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## *Materials Management*

## *Assuring the Supply Chain*

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*23rd October 2008 , IMB Information Day 2008*

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Cormac Dalton  
Inspector

# How was coffee break this morning ?



- Have you ever had a 'bad' cup of coffee ?



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# What is in a coffee bean ?

- Did you know that:
  - Arabica coffee beans command the highest prices
  - Robusta beans are low-grade beans, grown at lower altitude
    - They are **cheap** and principally used as **fillers**.
    - An 'inexpensive **substitute** for arabica'.
- And what is in these low-grade beans...
  - 'the high antioxidant...extract of low-grade coffee beans is due to the presence of **phenolic compounds** including **chlorogenic acids**'.



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# Coffee supply chain – an example

- Farmer plants and then tends to coffee trees (e.g. Africa)
- **Employees** of the farmers or who are **independent contractors** who are paid a couple of cents for every pound of coffee fruit that they harvest
- Coffee is sold to **wholesalers** or **collectors** or to the **cooperative** (Fair Trade route or alternative)
- Coffee is washed, dried (part manufacture) and packaged for export



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# Coffee supply chain – an example

- Coffee is sold to exporter
- Exporter sells to roasting company
- Roasting company 'blends' and prepares final product
- And today, over 100 cups of coffee were prepared and you drank them...
  - No questions asked !!



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# Medicinal product supply chain

- Should we expect more control with medicinal products?



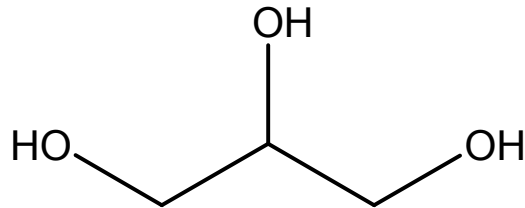
- An unsecure supply chain can result in counterfeit medicines which can cause death.



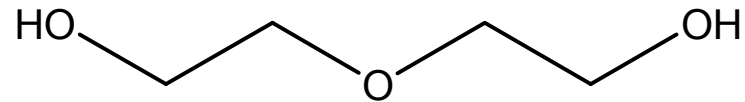
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# Diethylene glycol impurity & Glycerol

- Diethylene glycol = structurally it is **chemically** similar



**Glycerol**



**Diethylene glycol**



- **Physically** similar
  - Light coloured
  - Sweet taste
  - Slightly viscous at room temperature



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# Glycerol's tainted history

- **USA (1937)**  
More than **100 people died** after ingesting contaminated Elixir Sulfanilamide (antibiotic). Resulted in enactment of the Federal Food, Drug, and Cosmetic Act (FDA).
- **Haiti (1995-96)**  
At least **80 children died** due to contaminated paracetamol syrup.
- **Argentina, Bangladesh, India, and Nigeria (1990 to 1998)**  
Similar incidents of poisoning occurred resulting in **hundreds** of deaths.
- **Panama (September 2006)**  
Contaminated cough syrup resulted in dozens of hospitalizations for serious injury and **46 deaths**.



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# Glycerol supply chain in 2006 incident

- Manufacturer: Country A (non-EEA)
- Broker 1: Country A (non-EEA)
- Distributor: Country B (EU)
- Broker 2: Country C (Panama)
- FP manufacturer: Country C (Panama)

- **Complicated – but not atypical !!**



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# Activities performed at each stage

- **Manufacturer**
  - Substituted glycerol with diethylene glycol and labelled as 'glycerine substitute'
- **Broker 1**
  - Removed manufacturer name from CoA
  - Replaced CoA header with Broker company name
  - 'Translated' into English



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# Activities performed (continued)

- **Distributor**
  - Removed Broker details on CoA and replaced with own
- **Broker 2**
  - Changed the expiry date of the material
- **Finished product manufacturer**
  - Manufactured cough syrup using wrong excipient
- **Not one party tested the material once it left the raw material manufacturing site !!**



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# Glycerol Ph. Eur. testing

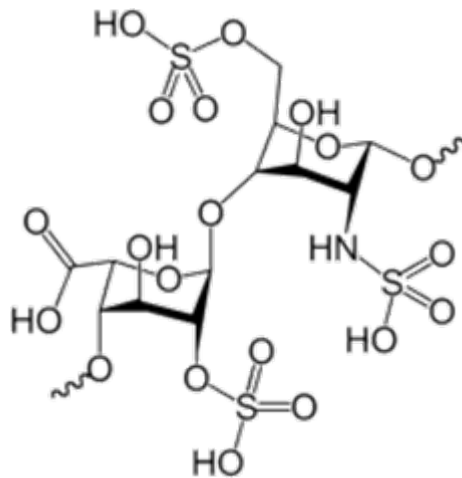
- Historically, the analysis of glycerol by the Ph. Eur. identity tests would only identify the diethylene glycol impurity at levels **above 10%**.
- Revised Ph. Eur. test (GC) and limit = NMT 0.1%
- It is expected that **identity testing** and the Ph. Eur. limit test for **diethylene glycol** will be performed on each container as a matter of routine.



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# OSCS impurity in heparin

- Over Sulphated Chondroitin Sulphate (OSCS)
- Structurally related 'bulking agent'



*Heparin backbone*



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# Heparin Ph. Eur.

- Numerous adverse reactions & deaths in numerous countries
- Revised Ph. Eur. Monograph contains:
  - It is produced by methods of manufacturing designed to minimise or eliminate substances lowering blood pressure and to ensure freedom from contamination by **over-sulphated glycosaminoglycans**.
- Thus additional Ph. Eur. tests
  - NMR & CE



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# Today's Presentation

- Current Vendor Verification Requirements
  - GMP for finished product manufacturers
  - GMP for API manufacturers
  - ICH Q9 Guidance
- Future proposals
  - European Commission Proposals
- Risk Assessment
  - Questions to consider within your Quality System



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# GMP for finished product (FP) manufacturers

## Chapter 1

- The **system of Quality Assurance** appropriate for the manufacture of medicinal products should ensure that arrangements are made for the manufacture, supply and **use of the correct starting and packaging materials**
- The **basic requirements of GMP** are that all necessary facilities for GMP are provided including **correct materials**, containers and labels
- The **basic requirements of Quality Control** are that adequate facilities, trained personnel and approved procedures are available for sampling, inspecting and **testing starting materials**, packaging materials etc.



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# GMP for FP manufacturers (cont'd)

- **Chapter 5**
- Starting materials should only be purchased from **approved suppliers** named in the relevant specification and, where possible, **directly from the producer**.
- For each delivery, the containers should be checked for **integrity of package and seal** and for correspondence between the delivery note and the supplier's labels.
- There should be appropriate procedures or measures to **assure the identity of the contents** of each container of starting material.
- **NOTE – Chapter 5 is currently under revision**
- **See also presentation on API Sampling by Laura Hickey**



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# GMP requirements for API manufacturers (Part II)

- There is a requirement to:
  - maintain records of suppliers
  - evaluate the suppliers of critical materials
  - purchase materials against an agreed specification from approved suppliers
  - manage changes to suppliers through Change Control
  - sample & test incoming production materials



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# GMP for API manufacturers (cont'd)

- **Part II, Section 17:** Agents, Brokers, Traders, Distributors, Repackers, and Relabellers
  - All parties comply with GMP
  - Traceability – full documentation of activities
  - Quality management system required
  - Repackaging, relabelling and holding of APIs
    - Avoid mix-up & cross-contamination
  - Stability data ~ if original manufacturers container changed
  - Complaints, recalls & returns procedures required



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# European Commission Proposals (March 08)

- Public Consultation in Preparation of a Legal Proposal to Combat Counterfeit Medicines for Human Use:
- Key Ideas for Better Protection of Patients Against the Risk of Counterfeit Medicines
- [http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2008/2008\\_03/consult\\_counterfeit\\_20080307.pdf](http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2008/2008_03/consult_counterfeit_20080307.pdf)
- Consolidated public/industry responses published June 08



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# Factors facilitating the rise of counterfeit

- Deficiencies in supply chain integrity:
  - **uncertainty** as to whether certain participants in the distribution chain are **subject to pharmaceutical legislation** (e.g. brokers, traders).
  - Lack of specific requirements for **supplier qualification**.
- Lack of transparency as to whether wholesalers and other actors in the distribution chain comply with **Good Distribution Practice (“GDP”)**.



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# Factors (continued)

- Shortcomings in **product integrity**, especially when packs are opened for **repackaging** and changed for **relabelling** purposes.
- Difficulties in conducting targeted **recalls**, in particular in the case of counterfeit products.
- Legal uncertainty and differing practices between Member States concerning the application of pharmaceutical legislation to **imports for the purpose of export**.
- Active substances may **not** be **manufactured in compliance with GMP** standards, in declared sites or in accordance with declared procedures.



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# Proposed Regulatory Amendments - 1

- **1. Tightening requirements for manufacture, placing on the market of medicinal products and inspections**
  - subjecting all parties in the distribution chain to pharmaceutical legislation;
  - improving product integrity and traceability;
  - sharpening the technical requirements for GMP and GDP;
  - tightening inspections and supervision; and
  - increasing transparency.



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# Proposed Regulatory Amendments - 2

- **2. Tightening requirements for the import/export/transit of medicinal products**
  - includes medicinal products intended to be placed on the Community market regardless of whether the product has been manufactured in the EU or in a third country;
  - the manufacturing of medicinal products in the EU, regardless of whether the product is exported or not;
  - the wholesale distribution of medicinal products;
  - the importation (including re-importation) of medicinal products into the EU.



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# Proposed Regulatory Amendments - 3

- **3. Tightening requirements for manufacture, placing on the market of active substances and inspections:**
  - Requirement of a mandatory notification procedure for manufacturers/importers of active substances
  - Enhancing audit and enforceability of GMP
  - Enhancing GMP inspections
- Additional guidance expected from the Commission in the near future.



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# ICH Q9 – Quality Risk Management (QRM)

- ICH Q9 provides examples where QRM may be applicable
- Incorporated into GMP Guide as Annex 20
- IMB are seeing more applications of use of QRM  
(see *IMB Newsletter Issue 29, January - April 2008*)
- Relevant section (for this presentation) is Annex II.5
- ‘QRM as Part of Materials Management’



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# ICH QRM as Part of Materials Management

- Assessment and evaluation of suppliers and contract manufacturers e.g. auditing, supplier quality agreements
- Quality of starting material from different suppliers / routes of synthesis
- Use of materials under quarantine
- Use of atypical material e.g. reprocessed, reworked & returned goods.



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# Questions – pre-audit activities

- Is an audit required when the site has a GMP Certificate as issued from a Competent Authority?
  - A GMP certificate alone cannot fulfil the **statutory obligations** of the manufacturing authorisation holder. A GMP certificate **may be used** together with other supporting information in a **risk-based approach** by the manufacturer in establishing priorities for its own audit programme.
- Are paper-based audits acceptable?
  - Such audits **cannot replace** on-site audits of active substance suppliers but can be a useful interim and temporary measure within the manufacturers audit programme.



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# Questions – pre-audit activities

- In relation to registering a new active substance supplier, a signed QP declaration if required stating that:
  - ‘the active substance manufacturer(s) referred to in the application operate in compliance with the detailed guidelines on good manufacturing practice for starting materials’  
[Ref: Variations Regulations \(2006\)](#)
- What extent is the QP involved in the supplier approval process?



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# Questions - sourcing

- Where are you sourcing raw materials from?
- How many parties are involved in the distribution chain before you receive the goods?
- Are brokers, traders, repackers or distributors involved?
- What activities is each party undertaking?
- What is the shipping route of raw materials to your manufacturing site – direct or via intermediaries?



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# Questions – Audit planning

- Which parties in the chain are included in your audit schedule?
- Who performs the audit?
  - Is it your 'global office' or your actual site?
  - If another site performs the audit, do you have access to the audit report?
- What standards are the audit performed against?
  - ISO, GMP, other..
- How do you deem someone suitable as an auditor?
- What training is provided to auditors?



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# Questions – the Audit

- Are the principles of Risk Management employed when performing an audit ?
- How do you plan the audit schedule?
  - Do you consider the nature of the material?
  - Do you consider the finished dosage form?
  - Do you consider the TSE risk?
  - Is the manufacturing site a dedicated facility?
  - Does the manufacturer produce 'highly potent' materials?
- What do you audit when your time is restricted?
- What is the minimum acceptable standard you will accept?



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# Questions – the Audit report

- Are the audit reports available to the QP especially if the audit is conducted by a third party or parent company?
- Are they formally reviewed?
- Are they sufficiently detailed?
- Must audit reports be available for review by an IMB Inspector?
  - **The answer is yes.**



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# Questions - outcomes

- If you perform an audit and are not happy with the potential 'supplier/manufacturer', what do you do next?
- Do you inform management and recommend that you do not do business?
- Do you inform another company?
- Do you inform the Irish Medicines Board?



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# Could it happen in Ireland ?

- put another way.....
  - Could another company, less conscientious, accept and process raw materials from a site that you deemed to be non-compliant?
  - Could that medicine end up in your home.....?



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# Questions – documentation

- What supporting documentation received with raw materials can guarantee that the material is authentic?
- Can a CoA on company headed paper with 'a' signature have been manipulated?
- What labelling details are acceptable?
- Do you keep Master Copies of acceptable CoA / labelling?
- Are translations involved – who is performing this?



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# Questions – goods received

- What checks are performed at goods receipt?
- How do you assure specific grades are purchased: e.g. micronised, milled, polymorph, Ph. Eur. vs. 'EP'?
- What tamper-proof measures are in place?
- What sampling / testing is performed?
- What is the rate / cause of rejection of materials?
- See also presentation on API Sampling by Laura Hickey



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# Atypical actives and excipients

- **Atypical Actives**
  - GMP requirements & difficulties in providing QP declaration re: atypical active substances is recognised.
- **GMP for Excipients**
  - ‘Specific Conditions of the Application of the Principles and Guidelines of Good Manufacturing Practice for Certain Excipients’
- Both topics are under discussion at EU level.
- Outcomes will be communicated to industry.



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# Final Comment

- Where are you sourcing raw materials from?
- How secure are the quality system(s)?
- Can improvements be made?
- **Protect the supply chain, protect public and animal health**



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# Acknowledgments

- Special thanks to the Compliance Department of the Irish Medicines Board
- Thank you for listening
- [Cormac.Dalton@imb.ie](mailto:Cormac.Dalton@imb.ie)
- [Compliance@imb.ie](mailto:Compliance@imb.ie)
- +353-1-6764971



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# Any Questions ?



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