Examples of critical and major observations from GMP inspections of Manufacturing, QC and Contract Research Organisations

Prequalification Programme: Priority Essential Medicines

Presented by
Ian Thrussell
Head of Inspections
thrusselli@who.int
Session Outline

• This presentation provides a summary of those areas of FPP and API manufacture and their control where deficiencies versus GMP are most commonly found

• Questions
In 2012 Poor quality continues to impact on the patient

- LAHORE: Isotab — contaminated isosorbide tablets supplied by a major cardiac care clinic
- Mystery behind the factors which have caused THE DEATH OF OVER 100 PATIENTS.
- Several thousand patients hospitalized
- Each of them had consumed a chronic overdose of Pyrimethamine every day, which caused immediate bone marrow suppression and a terrible drop in platelet and white blood cell counts, ultimately leading to their deaths.
- Root cause a simple mix up of an excipient and an API during manufacture
  - THE PRODUCT COMPLIED WITH ITS SPECIFICATION!!!!!!!
  - BUT WAS LETHAL!
GMP: assuring the consistency of quality

• Since the establishment of GMP the prime objectives set out in law and guidance has been to:

  – Ensure that products are manufactured batch upon batch, year upon year, to the appropriate and consistent quality standards and in accordance with regulatory requirements by requiring that there be a pharmaceutical quality system.
    – HAVING A QMS IS NOT NEW!
  – Require Marketing Authorisation holders to regularly review their products and their manufacturing processes to ensure that they keep up to date with scientific and technological progress
    – CONTINUAL IMPROVEMENT HAS ALWAYS BEEN A REQUIREMENT of most GMPs!
Prequalification: Inspection Processes

- By a team of qualified and experienced inspectors
  - WHO representative (qualified inspector)
  - Inspector from well-established inspectorate (Pharmaceutical Inspection Cooperation Scheme countries – PIC/S)
  - National inspector/s invited to be part and observe the inspection
  - Observer from recipient/developing countries (nominated by DRA of the country)

- Scope:
  - Compliance with specific GXP guidelines:
    - GMP for API and FPP sites,
    - GCP for CROs,
    - GLP for FPP/API factory QCL, CRO-BAL, NQCL, IQCL

  ➔ Data verification – data manipulation, falsification, (validation, stability, clinical, bioanalytical)
Risk-based approach in: definition and classification of deficiencies

• Deficiencies are descriptions of non-compliance with GMP requirements.

• A distinction is made between deficiencies as a result of: -
  – a defective system or,
  – failure to comply with the system.

• Deficiencies may be classified as:
  – Critical Observation – potential risk harm to the user
  – Major Observation – major deviation from GMP/GCP
  – Minor or Other Observation – departure from good practice
Classification of observations

Critical Observation
• An observation that has produced, or may result in a significant risk of producing, an API that, when used in a finished product, is harmful to the user.

Major Observation
A non-critical observation that:
• has produced or may produce a product which does not comply with its prequalification application (including variations); and/or
• indicates a major deviation from the GMP guide; and/or
• indicates a failure to carry out satisfactory procedures for release of batches; and/or
• indicates a failure of the person responsible for QA/QC to fulfill his/her duties; and/or
• consists of several other deficiencies, none of which on its own may be major, but which may together represent a major deficiency and should be explained and reported as such.

Other Observation
• An observation that cannot be classified as either critical or major, but indicates a departure from good manufacturing practice.

• A deficiency may be “other” either because it is judged as minor, or because there is insufficient information to classify it as major or critical.
WHO-PQ offers new avenues for collaboration in inspection

WHO-PQ Collaborative Procedure in Inspections

- nominated inspectors from NMRAs of selected member states are invited to participate in WHO-PQ organized inspections and in turn, the NMRAs is given appropriate access to outcomes of these inspections.
  - Capacity building of NMRAs inspectors.
  - Facilitating use of WHO-PQ inspection results in national regulatory environment for information and decision making.
  - Facilitation of harmonization through joint inspections and sharing of outcomes.
  - Share the workload and promote avoiding duplicative inspections.

Prequalification Programme: **International norms, standards and guidelines used in inspection activities to ensure wide applicability**

http://apps.who.int/prequal/assessment_inspect/info_inspection.htm#2
Quality Assurance and Quality Management

- Investigations
- Deviations
- Out of specification and out of trend results
- Root cause analysis
- Change Management
- Continual Improvement
- Quality Risk Management
- Quality Review - APRs
ICH Q10 Management commitment (2.1)

- Senior management has the ultimate responsibility to ensure an effective pharmaceutical quality system is in place to achieve the quality objectives and that the roles, responsibilities, and authorities are defined, communicated and implemented throughout the company.

----------*The concept of corporate governance*
Why do inspectors already look at an organisation’s QMS and QRM programmes during inspections?

- Looking at how companies react when things go wrong or are changing and are under pressure is a major diagnostic indicator of the robustness of the scientific and organisational integrity of a company’s operations
  - Do they investigate to improve knowledge or simply build arguments for release of product
  - Quality of investigations - appropriateness of depth of investigation
  - Reactive rather than proactive usage of knowledge
  - Quality is everyone’s responsibility – Is this true when things go wrong?
  - Is the company a learning organisation? And where is it on the learning curve?
Managing Knowledge: Out of Specification, deviations and process failures

OOS results may indicate a flaw in product or process design

• Lack of robustness in product formulation
• Inadequate raw material characterization or control
• Substantial variation introduced by one or more unit operations of the manufacturing process
• Combination of these factors

In such cases, it is essential that redesign of the product or process be undertaken to ensure reproducible product quality
Importance of root cause investigations and risk management
Have we identified and do we understand factors that impact product quality?

Information is not knowledge. Let’s not confuse the two.
- W. Edwards Deming

We are drowning in information but starved for knowledge.
- John Naisbitt
Quality philosophy – After W Edwards Deming

• Learning is not compulsory!
• Adaptation and improvement is not compulsory
• SURVIVAL IS NOT COMPULSORY
ICH Q10 (Management responsibility) … :

‘Leadership is essential to establish and maintain a companywide commitment to quality and for the performance of the pharmaceutical quality system’
Inspection of FPP manufacturers
Poorly understood and poorly designed processes

- Poor understanding of requirements
- Poor product understanding due to inadequate development
- Unvalidated blending at the unit dose level
Poorly designed processes

- Materials transferred between unit processes with inadequate assurance of integrity and contamination risks.
- Inadequate dust extraction and containment.
- Excessive holding times for intermediates that are unvalidated.

Diagram:
- Raw Materials
- Equipment
- Premises
- Environment
- Packaging Materials
- Validated processes
- Procedures
- Personnel
Drying Oven designs!

- Failure to use easy to clean equipment and closed transfers
- No or inadequate filters on the oven
- Difficult to load and unload cleanly without liberating dusts
An open tray drying process where containment is difficult.
Closed systems where containment is excellent
Poorly designed processes

- Raw material suppliers not audited but acceptance of side samples or CoAs accepted with no justification
- No understanding of ingredient variability and its effect on FPP
- Container suppliers and packaging material suppliers never audited
Poorly designed or maintained equipment

- Equipment not easy to clean – especially dust extracts
- No traps in dust extract systems
- Un-validated cleaning and re-use of filters
- Inappropriate filtration grades for the materials handled

Diagram:
- Raw Materials
- Packing Materials
- Premises
- Environment
- Equipment
- Procedures
- Personnel
- Validated processes
Procedures!

- Incomplete process descriptions
- No verification of tablet punch length (leading to greater variability of tablet weight and hardness)
- Sealing parameters – inadequately defined
Equipment
Poorly designed or maintained equipment

- Poor control over metal items – in particular sieves

![Image of metal sieve]
Construction activities

• Major construction in room next to personnel entry airlock (e.g., gowning).
  – Construction occurred over approximately one-month period and coincided with continued production
Premises!

- Inadequate containment or dedication to those materials that are recognised as highly potent or sensitising
- Inadequate dust extraction
- Inadequate filtration of recirculated air
Deficiencies observed during PQ Inspections

PREMISES

• Poor design and construction of premises:
  – Inadequate segregation.
  – Illogical process flow.
  – Inadequate provision for Utilities: HVAC, water, compressed gases

• Poor design and management of the HVAC system:
  – Multipurpose plant used re-circulated air but had no HEPA filters.
  – Adequate pressure differentials: reversal of air flow.
  – No sequence of switching on and off of AHUs of adjacent areas.
Lack of awareness on current guideline in TRS 957 - WHO good manufacturing practices for pharmaceutical products containing hazardous substances

- Inadequate facilities and equipment for handling potent hormone products
- Inadequate containment from both a GMP standpoint BUT also safety and environmental perspective (which are present in the WHO guidance unlike other GMPs)
  - Inadequate HVAC systems
  - Lack of training including hygiene practices, gowning
Lack of awareness on current guideline in TRS 957 - WHO good manufacturing practices for pharmaceutical products containing hazardous substances

• Not all products containing hazardous substances are equally potent and risk assessments should be carried out to determine the potential hazards to operators and to the environment.

• This guidance gives standards for the most potent but it is possible to justify other approaches depending upon risk.
  – Areas of the facility where exposed product presents a risk should be maintained at a negative air pressure relative to the environment.
  – The facility should be a well-sealed structure with no air leakage through ceilings, cracks or service areas.
TRS 957 Expectations

- Where possible, single-pass air-handling systems with no recirculation
- Exhaust air or return air should be filtered through a safe-change or bag-in-bag-out filter housing.
- Airlocks, pass-through hatches, etc., should have supply and extract air to provide the necessary air pressure cascade and containment.
- The starting and stopping of the supply and exhaust air fans, and associated system ventilation fans, should be synchronized such that the premises retain their design pressure.
Deficiencies observed during PQ Inspections

MATERIALS

• Inadequate goods and materials management
  – Starting materials: sourcing and sampling – ID per container.
  – Packaging materials: inadequate sampling – ISO2859 or BS6001.
  – Intermediate and bulk products – holding time not set, or justified, or respected.
  – Finished products: Release procedures – no adequate review by QA or QP.
  – Rejected materials and products: not adequate segregation or disposal.
  – Reagents and culture media: no GPT, positive and negative control
Poorly designed or executed micro monitoring

- Water TVC sample points for water not close to point of use
- Materials in use that are at risk of spoilage – coating solutions
- Monitoring is not risked based and “too routine”
Packaging
Packaging material control!

- No 100% verification of issued packaging materials at the point of use
- No 100% verification of filled blisters
- No in-process check for the integrity testing of blisters.
Raw Materials material control!

- No 100% verification of the identity of received raw materials
- Dispensing of materials carried out in a way that does not minimise the risk of cross-contamination
- Water hoses not drained fully after use. Common to see a number of hoses containing pooled water.
Validation!

- Non-risk based validation leading to a failure to concentrate on risks and doing non-value added validation by rote!
- Poor practices for usage and cleaning accepted as covered & justified by “passing” results of manual cleaning or residue testing!
- Good history does not mean failures do need not be investigated
Validation

- Incomplete validation of content uniformity and blending due to sample size taken
Poor cleaning practices

- Un-validated cleaning
- Heavy use of manual cleaning techniques which are difficult if not impossible to validate
- Risks from machine lubricants
- Long campaigns during which contamination accumulates
Deficiencies observed during PQ Inspections

**FPP manufacturers:** – sterile products

**Poor aseptic techniques:**

- Asepsis compromised by “safety” design
- Safe collection systems and vacuum can and have failed leading to contamination of cytotoxic injectables

**Alternative dosage forms:**

- Inadequate evidence of validity of media fill tests due to residues of potent materials
- The nature of the vehicle not taken into account when designing sterilisation validation
  - E.g. Does the sterilant reach the locations where microorganisms may be protected.
Deficiencies observed during PQ Inspections

**FPP manufacturers: – sterile products**

**Poor aseptic techniques:**
- Extensive movement of operators in Grade A close to the open vials.
- Vials that were not stoppered by the machine taken from the conveyor belt into class B area and manually placed back into class A to be manually stoppered.
- Inadequate Media Fill Tests

**Environmental monitoring:**
- The viable particle continuous monitoring for Grade A zone does not cover the whole time period of setting up of the equipment and the vial filling-capping process.
- Personnel garments and gloves were not monitored after manufacturing operations in grade A/B areas
Inspection of API manufacturers
Deficiencies observed during PQ Inspections
API manufacturers

- The most frequently found deficiencies were:
  - Material management
  - SOPs
  - Cleaning
- Others included:
  - Batch records
  - Labelling
  - Cross contamination
WHO GMP for APIs: Buildings, utilities and equipment

- Facilities, equipment and utilities system
  - Facilities designed to prevent mix-ups and contamination (4.10)
  - Precautions implemented based on a risk assessment
    - Utilities (HVAC, compressed air and other gases etc) qualified and monitored, as appropriate.
  - Buildings and equipment cleaning methodology and intervals appropriate to prevent build-up and carry-over of contaminants (degradants)
Why is a Split Unit bad news?

- RETURN AIR
- Poor quality Air filter
- Cooling Coil
- Condensate drip tray
- SUPPLY AIR
- Wards?
- Fan liberates dust into the air
WHO GMP for APIs: Production…

• Production
  – Blending operations (section 8.4)
    • Only batches meeting established specifications
    • Expiry or retest date of the blended batch based on the manufacturing date of the oldest batch included.
    • Should be controlled and documented – traceability
    • Validation for homogeneity following blending

OOS batches blended with others:
1. Blending small batches to increase batch size
2. Blending tailings

APIs for OSDs/ Suspensions
1. Particle size distribution
2. Bulk density
3. Tap density
WHO GMP for APIs: Reprocessing & Reworking

- Reprocessing or reworking for intermediates or APIs which do not conform to standards or specifications

  - Reprocessing (s. 14.2)
    - Repeating a step of the established manufacturing process
      - Crystallization, distillation, filtration, chromatography, milling, etc
      - Continuation to completes process after IPQC in not reprocessing
      - Introducing unreacted material into reaction is reprocessing
    - Included in the standard manufacturing process if reprocessing used for a majority batches

  - Reworking (section 14.3)
    - Reason for non conformance determined prior to any reworking
    - Involves a “treatment” different from the established one
      - Recrystallization with a a different solvent
    - Reworked batches to be subjected to appropriate evaluation, testing ± stability testing
      - Concurrent validation
      - Should have comparable impurity profile
WHO GMP for APIs: Recovery of materials

- Recovery of Materials and solvents
  - Reactants, intermediates or APIs may be recovered from mother liquor or filtrates.
  - Must use approved procedures and specifications.
  - Recovered solvents may be reused in same process or in different process if confirmed to meet appropriate standards.
  - Fresh and recovered solvents and reagents can be combined if their adequacy is confirmed.

1. No approved procedures
2. Specs – carry over impurities
3. Not adequately tested
4. Use not documented

1. Approved procedures
2. Suitable specs
3. Adequate testing
4. Use documented
Inspections of Contract Research Organizations (CROs)
CRO/BE Inspections: Problems with integrity, archiving and retrieval of documents
CRO/BE Inspections: Inadequate data integrity

Source data either not available or authenticity questionable:

• Source data could not be located to verify entries in VRFs
  – destroyed accidentally by fire or rain
  – Sponsor claims the data were kept by the CRO, and the CRO claims the data were kept by the sponsor

• Two of the ECGs shown to the inspectors, bearing different subject numbers and initials, were found to be identical.

• Other ECGs bearing different subject numbers and initials appear to have been recorded from a single subject. Out of 95 ECGs copied by the inspectors, 43 appear to have been recorded from the same and single subject during a single session.
CRO/BE Inspections: Data manipulation – inappropriate manual integration of peaks

- Manual reintegration of peak was done inappropriately and inconsistently for all peaks inclusive internal standard
  - For some samples checked, especially QCs or standards close or outside the 15% of their nominal concentration, the baseline of the chromatograms were modified manually. This was not done appropriately and consistently for all peaks inclusive internal standard. For modified integration, initial integration was not available.
- No paper or electronic audit trail of manual integration available.
- Each analytical run did not include calibration and quality control samples.
CRO/BE Inspections: Data manipulation - Identical chromatograms had different peak areas but the same area percent.
Deficiencies observed during PQ Inspections
QC Laboratories: Conclusions

• Data manipulation and misrepresentation is not acceptable to the WHO and according to the law of most national regulatory authorities (could result in the publication of NOC or NOS on behalf of the WHO).
• The honest way is always the "right way".
• Good ethics are key to reliable data.
• Always prioritize data integrity – not quick batch release at any cost.
Questions?