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DATA INTEGRITY IN THE SUPPLY CHAIN

10th NOVEMBER, 2017

Data Integrity: Reliability, Quality and Competitivness Factors of API Manufacturers

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WORKSHOP

10th NOVEMBER, 2017

DATA INTEGRITY	The extent to which all data are complete, consistent and accurate throughout the data life cycle
LIFE CYCLE	The data life cycle covers data generation, processing, reporting, archival, retrieval and destruction

Guideline Data Integrity

EUDRALEX	GMP Vol. 4 Part II Par. 5.4 Computerized System GMP Vol. 4 Part II Cap. 6 Documentation and Records Vol. 4 Annex 11 Computerized System
FDA	21 CFR part 11

MHRA GMP Data Integrity Definitions and Guidance for Industry March 2015

Data Integrity Trend

The role of data integrity must be assessed within the management and control of the production chain from the starting material to the finished product

Supply chain for pharmaceutical products commercialized in US and Europe covers different areas.

Starting material , intermediate and often API are supplied mainly from China India and other markets

FDA Data Integrity Focus

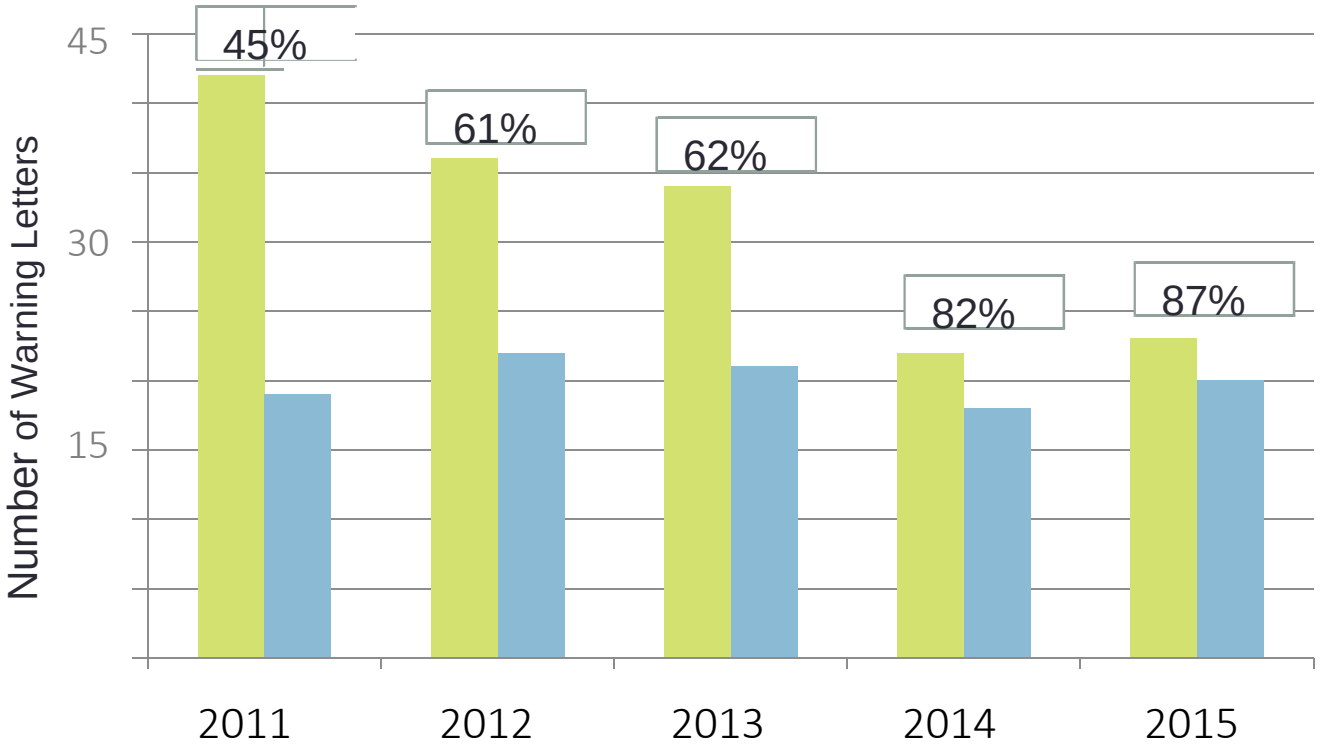
- most of pharmaceutical manufacturing activities to apply GMP was aimed at U.S. facilities. enforcement focus is now on pharmaceutical manufacturing facilities outside the United States

- Analysis of Warning Letters issued to pharmaceutical manufacturers relating to manufacturing issues shows:

  25 Warning Letters were issued in 12 months ending May 31, 2016.

  - ✓ 2 of those letters were issued for facilities in the United States
  - ✓ 16 of the letters reporting deviation of data integrity or deficient systems designed to protect data integrity.

WLs for Foreign Inspections (2011-15)

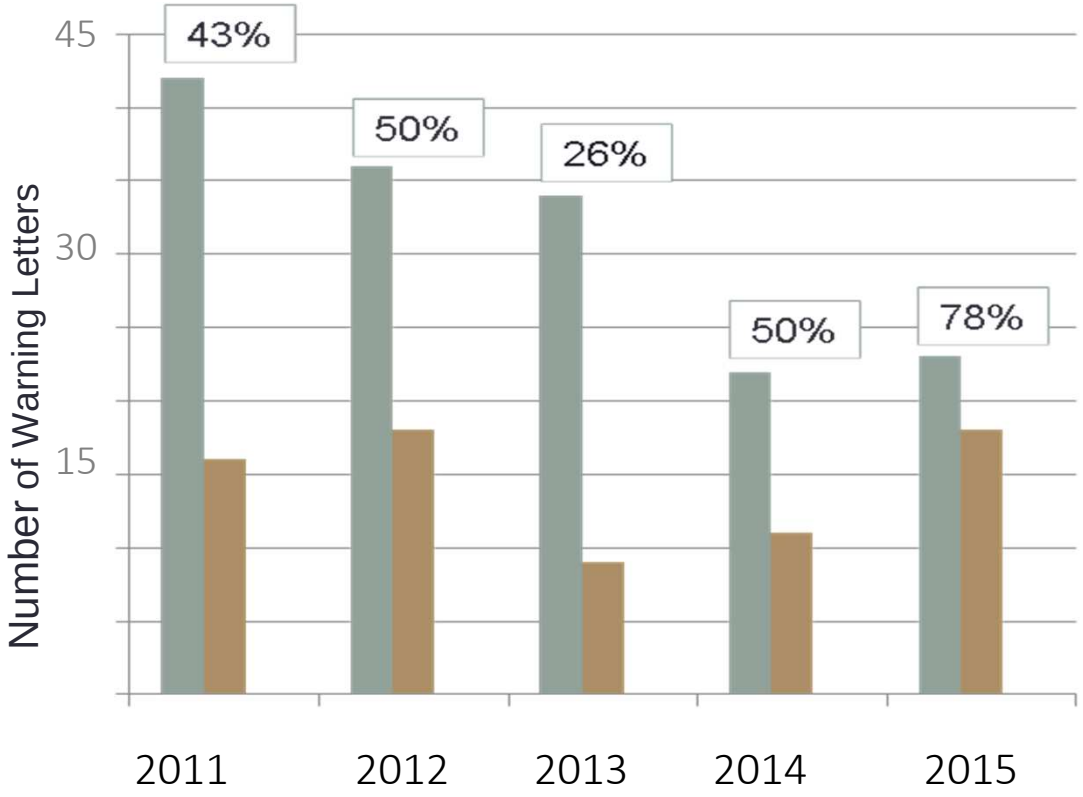


Total CDER cGMP Warning Letters (Worldwide)

CDER cGMP Warning Letters Result of extra US Inspection

Hyman, Phelps & McNamara PC
June 22, 2016

Data Integrity Issues



Total CDER cGMP Warning Letters (Worldwide)

CDER cGMP Warning Letters (Worldwide) Citing Data Integrity Issues

Hyman, Phelps & McNamara PC
June 22, 2016

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Data Integrity Findings in Warning Letters

- ✓ Failed analytic results that were hidden
- ✓ The firm routinely retested samples without justification (testing products into compliance) and/or deleting original results
- ✓ Altered time/date settings
- ✓ Analyses re-integrated to achieve passing results
- ✓ Completed batch records days after operations ended
- ✓ ”Off-book” CGMP analysis
- ✓ “Fabricated impurity data
- ✓ Disabling system audit trails

by Paula Katz, Director of Manufacturing Quality Guidance and Policy Staff in CDER Office of Compliance, to Parenteral Drug Association (March 16, 2016)

Guideline Supply chain

EUDRALEX Vol. 4 Part II par 16	Contract manufacturers
EMA/196292/2014	Guidance for the Template for the qualified person's declaration concerning GMP compliance of active substance manufacture «the QP declaration template»
EMA/CHMP/BWP/429241/2013	Guideline on the use of starting materials and intermediates collected from different sources in the manufacturing of non-recombinant biological medicinal products
FDA	Contract Manufacturing Arrangements for Drugs: Quality Agreements Guidance for Industry (November 2016)

Suppliers

- Selection of the supplier
- Detailed agreement defining expectations
- Audit, to maintain and verify evaluation of quality system

Selection of the suppliers

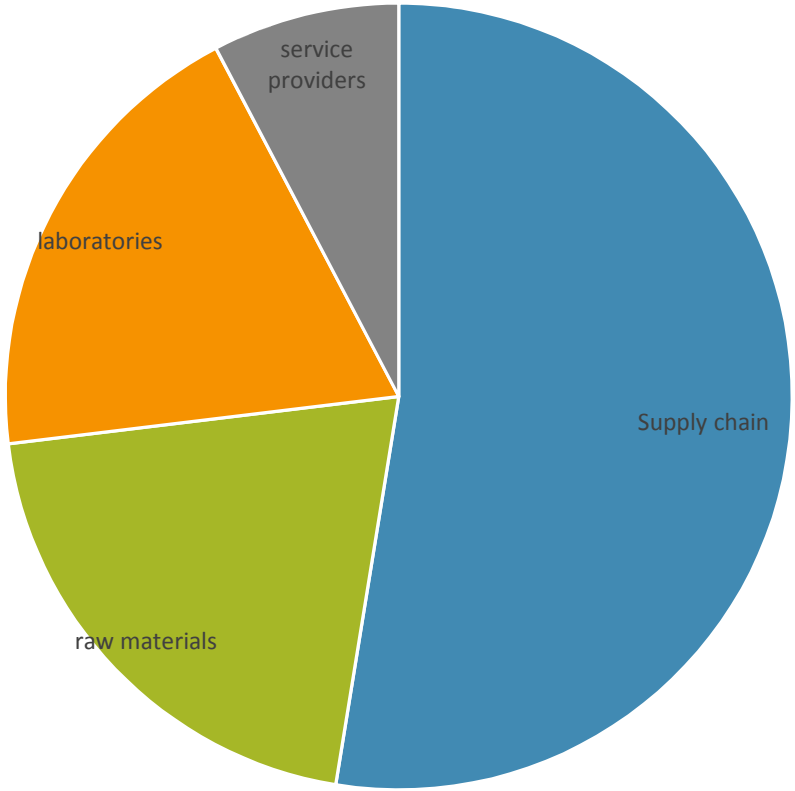
Supply chain

Manufacturers of Starting Materials
Manufacturers of Intermediate
Manufacturers of API
Manufacturers of drug product

Manufacturers of raw material

Distributors
Laboratories
Service providers

Risk evaluation



Supply Chain Quality Agreement

Eudralex Vol. 4 Part II par 16 Contract manufacturers

- ✓ All manufacturers should comply with GMP, preventing cross contamination and maintaining traceability
- ✓ Contract manufacturers should be evaluated by contract giver to ensure GMP
- ✓ Contract and agreement defining responsibilities
- ✓ The contract should permit the Audit activity
- ✓ Subcontracting has to be authorized
- ✓ Manufacturing records should be kept where the activity occur
- ✓ Changes should be made after approval

Quality Agreement

Quality Agreement defines expectations and responsibilities in a contract manufacturing arrangement

- a comprehensive written document that defines responsibilities of the Quality Units of each party. Each party is responsible for ensuring compliance
- detailed description of the materials, services , quality specifications, and communication mechanisms between the owner and contract facility.
- define documentation expectation, describe role in making and maintaining original documents, defining the life cycle of data

Clarify roles and responsibilities improves efficiency and oversight of outsourced manufacturing operations and relationships between parties

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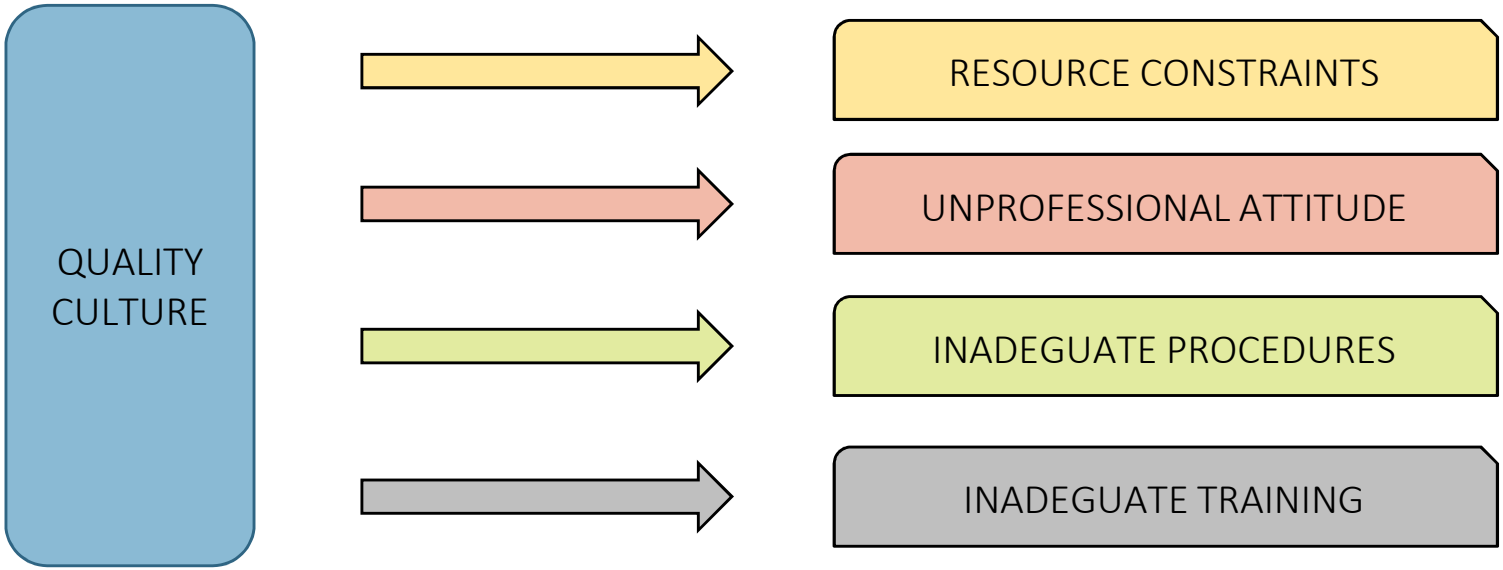
Audit

During an audit you may detect a poor quality culture that often brings to data integrity issues

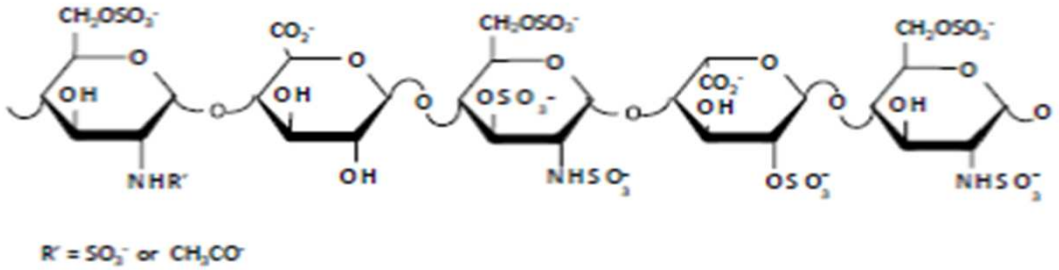


Audit

All documentation produced in any form should answer the A.L.C.O.A. requirements

GOOD DOCUMENTATION PRACTICE

Heparin



- Heparin is a heterogeneous mixture of highly sulfated glycosaminoglycan (GAG) molecules.
- Biological origin

Heparin

In 2008 after an extensive analysis, the presence of a contaminant has been identified in Heparin coming from Cina

Pharmeuropa Vol 23 jan 2011, **Heparins and Changing Regulatory Requirements in the EU**
This document underlines a clear lack of control of the heparin manufacturing process.

- Many parties are involved in DS manufacturing such as:
  - slaughterhouses,
  - casing and/or crude heparin workshops,
  - Crude heparin consolidators,
  - brokers and the drug substance manufacturer itself

  The supply of heparin

Heparin

- use of unauthorised sources and unapproved suppliers for heparin intermediates
- inspection revealed the existence of 'show factories' and 'shadow factories'
- inconsistent quality of documentation and forged documents

- Describes control measures for materials through the manufacturing chain
- Clarification on the status of heparins as 'biological medicinal product
- presents for the information to be provided on in their marketing authorisation dossiers

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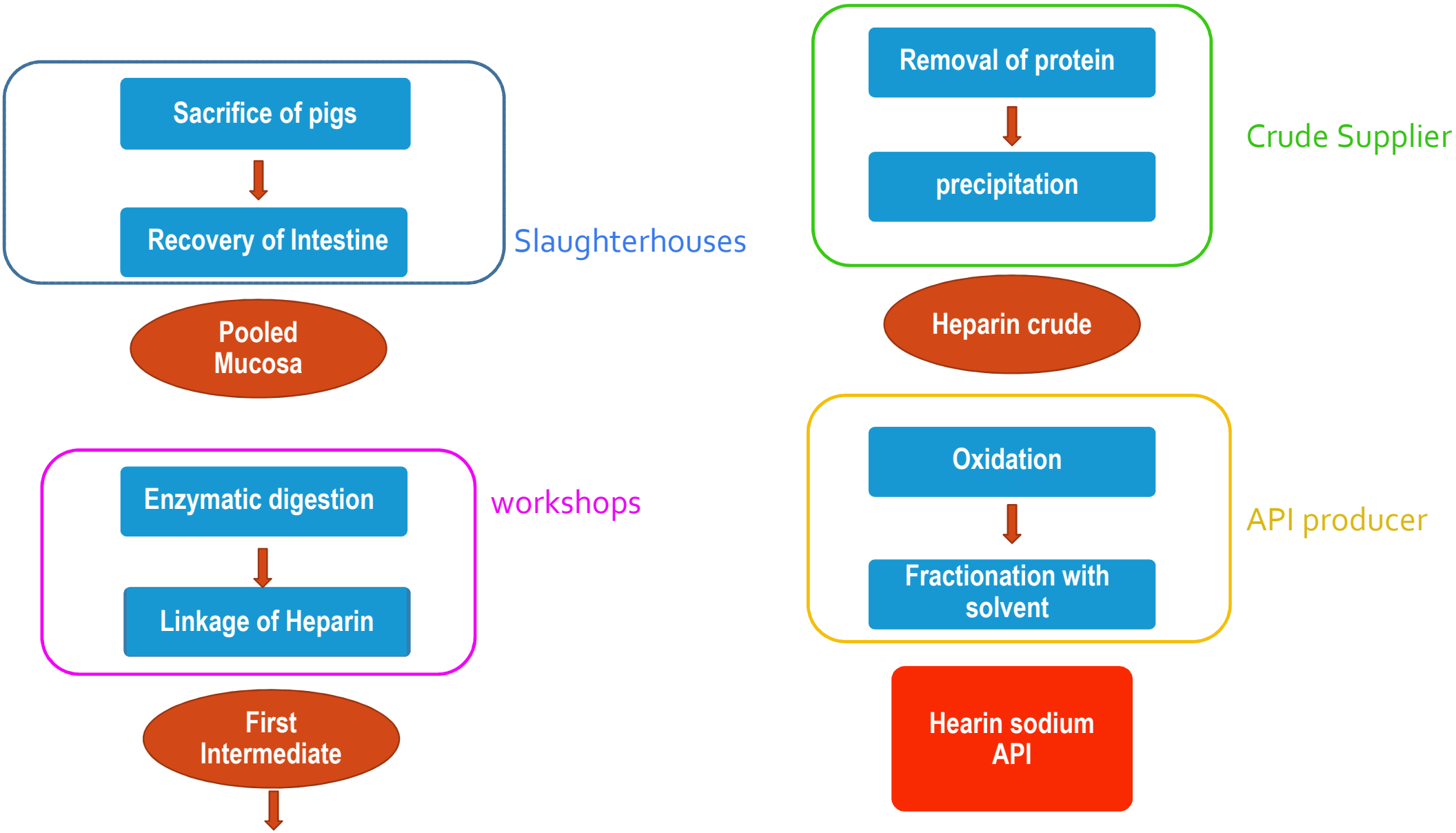
Heparin

Due to huge amount of starting material required to produce heparin a complex supply chain has to be guarantee and maintained under control

high number of suppliers at different stages of the process, with different quality parameters,

This heterogeneity requires a flexibility in capability to evaluate the “data Integrity”

high efforts necessary in revision and updating information and changes


Sacrifice of pigs
Recovery of Intestine
Slaughterhouses
Pooled Mucosa
Enzymatic digestion
Linkage of Heparin
workshops
First Intermediate
Removal of protein
precipitation
Crude Supplier
Heparin crude
Oxidation
Fractionation with solvent
API producer
Hearin sodium API

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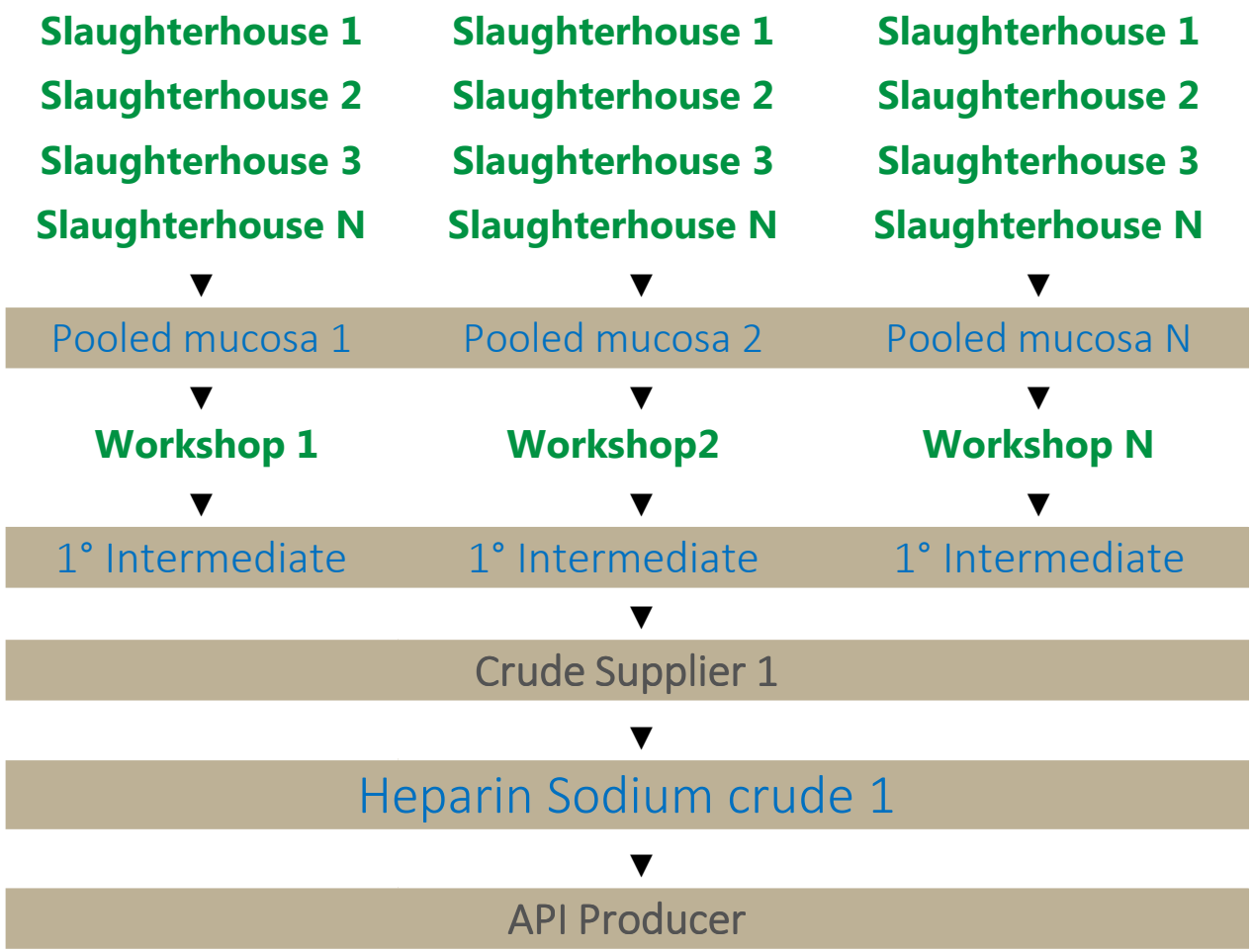
Supply Chain Heparin API



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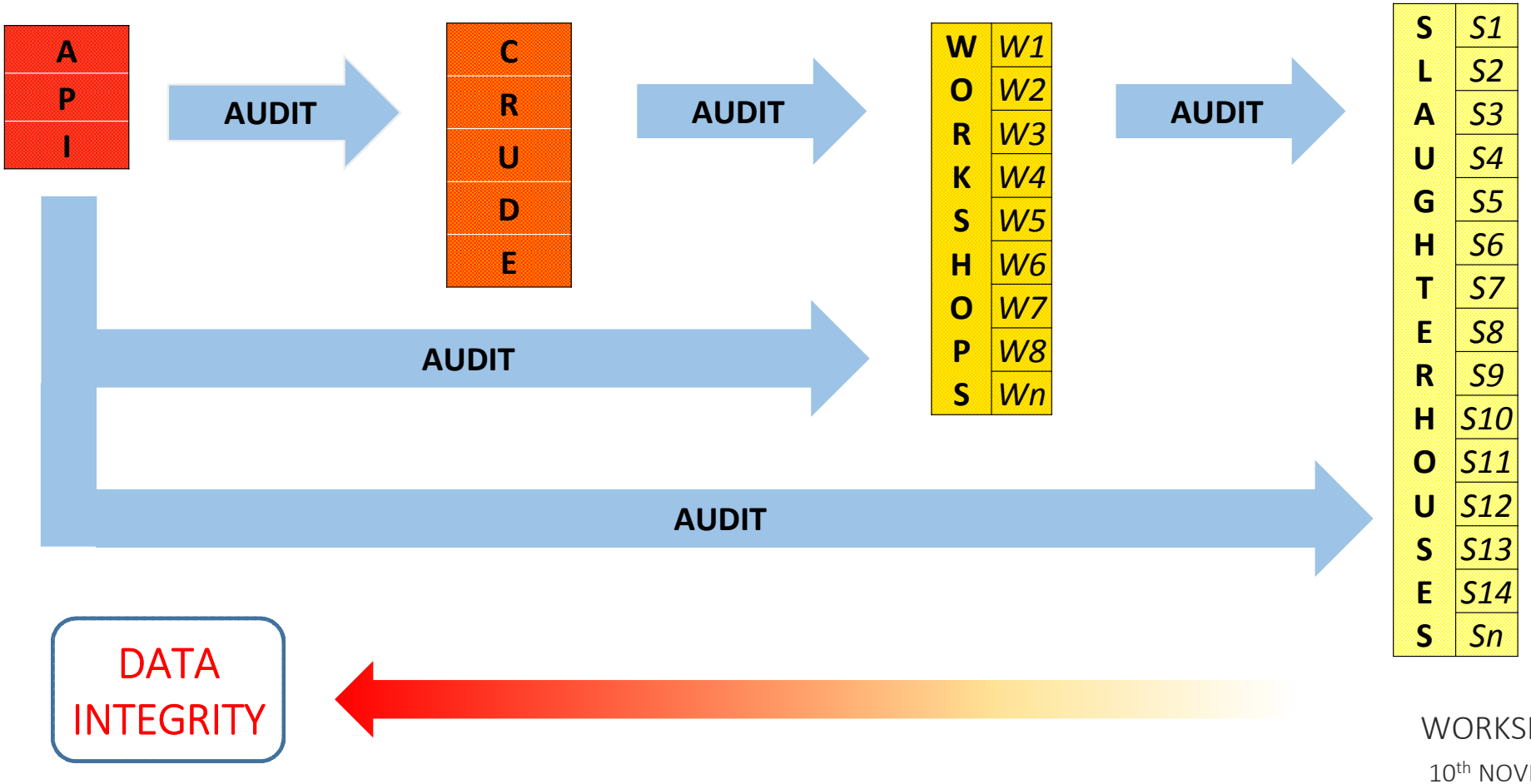
Supply Chain Heparin API



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Conclusions

- the data integrity has different level of application
- supply chain is represented from many entities and should be evaluated in relation to the degree of severity
- Each step needs an appropriate control system suitable to verify the data integrity

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THANK YOU

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