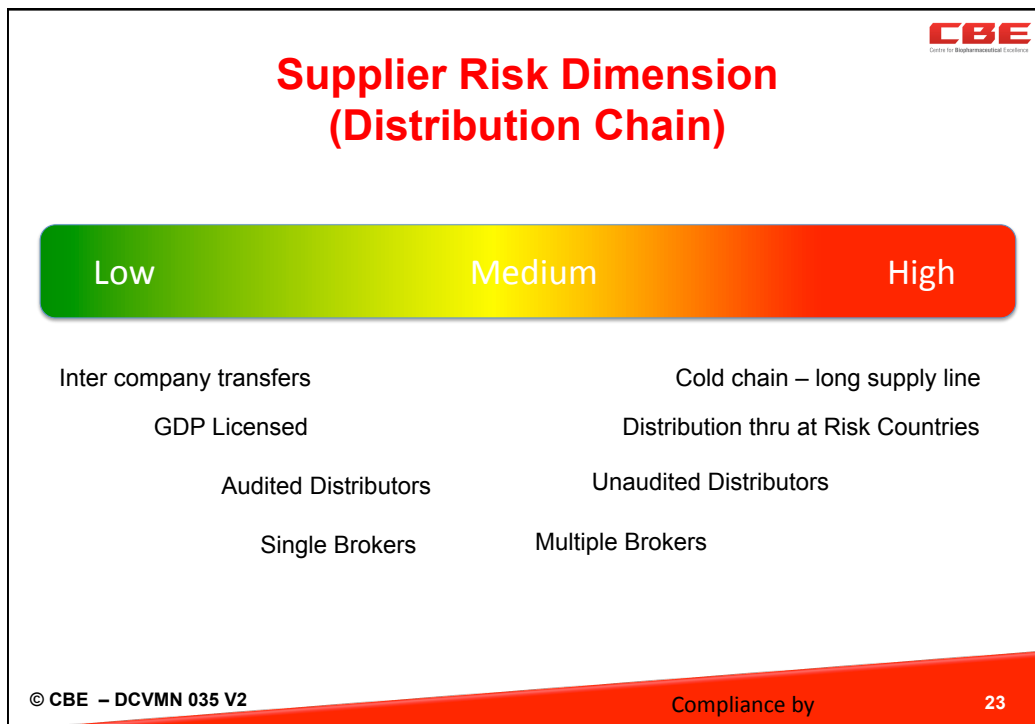
- The pharmaceutical form and use of the medicinal product containing the excipient (e.g. ointment product, injection/infusion etc.)
- The function of the excipient in the formulation (e.g. lubricant in a tablet product or preservative material in a liquid formulation etc.)
- The quantity used of the excipient for the manufacture of medicinal products
- Daily patient intake of the excipient
- Any known quality defects both globally and at a local company level related to the excipient;
- Whether the excipient is a composite
- Potential impact on the Critical Quality Attributes of the medicinal product

Proposed Response to Excipient Risk Profile

- A gap analysis of the required GMP against the activities and capabilities of the excipient manufacturer should then be performed.
- Data/evidence to support this should be obtained through audit or from information received from the excipient manufacturer.
- Quality system certification or accreditation held by the excipient manufacturer and the standards against which this has been granted should be considered as this may meet the required Good Manufacturing Practices.

Excipient Risk - Proposed Monitoring Expectations

- Number of defects on received batches of excipients
- Type/severity of defects on excipients
- Loss of relevant quality system accreditation by excipient manufacturer
- Observation of trends in drug product quality attributes (this will depend on the nature and role of excipient)
- Audit (re-audit) of excipient manufacturer.



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Considerations for Supplier Quality History (Probability)

- **Good Quality History**
 - Supplier audit : No critical and/ or < 3 majors
 - < 2 minor OOSs/ deviations in the last 10 lots received,
 - no OOSs relating to assay, efficacy, purity and safety in the last 10 lots
 - No material variability observed in qualification testing
- **Acceptable Quality History**
 - Supplier audit : ≥ 1 Critical and/ or ≥ 3 Majors
 - ≥ 3 minor OOSs/ deviations in the last 10 lots received, and/ or
 - ≥ 1 relating to assay, efficacy, purity and safety in the last 12 months
 - Material variability observed in qualification testing
- **Low Quality** – move away ASAP OR intensive testing

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Simplified Supply Chain Risk Factors

Patient/Product Risk Factor

Supplier Quality History

Supplier Profile and Rating

- 5. Parenteral/ Sterile / Biotech
- 4. Rx / prescription product
- 3. OTC
- 2. Complementary
- 1. Excipient (???)

- 5. Known poor quality
- 4. Unknown history / new vendor
- 3. Known quality – OK
- 2. >10 batches, all OK
- 1. Long good supply history

- 5. No site assessment
- 4. No International GMP licenses
- 3. International GMP audits
- 2. QA reviewed and approved
- 1. QA supplier audited >1 cycle - passed

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Supplier Risk Rating vs Auditing

		History x Profile (Probability)				
		1 - 6	7 - 10	11 - 16	17 - 21	22 - 25
Patient Risk / Severity	5	High	High	High	High	High
	4	Low	Moderate	High	High	High
	3	Low	Moderate	Moderate	Moderate	Moderate
	2	Low	Low	Low	Moderate	Moderate
	1	Low	Low	Low	Low	Low

High

Site Audit

Moderate

Monitor

Low

Survey

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Some Important Views on Risk Assessment

- Risk assessments are just tools to aid us – we should always check our reality
- Consequences can readily be hypothesised
- Probability estimate is often driven by our “degree of belief” rather than a mathematical table or formula.
- **Our “opinions or degrees of belief” about risk do matter, provided we are practical and have knowledge.**

Risk Mitigation and GMPs

- QA oversight as part of logistics team
- Understand/study the supply chain and players
- View site audit as an investment not a cost
 - *“A picture is worth 1000 words”*
- All new materials and changes to existing materials must be assessed and approved via the change control
- Review / Reassess Risk Profiles
 - Periodically / Annually
 - In response to significant events
- Link incoming QC program to risk profile
 - Utilise reduced, normal and tightened strategy
- Apply targeted sampling not random sampling

QA Oversight Responsibility

- Maintain register of all GMP related materials
- Work in tandem with logistics/purchasing
- Organise and review supplier surveys
- Approve risk profiles and updates of profiles
- Approve final status of suppliers
- Monitor supplier quality history
- Organise audit schedules based on risk
- Participate in audits / or approve 3rd parties
- Evaluate audit outcomes and resolve CAPAs
- Oversee “switching” of incoming QC test/ sample plans
- Approve specifications

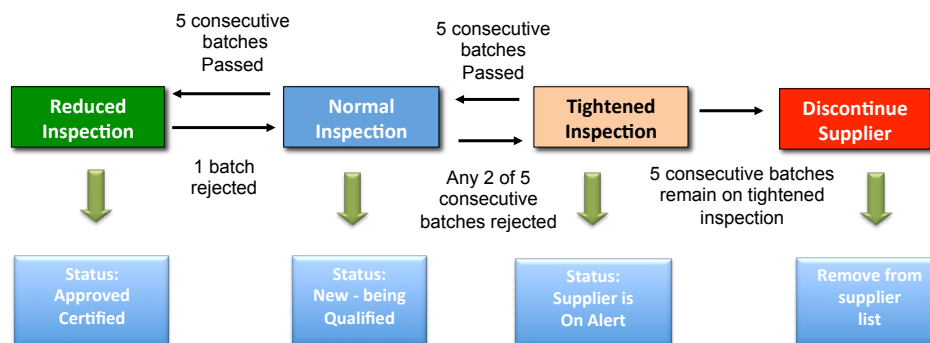
Quality Control / Monitoring of Suppliers

- The risk classification determines the minimum requirements for sampling and testing of incoming material.
- This sampling plan is reflected in the specification
- Sampling plan should be targeted
- Apply switching rules to incoming QC

Inward Goods QC and “Switching” Rules for Sampling



Some supplier control plans call for “switching” between sampling levels depending on the recent supply history. Levels can be **Normal**, **Tightened** or **Reduced** inspection.



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Mitigations of Supply Chain Counterfeiting Proposal EU



- **Track and Trace by Unique Identifier:** A unique identifier will be placed in a 2D barcode containing manufacturer code, a serialisation number, a national reimbursement number (if present), the batch number and the expiry date.
- **Medicine authenticity:** guaranteed by an end-to-end verification system supplemented by risk-based verifications by wholesale distributors. Medicines will be systematically verified before being dispensed to patients.
- **Wholesaler Checks:** Medicines at higher risk of falsification will be additionally checked at wholesaler level. Proposed obligation of verification
 - When the medicinal product is not obtained from the holder of the manufacturing authorisation or the marketing authorisation holder;
 - when products are returned by another wholesaler or a pharmacy.
- **EDQM (European Directorate for the Quality of Medicines and HealthCare)** launched a new database for counterfeit medicines

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Mitigations of Supply Chain Counterfeiting Proposal FDA



- "Drug Quality and Security" introduced Nov 2013.
- Authority to the FDA to build a system for the traceability of medicinal products (supply chain integrity).
- This traceability system should include all information down to the package level.
- unified standard - electronic system over a 10-year period ensuring the traceability of each single medicinal product all over the country.
- Serialisation of all medicinal products is planned.

- **USP developing an updated standard for GDP <1083>** to address material flow beginning with initial procurement and continuing throughout the supply chain to delivery to the end user. They apply to APIs, excipients, as well as to medicinal products and medical devices

- Reference: "[Drug Supply Chain Security Act \(DSCSA\) Implementation Plan](#)".



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