QUALITY COMPLIANCE CHALLENGES AND CURRENT TRENDS FOR PHARMACEUTICAL PRODUCTS

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AGENDA

■ Introduction
  • GMP Overview

■ Quality Systems & GMP Compliance
  • GMP Quality System: Deficiencies
  • Current trends
    – US FDA Warning letters
    – UK MHRA Observations
    – WHO Observations

■ Conclusion

■ Relevant links
GMP OVERVIEW (1/4)

- GMP is that part of Quality assurance which ensures that the products are consistently manufactured and controlled to the Quality standards appropriate to their intended use.

- "GMP" - A set of principles and procedures which, when followed by manufacturers for therapeutic goods, helps ensure that the products manufactured will have the required quality.

- Usually see “cGMP” – where c = current, to emphasize that the expectations are dynamic.
GMP OVERVIEW

SOURCES FOR GMP (2/4)

- EU
  - EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines and Annexes

- USA
  - 21 CFR Part 210/211

- ICH
  - Q7A GMP for APIs and guidelines, e.g. Stability studies, analytical method validation, etc.

- PIC/S
  - GMP Guides and Annexes

- WHO
  - Technical reports & guidelines on GMP, GDP (Shipping & packaging), etc.
GMP Covers...

- **ALL aspects of production;** from the starting materials, premises and equipment to the training and personal hygiene of staff.

- **Detailed, written procedures are essential for each process** that could affect the quality of the finished product.

- **There must be systems to provide documented proof that correct procedures are consistently followed at each step in the manufacturing process - every time a product is made.**
GMP OVERVIEW
GMP FOR FINISHED PHARMACEUTICALS (4/4)

- Quality Management
- Personnel
- Building & Facilities/Equipment
- Documentation
- Production
- Quality Control

- Contract Manufacture and Analysis
- Packaging & Labeling Control
- Handling & Distribution
- Complaints and Product Recall
- Self Inspection
Quality Management System
- QA unit: roles/responsibilities
- Change control
- CAPA system
- Deviations/OOS investigations
- Root cause analysis
- Trends/evaluation of recurrence
- Unclear concepts core systems

Personnel
- Training program
- Regular GMP training
- Job descriptions
- Permanent staff vs. temporary staff
- Personnel Qualification: i.e.: fill & finish area and gowning
- Training on SOPs
- Assessment of training
Building & Facilities/Equipment/Production

- Facilities not adequate for the intended use
- Layout and contaminations/cross-contamination
- Qualification of areas (A/B/C/D)
- Monitoring (T, RH, EM)
- Pest control program
- Preventive Maintenance program (calibration, qualification, cleaning)
- Equipment management: Qualification, calibration, cleaning, service & periodic maintenance.
- Sterile suite: gowning qualification, media fill.
- Raw materials & controls
GMP QUALITY SYSTEM: DEFICIENCIES (3/5)

- **Documentation**
  - SOPs not followed
  - Activities not documented
  - Data integrity issues
  - Lack of supporting data, traceability
  - Inconsistencies in data recorded
  - Approvals records/ SOPs/etc
  - e-QMS systems validation (audit trails, review)

- **Quality Control**
  - Analytical methods not validation/ transferred/ verified.
  - Qualification of primary standards / accountability
  - Management of analytical equipment
  - Raw materials:
    - Lack of testing/ acceptance criteria/specs;
    - EP/USP testing (management of updates)
  - Disinfectants/cleaning agents: validation/effectiveness
Contract Manufacturing / Suppliers / 3rd Parties
- Quality agreements & responsibilities
- Management of Subcontractors & Suppliers
  - Qualification process (disqualification included)
  - Monitoring
  - Procedures

Packaging & Labeling Control
- Reconciliation
- Storage of labels
- Documentation
Handling & Distribution
- Warehouses: qualification
- Shipment: validation (airplane, road)
- Shipping boxes (cold store): qualification
- Temperature Monitoring
- Logistics/ Customs delays

Complaints and Product Recall
- Management of complaints (PTC & PV) and call tree.
- Recall: procedures / mocks
14 manufacturers of APIs received a Warning Letter (WL)

> 3 times than in the previous fiscal year = 5 Warning Letters

Location: China, India, Canada, Spain, UK & US

US FDA almost always found deficiencies in the area of analytics:
  - Use of not validated analytical methods,
  - Lack of appropriate processes as well as instructions for investigations following OOS results.
  - Handling of documentation and analytical raw data.

Source: Dr. Gerhard Becker, CONCEPT HEIDELBERG, Inadequate Validation of Analytical Methods remains permanent Topic in Warning Letters to API Manufacturers, ECA 18/Jan/2012.
MAIN FINDINGS:
ASIAN API MANUFACTURERS (2/4)

Systemic Deficiencies:
- No PQ and Calibration of lab devices
- Inadequate analytical procedures
- No analytical methods validation, no confirmation of stability indicating significance
- No qualification and calibration of QC laboratory instruments
- No testing of solvents before batch certification despite confirmation on the certificate
- No raw data from incoming test
- No SOP for OOS investigations, management of deviations. Incomplete investigation after OOS results

Other issues:
- No SOP for Change Control, in production
- No SOP for complaint management, annual product review
- No process validation
- Incomplete cleaning validation
- Impurities due to inappropriate building design
- No investigation of cause after complaints
- No SOP for preventing cross contamination

Source: Dr. Gerhard Becker, CONCEPT HEIDELBERG, Inadequate Validation of Analytical Methods remains permanent Topic in Warning Letters to API Manufacturers, ECA 18/Jan/2012.
Systemic deficiencies:
• Handling of raw data not GMP compliant
• No stability studies to support the expiration date
• Inappropriate analytical methods
• No stability testing
• No investigation following OOS results
• Inappropriate analytical methods
• Missing analytical raw data

Other issues:
• No qualification of the equipment for purified water
• Inadequate deviation management by the quality unit
• No process validation

Source: Dr. Gerhard Becker, CONCEPT HEIDELBERG, Inadequate Validation of Analytical Methods remains permanent Topic in Warning Letters to API Manufacturers, ECA 18/Jan/2012.
### Main Findings: API Manufacturers USA (4/4)

#### Systemic deficiencies:
- Inadequate documentation and misinterpretation of analytical data
- No analytical methods validation
- No investigation following OOS results
- No qualification of analytical instruments
- No calibration of balances
- No methods validation

#### Other issues:
- Subsequent entry in the batch protocol
- No cleaning protocols
- Batch certification with invalid specifications
- Release of an outdated Certificate of Analysis
- No investigation of cause after complaints
- No qualification of contract labs, no supplier qualification
- Poorly trained personnel

Source: Dr. Gerhard Becker, CONCEPT HEIDELBERG, Inadequate Validation of Analytical Methods remains permanent Topic in Warning Letters to API Manufacturers, ECA 18/Jan/2012.
CONTINUING TREND: USFDA JAN-SEP/2012 WL (1/1)

- Warning letters mainly addressed to EU API manufactures.
- Similar trend as 2011 with main findings in:
  - Analytics area:
    - Use of unsuitable laboratory instruments,
    - GMP non-compliant handling of raw data,
    - Lack of appropriate analytical processes as well as the requirements for investigating OOS-results,
    - Inadequate management of reference standards
  - Main findings Buildings/ Facilities & Cross Contamination:
    - No adequate maintenance SOP to prevent contamination or carry-over of a material that would alter the quality of the API.
    - Failure to use dedicated production areas, including facilities and air handling equipment, and process equipment.
    - No procedures to adequately clean and store equipment und utensils to prevent contamination or carry-over of material that would alter the API beyond the established specifications.
    - Lack of maintenance of buildings and equipment.

Source: Dr Gerhard Becker, CONCEPT HEIDELBERG, Continuing Trend: Again, Numerous Warning Letters issued to European API Manufacturers, ECA 25/Jul/2012.
Production and process controls

- Failed to establish and follow written production and process controls for the execution of various production and process control functions
- Failed to assure an adequate system for monitoring environmental conditions
- Failed to assure an adequate system for cleaning and disinfecting aseptic processing areas and equipment
- Failed to establish and follow a written testing program designed to assess the stability characteristics of drug products

Source: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm
Failure investigations

- Investigations into the failure of a batch or any of its components are inadequate
- Investigations of process failures are incomplete and/or corrective actions are inadequate (not extended to other impacted areas)

Laboratory controls

- Assay XXX for Influenza Vaccine not validated
- No data to support the acceptance range of the assay.
- Failed to establish the accuracy, sensitivity, specificity, and reproducibility of test methods

Source: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm
UK MHRA TRENDS:
MAR 2010 – APR 2012 DEFICIENCIES (1/2)

- 303 inspections with 26 critical observations and 644 major observations

- Deficiency Categories:
  - Investigation of Anomalies - CAPA
  - Quality Management - Change Control
  - Complaints and Product Recall
  - Quality Management
  - Supplier and Contractor Audit
  - Contamination, Chemical/Physical - Potential For
  - Documentation/ Procedures/ Technical Agreements/ Manufacturing
  - Process Validation

Investigation of anomalies (97 cases)

Change Control (70 cases)

Direct contaminations of product (75 times):
  • 44 of which were chemically/physically based and 31 microbial.
  • "Contamination" is for the first time one of the "Top Ten".

CAPA (63 cases).

Personnel training and hygiene (57 cases)

Investigation of OOS (33 cases).

Source: Axel H. Schroeder, CONCEPT HEIDELBERG (a service provider entrusted by the ECA Foundation) – 04/Jul/2012.
WHO INSPECTIONS
NOTICES OF CONCERN (NOC), MAY-NOV 2011

- NOC available on WHO website
- Manufacturers: 3 sites in India reported
  - Facilities not adequate to the intended purpose
    - Areas used in production of sterile products not classified.
    - Failure to comply with EM requirements
  - Failure to handle deviations
  - Failure to appropriately ensure the quality of key material (including starting materials) before being used in the manufacture process.
  - Not adequate equipment management & maintenance activities
  - Not appropriate laboratory controls
    - e.g. Audit trail for HPLC, calibration activities, etc
  - Inadequate validation documentation.

Source: http://apps.who.int/prequal/assessment_inspect/info_inspection.htm#6
CONCLUSION (1/3)

- **EQUIVALENT PRINCIPLES**
  - for GMP Quality System (ICH, WHO, etc.)

- **SIMILAR TRENDS**
  - for GMP Quality Deficiencies identified and published by WHO and Health Authorities (US FDA, UK MHRA)

- **SYSTEMIC DEFICIENCIES**
  - Identified by US FDA in Asia, EU, USA:
CONCLUSION (2/3)

KEY QUALITY AREAS IMPACTED

- Quality Management
  - CAPA, Deviations, OOS & investigations, Change Control, etc
- Personnel
- Building & Facilities/Equipment
- Documentation
- Production & Quality Control
  - Process validation, analytical methods validation, etc
- Supplier management
- Complaints and Product Recall
- Warehousing and Distribution
CONCLUSION (3/3)

Learning from GMP Compliance Deficiencies not only from
the internal audit program, but also from external sources
is a

- powerful quality management tool
- to continuously improve the quality system and
- avoid future failures and/or recurrence
RELEVANT LINKS


- WHO “World Health Organization” website: [www.who.int](http://www.who.int)
  - WHO NOC: [http://apps.who.int/prequal/assessment_inspect/info_inspection.htm#6](http://apps.who.int/prequal/assessment_inspect/info_inspection.htm#6)

- USFDA “US Food and Drug Administration” website: [www.fda.gov](http://www.fda.gov)

- UK MHRA “Medicines and Healthcare products Regulatory Agency” website: [www.mhra.gov.uk](http://www.mhra.gov.uk)

- PIC/S “Pharmaceutical Inspection Co-operation Scheme »: [www.picscheme.org](http://www.picscheme.org)
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