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Important findings from a 2008 API market surveillance exercise at finished product manufacturers

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Outline

- Purpose/Scope of sampling exercise
- Knowledge of supply chain
- Consequences of not knowing your supply chain
- Important GMP requirements related to receipt & checking at goods-in
- Specific issues identified during IMB sampling activities in 2008
- Summary of findings
- Key points to note
- Recommendations & Opportunities for improvement

Purpose & Scope of API Sampling Exercise (1)

- The primary purpose of this exercise was to carry out market surveillance on APIs from third countries.
- Samples taken at a number of finished product manufacturers.
- A total of 72 API samples (mainly of Chinese and Indian origin) were sent for laboratory analysis in the IMB sampling and analysis programme.
- In addition consideration was given to the controls in place at goods inward for the receipt and checking of APIs
- Opportunities for improvement (OFIs) were identified



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Purpose & Scope of API Sampling Exercise (2)

- During the sampling exercises the IMB took the opportunity to, examine the controls in place for the receipt and checking of APIs at goods-in, with regards to:
 - Examination of drum labels
 - Examination of Delivery documentation
 - Use of Approved Supplier List (or equivalent document or control system) at goods-in
 - Adequacy of Staff Training in the goods-in area
 - How Approved Supplier List, QC Specifications and Drum Labels correlate



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Knowledge of supply chain

- Other aspects of supply chain covered in Materials Management presentation by Cormac Dalton
- Re receipt & checking, do you know if the material you received is the one that's registered or expected?
- How do your staff use your company's Approved Supplier List (or an equivalent document or system)?



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Consequences of not knowing your supply chain

- Poor control in the supply chain can result in the:
 - Receipt of the wrong material
 - The introduction of:
 - substandard
 - adulterated
 - counterfeit material
- which can lead to toxic (medicinal) products on the market.
- The need for a cessation of batch release
 - Product Recalls
 - The receipt of significant deficiencies during inspection



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Past Examples - Cessation of batch release

- Example 1

In one company 4 different products were affected when APIs were used from unregistered suppliers.

- All specifications for the products were met
- The unregistered sites were determined to be GMP compliant and as a result no recall action was taken.
- However any further QP release was ceased until a marketing authorisation variation to include these suppliers was submitted and approved.
- This non-compliance was not picked up at the goods-in check for the API batches.

- Example 2

A product manufactured in Ireland for marketing in the UK was using API from 2 different sources, only one of these sources was registered.



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Major deficiency identified during past inspection

- Example 3

The control of starting materials was deficient in that starting materials from manufacturers other than approved manufacturers specified on the starting material specification document were accepted for use. This resulted in the issuance of a major deficiency.



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Receipt & Checking - Important GMP requirements

- Points to consider:
 - Reduced testing
 - Purchase orders
 - Approved suppliers
 - Delivery notes
 - Container specification and labelling
 - Certificates of analysis
 - Lot Traceability



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EU GMP guide - Production Chapter 5

- 5.3 All incoming materials should be checked to ensure that the consignment corresponds to the **order**.
- 5.25 The purchase of starting materials is an important operation which should involve staff who have particular and thorough knowledge of the **suppliers**.
- 5.26 Starting materials should only be purchased from **approved suppliers** named in the relevant specification and where possible directly from the producer.
- 5.27 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**.
- Chapter under revision



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EU GMP Guide Part 2

- 7.12 Materials should be purchased against an **agreed specification**, from a supplier or suppliers approved by the quality unit(s).
- 7.20 Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for **correct labelling** (including correlation between the name used by the supplier and the in-house name if these are different), container damage, broken seals and evidence of tampering or contamination.



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EU GMP Guide Part 2

- 11.43 **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. Where the analysis has been carried out by a repacker or reprocessor, the COA should show the name, address and telephone number of the repacker/reprocessor and a reference to the name of the original manufacturer.
- 17.2 **Traceability** of APIs – Agents, brokers, traders, distributors, repackers or relabellers should maintain complete traceability of APIs they distribute. (identity & address of original manufacturer, batch number, purchase orders, all COAs etc. must be traceable to the API received).



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EU GMP Guide – Annex 8

- 2. The identity of a complete batch of starting material can normally only be ensured if individual samples are taken from all containers and an identity test performed on each sample. **It is permissible to sample only a proportion of the containers where a validated procedure has been established to ensure that no single container of starting material has been incorrectly labelled.**



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EU GMP Guide – Annex 8

- 3. This validation should take account of at least the following aspects:
 - Nature & status of the manufacturer & of the supplier & their understanding of the GMP requirements of the Pharmaceutical Industry
 - The Quality Assurance system of the manufacturer of the starting material
 - The manufacturing conditions under which the starting material is produced & controlled
 - **It is improbable that a procedure could be satisfactorily validated for starting materials supplied by intermediaries such as brokers where the source of the manufacture is unknown or not audited.**



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Specific issues identified during the IMB sampling exercise:

- API name & form issues
- API manufacturer name and address issues
- Broker issues
- Personnel/Training issues



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API name & form issues (1)

- On the ASL (Approved Supplier List) salt forms were either not listed or were incorrect.
 - the drum label showed a different salt form to that on the ASL (eg. ABC Dihydrochloride Vs. ABC Hydrochloride).
- In some cases the compendial reference (eg. USP) for the API was listed on the ASL but not on the drum and vice versa.



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API name & form issues (2)

- It was found in some cases that the word micronised was on the drum label for the material but not on the ASL. In other cases the word micronised appeared on the ASL but did not appear on any of the material labels or COAs.
 - It was unclear whether the material that had been received was the correct grade.
 - As no particle size testing was performed in-house, there was no clear mechanism by which the company verified that they had received the micronised grade that had been ordered.
 - This can be very important for low bioavailability finished products.



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API name & form issues (3)

- The specific grade of the active substance that was approved for purchase was not listed on the ASL. (eg. XYZ HCl Ph. Eur vs. XYZ HCl (Form 1) Ph. Eur.)
- In one case, the ASL had a section for brand names for APIs
 - on further investigation it emerged that these “brand names” were in fact not brand names but were references to the material code number on the QC lab test reports of the API manufacturer
 - the inclusion of these “brand names” onto the ASL had clearly not been reviewed sufficiently



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API Manufacturer name & address issues (1)

- Instances where no checks were being carried out to ensure that the labelled name and address of the manufacturer matched that on the ASL when API batches were received.
- The API manufacturer name & address was sometimes not stated on the ASL.
- The manufacturer's details were sometimes incomplete on the drum labels and so it could not be ensured that the material was received from the approved site.



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API Manufacturer name & address issues (2)

- In 2 cases the names of the API manufacturers were not stated anywhere on the drum labels.
- API drums sometimes had a label stating the name, grade and lot number of the material, but it was unclear whether the manufacturer or broker had applied these labels, as no company name was stated on the labels.
- In one case, drums were labelled with a name of a manufacturer that was completely different from that stated in the ASL, this was not detected during goods-in checks or later.



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Broker issues (1)

- For APIs that were purchased from a broker, instances where the name and address of the broker was either not stated on the ASL, or was incomplete on the ASL.
- Instances where a broker's label had been applied to a drum, the broker's name and address on the ASL did not match that on the drum label - this was not detected during goods-in checks or later.
- In one company the policy was that the broker could not over-label the drums. However, labels were detected by the IMB on some drums and this was not detected in-house.



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Broker issues (2)

- In one case a material was being purchased from a UK broker, the material was manufactured in China, however the ASL wrongly stated that the manufacturer was the UK broker company.
- The UK broker was supplying a COA which was a transcription of the test results reported by the manufacturer, but there was no reference on the broker COA to indicate that the results were transcribed from the manufacturer COA.
- The original COA from the manufacturer was not available to the Irish finished product manufacturer who was under the impression that the COA related to tests that the broker company had carried out on the material - this was incorrect.



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Broker issues (3)

- An API, that was being purchased from a broker in India, was stated on the company ASL as coming from a broker in Switzerland - this was not detected during goods-in checks.
- In some cases the label applied to a drum by a broker described the API as being micronised whereas the manufacturer's label did not indicate this.



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Personnel/Training issues (1)

- In one company different APIs were purchased from 2 very similarly named manufacturers
- The two manufacturers had almost identical addresses
- The names and addresses were not accurately reflected in the Approved Supplier List at the company



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Personnel/Training issues (2)

- Instances where warehouse staff were unsure about what to do when specific reference to the nature of the material (eg. micronised) was stated on the ASL for a particular material.
 - This led to the material being accepted regardless.
- In one company the ASL stated the type of packaging that a material should be received in.
 - However it was noticed that some APIs were being received and approved in different packaging to that stated in the ASL. This packaging difference was not noted or investigated by the company.



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Personnel/Training issues (3)

- The words “broker”, “supplier” and “vendor” were in use and staff sometimes did not know the meaning of each, or how to use these fields on the ASLs.



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Summary of findings

- Goods-in checks
- Approved suppliers lists



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Summary of findings (1)

Recurring issues were identified during these sampling exercises

- Instances where goods-in controls were deficient in checking that:
 - The material received was the correct material
 - The labelled manufacturer was the manufacturer approved for that material
 - The supplier was the approved supplier for that material



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Summary of findings (2)

- Instances where goods-in controls were deficient in checking that:
 - The consignment received was in accordance with the purchase order
 - Goods received were in compliance with the specific information listed in the ASL, such as labelling performed by the broker and the packaging in which the API should be received



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Summary of findings (3)

- ASLs were deficient in that they often included:
 - Incomplete active names & salt forms
 - Incomplete/incorrect or no manufacturer names and addresses
 - Incomplete/incorrect supplier and broker information
 - Incorrect information regarding activities of brokers
 - Incorrect information regarding type of packaging in which the API is expected to be received
 - Incorrect reference made to “brand names”



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Do you know your supply chain?

- Are you adequately protected from the risk of an API from a questionable source being received and approved for use in your manufacturing plant?
- In relation to receipt and checking at your site:
 - Do you know if the material you received is the one that's registered or expected?
 - Does your ASL provide sufficient detail to facilitate robust goods-in checks?
 - How do your staff use your company's ASL (or an equivalent document or system)?
 - Have you established & agreed with manufacturer/broker/supplier exactly how each drum will be marked batch to batch?



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Key points to note

- Totality of checks and controls in place for incoming materials should give assurance that adulterated or counterfeit lots of an active substance (or other material), if received, will be identified and not be approved for use in finished product manufacture.
- Checks and controls should also ensure that the material received is the registered or expected material as described in the MA dossier (if applicable).
- A substantial level of reduced testing was observed. The effectiveness of the controls in place for ensuring the right material was ordered and received should be one of factors when considering move to reduced testing.
 - This is especially important for APIs where a specific grade, form or particle size profile is required.



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Recommendations & OFIs (1)

- The active substance name, salt form, grade and compendial specification should be clearly documented on the ASL or equivalent document system, on the purchase order and on the QC testing specification documents. There should be no discrepancies between these documents.
- Names and full addresses of the active substance manufacturer should be clearly documented on the ASL and purchase order.
- Names and full addresses of brokers, if any, should be clearly documented on the ASL and purchase order.
- The activities of brokers should be known, especially with regards the number of brokers involved, their labelling of drums and their issuance of COAs.



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Recommendations & OFIs (2)

- If the ASL contains a heading for suppliers, it should be clear to all what this means – is it the broker or manufacturer or someone else, eg. a shipping co.?
- Material brand names (if any), their significance/meaning and how these are used by goods-in staff should be clearly documented on the ASL and understood.
- It should be ensured that goods in staff have a copy of the ASL or equivalent document system as well as the relevant purchase order documents to ensure the right material was received.
- The procedures that are in place for the checking of received materials, drum labels, drum packaging, delivery notes and COAs should be regularly reviewed and their effectiveness assessed via self inspection.



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Recommendations & OFIs (3)

- Staff involved in goods-in checks should be included in an on-going training programme e.g. induction, refresher training designed for their particular needs.
- ASLs or equivalent document system should be regularly reviewed and updated e.g. if MA varied to remove API manufacturer, ASL amendment should be part of the change control
- If 4 API manufacturers listed but 2 are used only as back up, is their status still correct and acceptable?
- The ASL and goods-in procedures should be subject to self-inspection:
 - Are adequate procedures in place for the action that needs to be taken when information on the ASL does not match what is on the drum labels?
 - Do you adequately audit these procedures?



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Recommendations & OFIs (4)

- Reduced testing should only be considered when a validated procedure has been established to ensure that no single container of starting material has been incorrectly labelled (annex 8) (ID required for each container of API & other material used in steriles)
- Have agreed sample supplier labels and delivery notes available to aid goods-in check at receipt of each order



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Thank You



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