



Responsible Care[®]

A Signature Ethic of the Global Chemistry Industry





Responsible Care[®] Introduction

- ✿ Launched in Canada in 1985
- ✿ Expanded to more than 50 associations today
- ✿ Praised by Kofi Annan at the 2006 UN International Conference on Chemicals Management, and recognized at the 2002 UN World Summit on Sustainable Development (WSSD), and other international recognition
- ✿ Signature ethic of the global chemistry industry and key component of corporate responsibility programs





Responsible Care Mission

- ✿ Defines industry commitment to:
 - ✦ Improve safety, health, product stewardship and environmental performance of products and processes
 - ✦ Listen and engage with stakeholders
 - ✦ Contribute to sustainable development and corporate responsibility programs
- ✿ Provides companies with a management platform to:
 - ✦ Realize internal value
 - ✦ Enhance dialogue with stakeholders and international organizations





Responsible Care[®] Associations





Responsible Care[®] Global Charter

- ✦ Launched publicly at the **International Conference on Chemicals Management** (ICCM), Dubai, February 2006
- ✦ Sets a global vision of improved performance, enhanced public confidence, transparency, and strengthened engagement with stakeholders
- ✦ Seeks global consistency of key program elements across implementing companies and associations for more effective communication
- ✦ Strengthens product stewardship management, through consistent guidelines, and builds commitments from downstream users with Global Product Strategy
- ✦ Provides a critical performance foundation and management system to strengthen Responsible Care





Responsible Care[®] Value



Companies

- ✓ Save time and money
- ✓ Improve performances and processes
- ✓ Reduce risks and liabilities
- ✓ Enhance reputation and license to operate
- ✓ Improve worker, customer and environmental protection



Associations

- ✓ Increase their leverage in policy debates
- ✓ Enhance their reputation and that of the industry which they represent
- ✓ Create mechanism to derive value for members



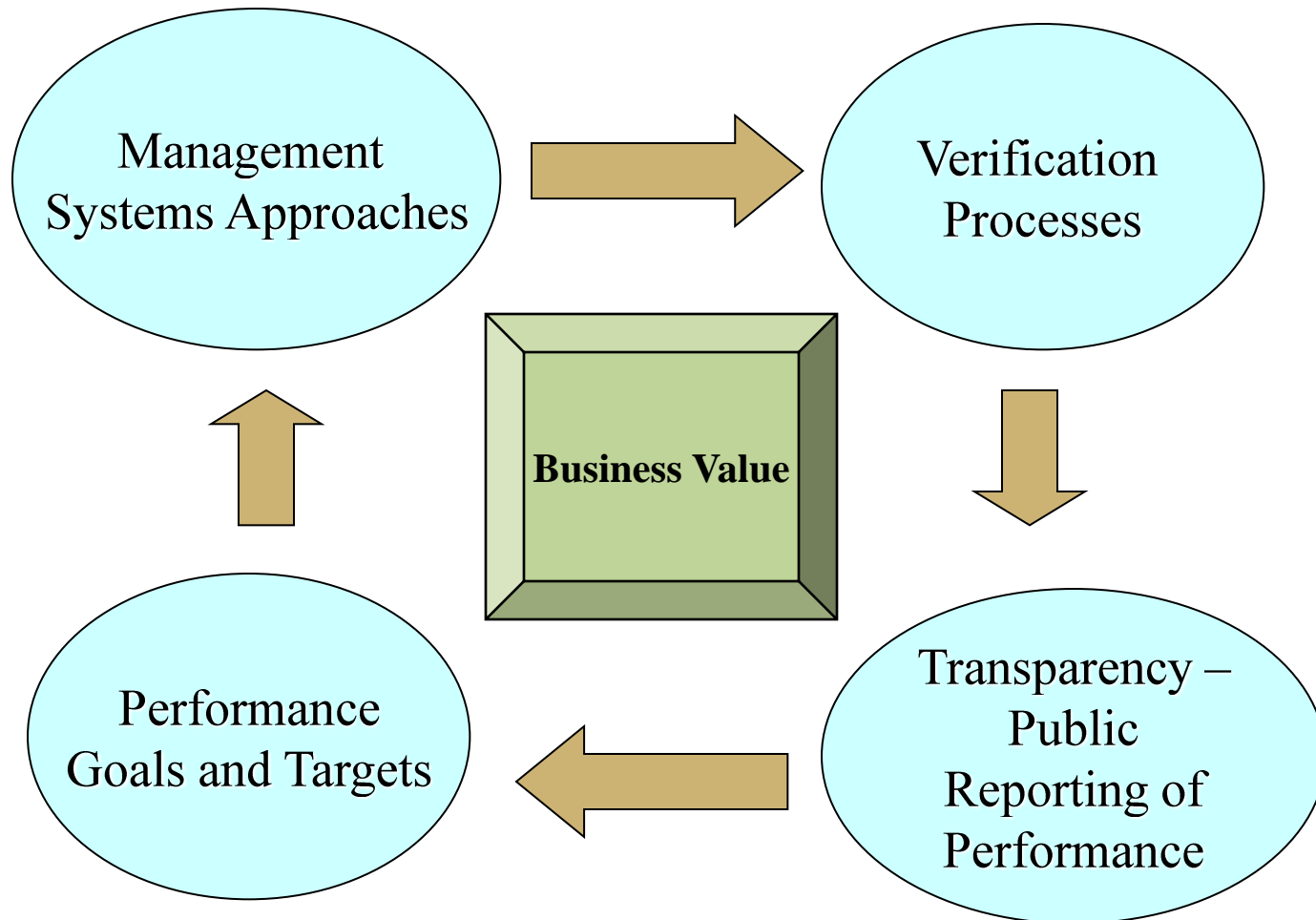


Responsible Care[®] Value - Examples

- ✿ Government Recognition
 - ✦ Eased permit negotiations: worldwide
 - ✦ Agreements with regulatory agencies: Canada, United Kingdom, U.S., emerging economies
- ✿ Financial Recognition
 - ✦ FTSE4Good Index - London Stock Exchange
- ✿ International community and customer recognition
 - ✦ Responsible Care as a prerequisite for business relationships
 - ✦ Recognition by the United Nations
 - ✦ Resolutions from customer groups
- ✿ Business Recognition
 - ✦ Reduced costs through systems improvements
 - ✦ Reduced insurance premiums



Responsible Care[®] Value Cycle





Responsible Care[®] Sources

- ✿ ICCA Responsible Care website:
<http://www.responsiblecare.org>
- ✿ UN International Conference on Chemicals Management – the ICCA web site, at
<http://www.icca-at-dubai.org>
and the UN Environment Program web site at
<http://www.chem.unep.ch/ICCM>
- ✿ ICCA general website:
<http://www.icca-chem.org>



Responsible Care

Path to 3rd Party Verification

Irish Chemical Marketers Association (ICMA)

Alan Looney

President Irish Chemical Marketers Association

Managing Director The National Chemical Co. Ltd. (NCC)

President PlusChem European Speciality Chemical Distribution Alliance

Executive Board Member FECC



Driver: Why go 3rd Party?

- Irish Market – Typically local SME Distributors serving Multi-National Suppliers and Customers
- Objective to raise standards gaining greater company acceptance among customers, suppliers, regulatory authorities, public and insurers

Step 1: Self Assessment

- ✚ RC Committee Formed
- ✚ Members CEO required to sign up to 8 guiding principals - Mandatory
- ✚ RC Co-ordinators appointed
- ✚ Workshops set up on 8 guiding principals, Legislation, and Emergency Response
- ✚ Self Assessments carried out 1997
- ✚ Self Assessments reviewed by RC Chair
 - a retired Major Company Executive serving on Irish Health and Safety Authority

Step 2 Peer Assessment

- ✦ New RC Chairman from NCC appointed and elevated to board
- ✦ Recruitment of Logistics Providers as Associate members
- ✦ Identified weaknesses from self assessments addressed
 - ✦ Commissioning of web based legislative register (now a key member benefit)
 - ✦ Emergency Response Systems Testing
- ✦ Regional Big to Small Company Support Groups established
 - ✦ Site visits on request
- ✦ Indices of Performance Correlated Centrally by ICMA for FECC
- ✦ RC Assessment paper based Audit by Parent Trade Association Industry Experts 1998/1999
- ✦ Minimum Standard Required
- ✦ Recommendations made for continuous improvement
- ✦ Upon acceptance Fanfare presentation of Certificates at ICMA

AGM

No membership attrition

Step 3 3rd Party Assessment

- ✦ Adoption of European Single Assessment Document (ESAD) as RC Tool
 - ✦ FECC Auditor Qualifications
 - ✦ National Standards Authority (NSAI) mapped ESAD 1 and ISO
 - ✦ Pilot Assessment carried out at NCC and it's main logistics provider Feb 2002
 - ✦ Other Assessment Bodies briefed on ESAD and RC
 - ✦ ESAD 1 issued to members for self assessment
 - ✦ NSAI etc. conducted 3rd Party ESAD 1 based Audit with some Site Visits
- 2002/4
- ✦ Assessments combined with ISO 9001 Audits
 - ✦ Continuous Improvement Action Plans issued by Auditor
 - ✦ Some Logistics Providers audited to SQAS
 - ✦ Fanfare presentation of Certificates at ICMA AGM
 - ✦ Accreditation Bodies reported general findings to ICMA
 - ✦ Main weakness identified as Risk Assessments
 - ✦ Only two members yet to be 3rd Party Assessed extensions given

The Future Challenges

- ✦ Adoption of European Single Assessment Document (ESAD II) as RC Tool
- ✦ ESAD II will be voluntary initially from 2006
- ✦ National Standards Authority NSAI trained by CEFIC to conduct ESAD II Assessments
- ✦ Good Trade & Distribution Practice Directive in force October 2005 for Excipient Pharmaceutical Raw Material Suppliers
- ✦ Extension of ESAD II Food & Pharma Appendix to GTDP Required
- ✦ Separate audit now likely so higher costs
- ✦ Greater recognition by customers and insurers required to establish more tangible benefits for members
- ✦ Need to extend gains in Road Haulage compliance to more smaller groupage operators
- ✦ Need for more Associate Logistics provider members
- ✦ More enforcement by Authorities required



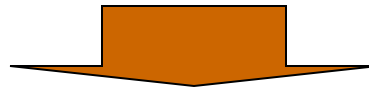
Good Trade & Distribution Practice



How do national authorities secure "healthy medicines"?

Manufacturers of medicines have to be approved by

- ✚ Several quality standards defined by national authorities in order to get
- ✚ Marketing authorisation for a given medicine

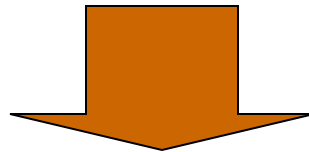


GMP – Good Manufacturing Practice



- ✿ Until 2005 GMP is limited to the manufacturing of finished medicinal formulation
- ✿ From 2005 GMP is **extended to** cover certain **manufacturers of raw materials** used in production of medicines and

Their Distributors



Part of Pharmaceutical Supply Chain

Products and customers

Products

- ⊕ API – Active Pharmaceutical Ingredients
- ⊕ Excipients (Wide definition expected)
- ⊕ Pharmaceutical Intermediates

Customers

- ⊕ Manufacturers of medicines (ethical, generic, botanical ...)
- ⊕ API manufacturers both Synthesis and Biotech



Definitions



✚ Active Pharmaceutical Ingredient (API)

- Any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in the production of a drug becomes an active ingredient of the medicinal product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

✚ Intermediate

- A material produced during steps of the processing of an API which must undergo further molecular change or purification before it becomes an API.

What Are Pharmaceutical Excipients ?

✚ **Excipients (WHO Definition)**

- ✚ A substance or compound, other than the active pharmaceutical ingredient and packaging materials, that is intended or designated to be used in the manufacture of a pharmaceutical product.

✚ **Examples:**

✚ **Solvents**

- e.g.: Isopropyl alcohol, Acetone, Ethanol etc.

✚ **Liquids**

- e.g.: Glycerol; Propylene glycol; Polyethylene glycols; Fatty acids; alcohols and oils; Sorbitol etc.

✚ **Solids**

- e.g.: Lactose, Sodium bicarbonate, Calcium carbonate, Cellulose derivatives, Waxes etc.

✚ **Pharmaceutical Grades**

✚ **Grades according to Pharmacopoeias**

- European Pharmacopoeia (Ph. Eur.)
- Unites States Pharmacopoeia (USP)
- Japanese Pharmacopoeia (JP)

Current Status of **Excipient Supply Chain**

- ✿ **Starting Materials quality is part of medicinal product quality**
 - ✦ Quality problems with excipients have direct impact on drug safety
- ✿ **Majority of chemical distributors supply excipients to pharmaceutical industries**
- ✿ **Often no traceability (known origin and intermediaries) and no control of supply chain processes (transport, repackaging)**
- ✿ **Full responsibility of customers for excipient safety and quality**
 - ✦ Development of supplier qualification programs
- ✿ **No regulation in Europe until May 1st, 2004**
- ✿ **Full GMP requirements for excipients in USA and France**
 - ✦ Including distribution!!

Expectations of Customers and Authorities

- ✚ **Traceability of excipient supply chain**
 - ✚ Documentation of each step
- ✚ **Prevention of contamination and cross-contamination**
 - ✚ Repackaging, bulk transport etc.
- ✚ **Quality control data and quality assurance**
 - ✚ Certificates of Analysis, Pharmacopoeia analysis and know-how
- ***Application of GMPs in the supply chain***

Upcoming/Current Regulation in Europe

✿ Article 46 (2004/27/EC)

The holder of a manufacturing authorization shall at least be obliged:

- f) To ... use only active substances employed as starting materials which have been manufactured in accordance with detailed guidelines on **good manufacturing practice for starting materials**.

This point shall also be applicable to **certain excipients**, the **list** of which and the specific conditions of application shall be established by a Directive...

✿ Article 46a

For the purpose of this directive, manufacture ... shall include ... the various processes of **dividing up, packaging or presentation prior to its incorporation into a medicinal product, including repackaging or re-labeling, such as carried out by a distributor of starting materials,...**

- **Distributors of “certain excipients” will have to apply GMP/GTDP in their operations !!!**

Distributors Key Topics

- ✦ EU Guide to Good Manufacturing Practice
 - ✦ Annex 18 – Good Manufacturing Practice for Active Pharmaceutical Ingredients
 - Chapter 17 – **Agents, Brokers, Traders, Distributors, Repackers, and Relabellers**
 - Applicability
 - Traceability of Distributed APIs and Intermediates
 - Quality Management
 - Repackaging, Relabelling and Holding of APIs and Intermediates
 - Stability
 - Transfer of Information
 - Handling of Complaints and Recalls
 - Handling of Returns

Source: The Rules Governing Medicinal Products in the European Union

Traceability of Distributed Products

- ❖ Complete traceability of distributed products should be maintained. Documents that should be retained and available include:
 - ❖ Identity of original manufacturer
 - ❖ Address of original manufacturer
 - ❖ Purchase orders
 - ❖ Bills of lading (transportation documentation)
 - ❖ Receipt documents
 - ❖ Name or designation of product
 - ❖ Manufacturer's batch number
 - ❖ Transportation and distribution records
 - ❖ All authentic Certificates of Analysis, including those of the original manufacturer
 - ❖ Retest or expiry date



Quality Management



- ✿ Quality should be the responsibility of all persons involved.
- ✿ An effective system of managing quality that involves the active participation of management and appropriate personnel should be established, documented and implemented.
- ✿ The system for managing quality should encompass the organisational structure, procedures, processes and resources, as well as activities necessary to ensure confidence that the product will meet its intended specifications for quality and purity. All quality related activities should be defined and documented.
- An e.g. ISO 9001-compliant Quality System will probably cover these requirements

Repackaging, Relabelling and Holding



Good Storage Practice

- ✚ design ensures good storage conditions
- ✚ sufficient capacity
- ✚ materials and products stored off the floor
- ✚ pallets in a good state of cleanliness and repair
- ✚ adequate lighting
- ✚ dry
- ✚ well ventilated
- ✚ 15 – 25 °C (max. 30 °C)
- ✚ no extraneous odours
- ✚ no contaminations
- ✚ no intense light

Warehousing and storage

Good Trade and Distribution Practice requires to :

Handle, store and transport all materials under conditions and for a period that have no adverse affect on their quality and in a manner to prevent degradation, contamination and cross-contamination even if all this activities are subcontracted.

Maintain record of specific storage conditions.

Release the products for distribution only after approval from the Quality Unit.

Transfer of Information

- ✿ All quality or regulatory information received from a manufacturer to the customer, and vice versa should be transferred.
- ✿ The name of the original manufacturer and the batch number(s) of the product supplied should be provided to the customer.
- ✿ The identity of the original manufacturer should also be provided to regulatory authorities upon request.

Transfer of Information: *Certificate of Analysis (CoA)*

- ⊗ Authentic CoAs should be issued for each batch.

- ⊗ Information on
 - ⊗ the name of the product including its grade, where appropriate,
 - ⊗ the batch number,
 - ⊗ the date of release, and
 - ⊗ the retest (or expiry) dateshould be provided on the CoA.

- ⊗ The CoA should list each test performed in accordance with compendial or customer requirements, including the acceptance limits, and the numerical results obtained (if applicable).

Transfer of Information: *Certificate of Analysis (CoA)*

- ❖ CoAs should be dated and signed by authorised personnel of the quality unit(s) and should show the name, address and telephone number of the original manufacturer.
- ❖ If new CoAs are issued, these CoAs should show the name, address and telephone number of the laboratory that has performed the analysis. They should also contain a reference to the name and address of the original manufacturer and to the original batch CoA , a copy of which should be attached.

Handling of Complaints, Recalls and Returns

- ✿ Standard Operating Procedures should be in place regarding
 - ✦ Handling of Complaints
 - ✦ Handling of Recalls
 - ✦ Handling of Returns

Fundamentals of *Compliance with GMP*

- ✚ Defined processes, including clear and unambiguous written instructions and procedures
- ✚ Suitable environment
- ✚ Training of personnel
- ✚ All quality related activities are recorded at the time they are performed.
- ✚ Complete traceability is maintained
- ✚ The distribution of the products minimises any risk to their quality
- ✚ A system is available to recall any batch of product
- ✚ Complaints are examined and appropriate corrective measures taken



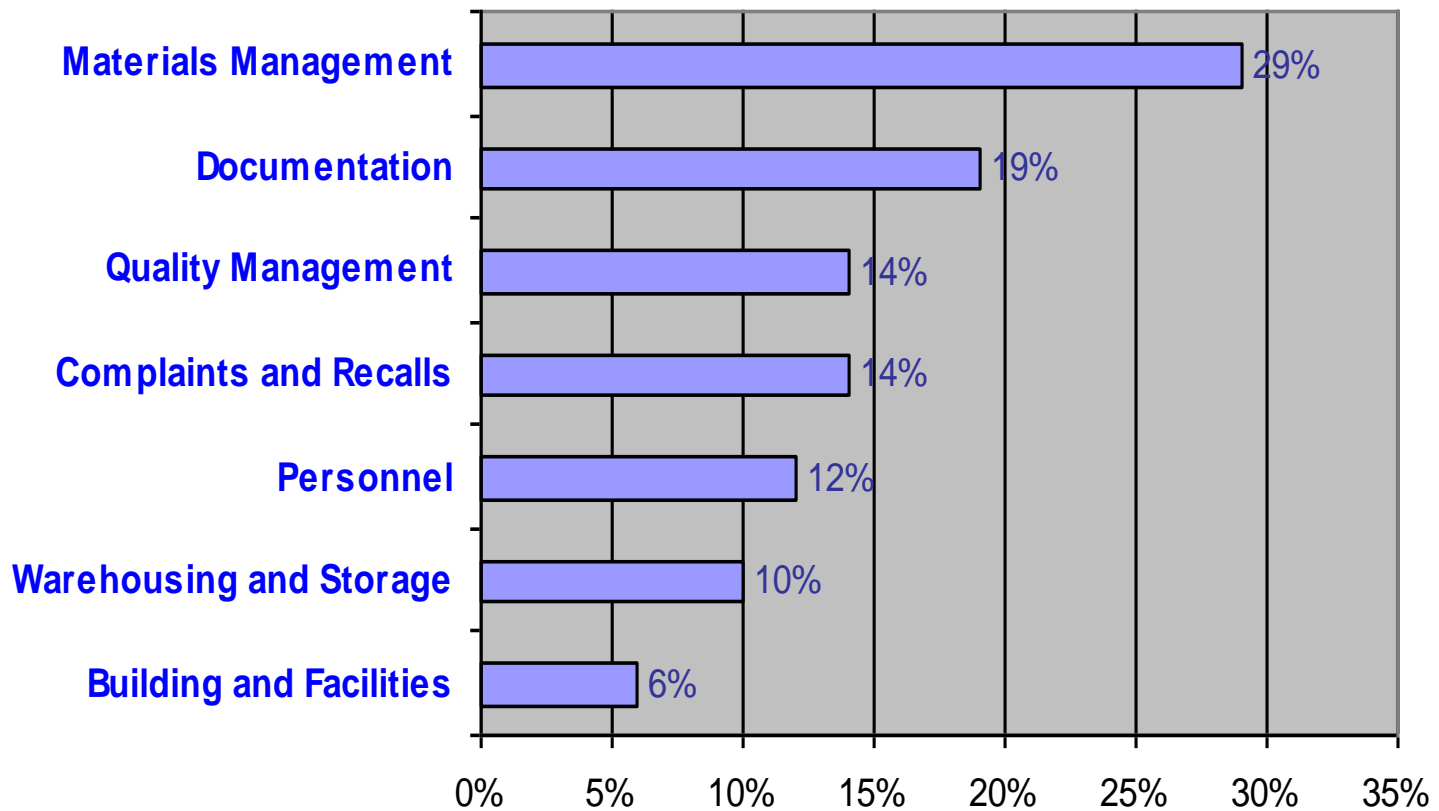
GTDP Quality Auditing



Results of inspections of pharmaceutical
ingredients traders and distributors in
Europe.



Deficiencies observed



Material Management

No procedures describing the receipt, identification, storage, handling and testing of the incoming materials.

No procedure describing the approval or rejection of materials even for sterile or pyrogen free products.

No appropriate examination and testing of materials.



Material Management



Examination before acceptance does not include :

- *Each container or grouping of containers*
- *Correct labelling (supplier identification, product name)*
- *Container damage*
- *Broken seals*
- *Evidence of tampering or contamination.*

No list of critical points to be examined.

No agreed specifications of the critical check points.

No release for use or further distribution.

Material Management

No system for the qualification or evaluation of suppliers:

- No knowledge of the suppliers activity or history*
- No audit of the suppliers*
- No justification of the absence of periodical full analysis of the materials*
- Testing on in-house samples.*
- No regular check of the reliability of the CoA.*

No approval of the supplier by the Quality Unit and no knowledge of approved suppliers.

Material Management

No knowledge of the name and the address of the original manufacturer.

No test to verify the identity of the each batch of materials.

No defined location for the sampling to prevent contamination.

Storage conditions which do not prevent degradation or contamination.

Materials stored on the floor.



Documentation



No possibility to trace back to the original manufacturer.

No possibility to trace back all parties handling the product.

Re-labelling without the original batch number or supplier identification.

No transfer of original quality information to the customer.

Modification of the information mentioned on the labels with or without re-packaging.

No appropriate certificates of analyses provided with the product.



Documentation



No original nor copy of the CoA provided or shipped with the product.

No reference to the original manufacturer or to the original batch number on the copy CoA.

No mention on the CoA of the analytical methods used nor of the specifications of the product.

Original or copies of CoA neither dated nor signed by an appropriate person.

Quality Management

No Quality Unit, Quality Assurance System or non independent or in development.

No definition or documentation of quality related activities as job descriptions, reception of products, suppliers qualification, storage conditions.

No records of quality related activities.

No person in charge with acceptance or rejection of products based on quality related matters.

No handling of complaints and recalls in order to improve product quality.

No investigation of quality related deviations.

Warehousing and storage

No appropriate storage conditions.

No procedures describing handling, storage distribution and transport of the products.

Distribution without product- release by the Quality Unit.

No records of the storage conditions as controlled temperature and humidity.

No contract with the contractors for storage or transportation, even for liquid products in tanks.

No audits of contract acceptors.

Inspection Programs

Routine inspection of trade and distribution activities

Distribution and traceability of TSE risk products

Distribution and traceability of Narcotic products

Distributors holding Certificates of Suitability of
Monographs of the European Pharmacopoeia