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# The Quality Defect & Recall Programme

## Key Features & Expectations

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*Crowne Plaza, 23<sup>rd</sup> October 2008*

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- What is a Suspected Quality Defect?
- Overview of a Quality Defect Investigation
- Most Frequent Quality Defect Reports
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# Content

- IMB Expectations of a MAH/Manufacturer During a Quality Defect Investigation
  - Initial Reporting
  - Initial Investigation/Information Gathering
  - Risk-Based Decisions
  - Market Actions
  - Recall/Investigation Reports



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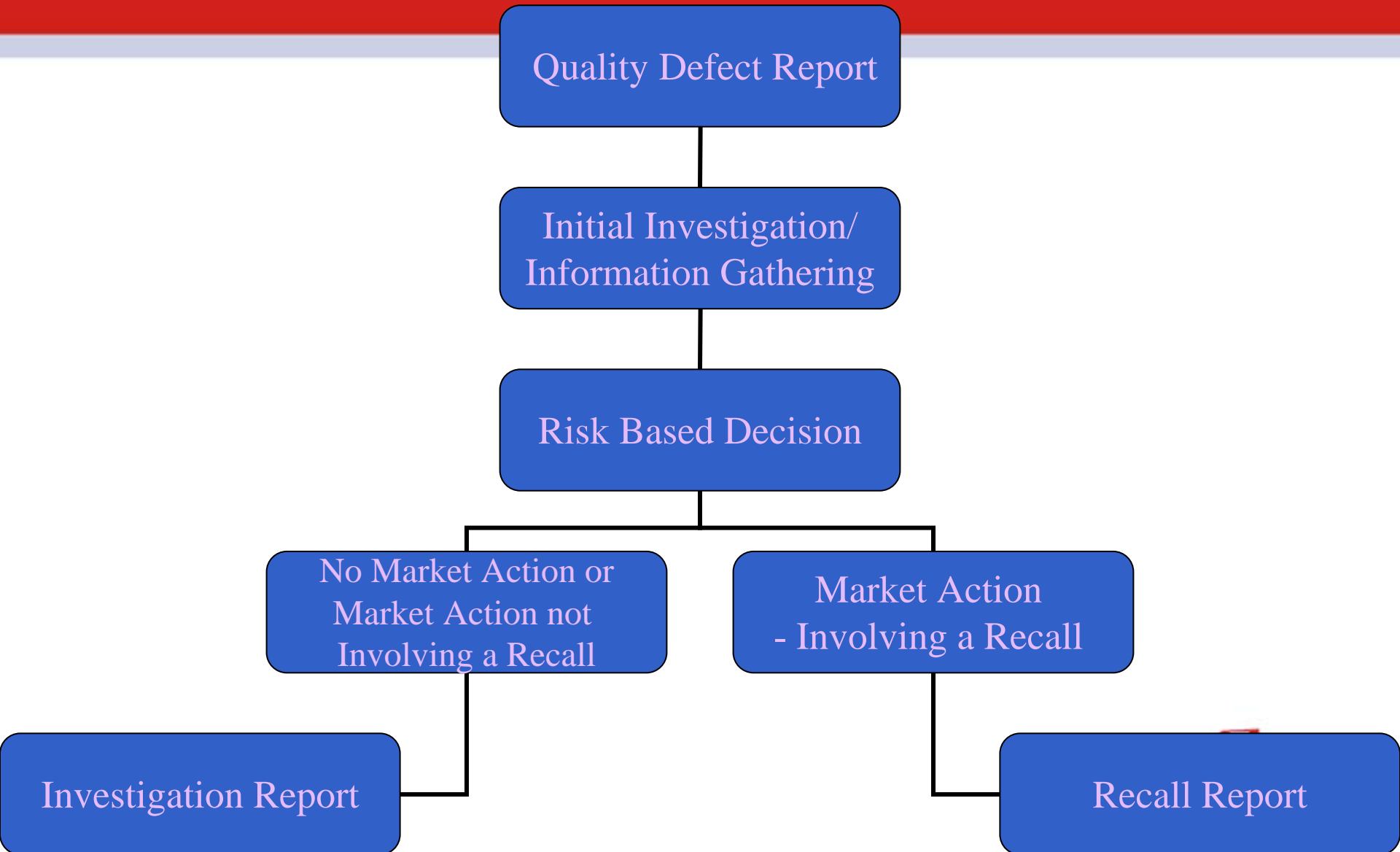
# What is a Quality Defect?

- An unplanned attribute of a Medicinal Product, or component, which may affect the quality, safety **and/or** efficacy of the product **and/or** is not in line with the approved marketing authorisation/product registration file for that product or component.
- Market Compliance Section (MCS) co-ordinates all Quality Defect investigations and liaises with relevant departments of the IMB as necessary



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# Overview of a Quality Defect Investigation



# Most Frequent Quality Defect Reports

- Most Frequent Quality Defects\*
  - Packaging/Labelling Issues – 40%
  - Contamination Incidents – 15%
  - Stability Issues – 11%
  - Non-Compliance with Test Specifications – 7%

\* (Reported during the period January-September 2008)



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# Case Study 1 – Stability OOS Issue

- **Case 1 - Confirmed Stability OOS Result**
  - **Product:** Powder & Solvent for Solution for Injection
  - **Reported by:** Manufacturer
  - **Product Authorisation:** National Authorisation
  - **Non-compliance/Defect Details:**
    - Confirmed Stability OOS result (1 batch)
    - OOS clarity result at 5°C/ambient, 21 days after reconstitution at 12 month time point (product shelf-life is 24 months)
    - Batch was on the Irish market



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# Case Study 1- Determine the Extent of the Defect

- Key information required by the IMB:
  - Can the batch concerned be expected to remain within specification under its labelled storage conditions in the marketplace?
  - What is the potential impact of the OOS result on the quality of other batches of this product in the Irish marketplace in the same packaging, labelled with the same storage conditions and the same shelf-life?
  - What is the potential impact of the OOS result on the quality of other related products, for example, different strengths of the same product, which are in the same packaging, labelled with the same storage conditions and the same shelf-life?

# Case Study 1 – Determine the Risk to Patient/Animal

- On extrapolation of the stability test result profile for the test parameter in question for the batch(es) at the end of batch shelf-life is an OOS identified?
  - If so, provide a medical opinion as to the clinical impact of that extrapolated stability test result profile on batch efficacy and safety
- Have all other Competent Authorities which have authorised this product for their marketplace been notified of the OOS stability result(s) if they require such notifications?
  - If all relevant Competent Authorities have not been informed, please state which countries have and have not been notified, and provide the justification for this



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# Case Study 1- Risk Assessment

- The root cause was identified promptly by the manufacturer as the presence of silicone in the solution (testing of retained samples from the batch)
- Silicone expected but higher than normal levels observed and were confined to one batch
- Toxicological and Medical related risk assessment by manufacturer indicated no increased risk to patient health based on levels of silicone present
- QDR group reviewed risk assessment and were satisfied with its conclusions and requested an opinion on medical aspects
- IMB Medical staff confirmed risk assessment as acceptable
- IMB Pharmacovigilance database searched to identify any related adverse reactions – none identified



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# Case Study 1- Outcome of the Investigation

- Discussions within the QDR group led to the following decisions:
  - No market action required for units of the batch remaining on the market (IMB decision based on risk considerations)
  - No further units of the batch were sent to Primary Distributor (company decision as a precautionary measure)
  - Batch on the marketplace to be monitored until the end of shelf life for any related complaints or adverse reactions
  - Full investigation report requested including corrective and preventative measures



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# Case Study 2 – Non-Compliances with GMP at API Sites

- **Case 2** - Withdrawal of an Active Pharmaceutical Ingredient (API) CEP by EDQM
  - Number of cases have more than doubled already in 2008 compared to 2007
  - **Product(s)**: An API manufactured at a recently inspected site in China
  - **Reported by**: French Competent Authority (afssaps)
  - **Non-Compliance/Defect Details**:
    - The API manufacturer held a CEP however the building which was registered to manufacture the API had in fact been demolished some months prior to the inspection



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# Case Study 2–Identification of Affected Products in Ireland

- Key Question for the IMB – Are products on the Irish market affected?
  - QDR group searched:
    - The IMB product databases by active substance to identify any PAs/VPAs/PPAs, Clinical Trials, CAPs using implicated API from that manufacturing site (correct name and address of the site is vital)
    - The IMB Notification System database for any exempt products containing the APIs in question
  - QDR group contacted the Irish Pharmaceutical Union to search their database for exempt products sourced prior to Feb 2008



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## Case Study 2 – Assessment by MAH/Manufacturer

- MAH/Manufacturer of identified finished products (FP) were contacted by the IMB to confirm supplier of API and marketing status of the FP
- Requested details of quantities of any in-date FP batches containing the API
- Risk assessment requested regarding:
  - Product on the Irish marketplace containing the implicated API
  - The future release of FP containing API from the supplier in question
- Alternative API supplier available?



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## Case Study 2 – Assessment by MAH/Manufacturer

- MAH confirmed that last API batches were manufactured prior to demolition of the building
- No market action e.g. recall, requested by afssaps in France
- Risk assessment and production/analytical data was provided and concluded that the API batches were of appropriate quality – IMB agreed with the findings
- MAH to vary licence to remove the manufacturer as an API supplier



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# Case Study 3 – Packaging Error

- **Case 3** – Package Leaflet Error
  - **Product:** 100mg Powder and Solvent for Solution for Injection
  - **Reported by:** MAH
  - **Non-Compliance/Defect Details:**
    - The Package Leaflet contained incorrect instructions for solvent volume to use for reconstitution
    - Potential for over-dosage as the dose is calculated based on weight of the patient
    - The stated volume was approx. 50% less than that required



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## Case Study 3 – Extent of the Defect

- MAH confirmed that the defect was confined to 1 batch distributed to Ireland only
- Error on Package Leaflet only – SPC and outer carton contained correct reconstitution details
- Quantities remaining at Warehouse, Primary Wholesaler and Secondary Wholesalers confirmed and quarantined
- Quantities distributed to pharmacies were calculated and recipient pharmacies were identified



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# Case Study 3 – Risk Assessment by MAH/Manufacturer

- The following aspects were included in the risk assessment provided by the MAH/Manufacturer:
  - Overdose is possible but likelihood of occurrence is low
    - Information correct on outer carton, SPC and Educational Information provided to Healthcare Professionals
  - Patient group involved are infants and neonates
    - Vulnerable patient group (low body weight)
  - Limited data available on effects of overdose with this substance



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# Case Study 3 – Risk-Based Decision

- Ideal Actions Required;
  1. Recall required to retrieve affected batch from the marketplace
  2. Rework of remaining stock at manufacturer to include correct Package Leaflet
- Considerations for the above actions;
  - 1.a Alternative compliant batch available?
  - 1.b Alternative therapeutically equivalent product available?
  2. Timelines for the approval, correction and reprinting of the Package Leaflet?



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# Case Study 3 – Market Action

- No alternative batches available
- No therapeutically equivalent product readily available
- Timeline for rework (2 months) would result in an out of stock situation
- Therefore an alternative approach was required to ensure continuity of supply
- For stock already on the market the QDR group instructed the company to:
  - Identify all affected pharmacies and contact them via telephone to inform Pharmacists of the error and obtain prescribers contact details



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# Case Study 3 – Market Action

- Issue a Dear Doctor Letter (DDL) to all prescribers and possible administering Healthcare Professionals
- Pharmacies with remaining stocks were issued the DDL and asked to provide a copy of DDL with each pack dispensed
- For stock at the manufacturer (manufacturer supplies directly), the QDR group instructed the company to:
  - Attach the DDL to the outer carton of all remaining packs to make Healthcare Professionals aware of the error
  - Document the operation of attaching the DDL to remaining packs
    - Overseen by QP or RP
    - Packs not to be opened



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# Case Study 3 – Investigation Report

- Investigation report was requested once initial remedial/corrective actions were completed
  - Root cause was identified as ‘copying’ text for a different strength when updating the Package Leaflet but failing to alter the reconstitution details
  - This is a very common type of error
  - Error not identified during QA checks
  - SOP updated to prevent ‘copying’ when drafting changes to artwork components
  - Automated proof-reading implemented for QA checks

# When Should a MAH/Manufacturer Report a Quality Defect to the IMB?

- Both Human and Veterinary EU Directives, **2001/83/EC** as amended and **2001/82/EC** respectively, state that manufacturers of medicinal products must comply with the relevant EU Good Manufacturing Practice Directives
- Relevant articles in each:
  - GMP Human Medicinal Products – **2003/94/EC Article 13(1)**
  - GMP Veterinary Medicinal Products – **91/412/EEC Article 13**
- EU Guidelines to GMP for Medicinal Products for Human and Veterinary Use
  - **Chapter 8 – Complaints and Product Recall**
    - Chapter 8 – Specifically 8.8



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# When Should a MAH/Manufacturer Report a Quality Defect to the IMB?

- **Medicinal Products (Control of Manufacture) Regulations 2007, SI 539 of 2007; Schedule 2, paragraph 31 –**

*'Where the authorisation holder considers that there may be grounds for the recall, or for the imposition of an abnormal restriction on the supply of a particular medicinal product manufactured by him or her, or of a batch or part of batch thereof, he or she shall consult with the board in relation to the action which may be considered appropriate in the circumstances'*

- **Medicinal Products (Control of Placing on the Market) Regulations 2007, SI 540 of 2007; Part 3, paragraph 6 (j)-**

*'The holder of a marketing authorisation, certificate of registration, or certificate of traditional use registration shall promptly inform the board of any defect that **could** result in a recall **or** abnormal restriction on supply of the medicinal product concerned'*



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# When Should a MAH/Manufacturer Report a Quality Defect to the IMB?

- **European Communities (Animal Remedies No.2) Regulations 2007, (SI No. 786 of 2007), Schedule 5 paragraph 23:**

*'If the licence holder considers that there may be grounds for the recall, or for the imposition of an abnormal restriction on the supply of an animal remedy manufactured by him or her, or of a batch or part of a batch thereof, he or she shall consult with the Board in relation to the action which may be considered appropriate in the circumstances'*

- If in doubt, contact a member of the QDR Programme (Names provided on last slide)



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# Initial Quality Defect Report Requirements

- MA Number(s)
- Exact Product Name and Dosage Form
- Active Ingredient(s) and Strength(s)
- Batch Number(s) and Expiry Dates of the affected batches
- Complete Description of the Defect
- Extent of the Defect
- Sample of the affected product, (if appropriate)



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# Initial Investigation/Information Gathering

- Determine the extent of the defect:
  - Number of batches affected
  - Number of affected units in each batch
  - Number of units of each batch at Primary Wholesaler
  - Distribution details including date of first distribution for each affected batch in Ireland
  - Number of similar complaints against the batch or product from any marketplace
  - Other products affected or potentially affected by the same defect



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# Initial Investigation/Information Gathering

- Assessment of the Risk to the Patient, Animal or other End-User
  - Seriousness of the defect
  - Route of product administration
  - Patient groups
  - Method of Sale or Supply
    - Prescription versus OTC
    - Hospital only product versus non-hospital product
  - Detectability of the defect & other risk-mitigating controls



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# Risk-Based Decisions

- Risk to the end user and the extent of the defect is assessed by the QDR group based on the information provided by the Manufacturer or MAH and knowledge of IMB staff
- Defect classified as Critical, Major, Minor or Non-Justified,
- Requirement for market action is considered ;
  - Replacement batches available?
  - Availability of alternative products?
  - Patient impact of a disruption in supply?
- Most QDR cases **DO NOT** result in any market action



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# Risk-Based Decisions (2007)

No. QDRs 2007	473	(100%)
No. Recalls 2007	97	(20%)
No. CIUN/DDDL 2007	21	(5%)

- 25% of QDRs Resulted in Market Action in 2007



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# Market Action - Recalls

- A recall may be defined as the retrieval from the marketplace of a batch or a number of batches of a medicinal product as a result of a quality defect or a non-compliance
- Retrieval of a batch or batches is considered a recall once the batch(es) has been QP released and left the site of the manufacturer that QP released the batch(es) to the Irish market
- Different types of Recalls – See recall guidance note on IMB Website (Soon to be updated)
  - Batch or Product Recalls
  - Different Levels of Recall
  - Targeted or Blanket Recalls



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# Market Action – CIUN/DDDL

- Used to inform relevant Healthcare Professionals of a Quality Defect or other safety concern so that they may deal with it accordingly and take the necessary risk-mitigating cautionary measures
- Issued when a recall to retail/hospital/pharmacy level is not desirable or possible but where the issue needs to be highlighted to Healthcare Professionals so that additional caution may be exercised when
  - Dispensing
  - Administrating
  - Monitoring the patient
- Targeted or Blanket Notification
- Community and/or Hospital pharmacies
- Relevant Doctor Groups



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# Recall Action - Recall Reports

- Recall Reports due approximately 6 weeks after the start of a recall
- Detailed guidance available on IMB website for content and format
- N.B. Root cause, corrective and preventative measures and reconciliation details for all batches recalled



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# No Recall Action – Investigation Report

- If no market action is deemed necessary by the IMB, a full quality investigation report is still required to be submitted by the MAH/Manufacturer approximately 4 weeks after initial investigation began
- Guidance for content and format available on IMB website
  - N.B. Root cause, corrective actions and preventative measures
- Review may close out the QDR case or result in further action if required



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# Useful Information

- Recall Guidance Note & Investigation Report Guidance Note
  - [www.imb.ie](http://www.imb.ie)
  - Publications Section » Category: 'Safety & Quality – Guidance'
- QDR Group Contact Details:
  - [recallsandqualitydefects@imb.ie](mailto:recallsandqualitydefects@imb.ie)
  - (01) 6764971
- Deirdre Breen (Market Compliance Administrator)
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# Questions

