Centre for Biopharmaceutical Excellence

# Quality System Gap Analysis

## Readiness for Pre-Certification Inspection





# Some Useful Reference Documents

- WHO – GMP: Main Principles for Pharmaceutical products,
- EU/PICs/TGA cGMPs – Chapter 1 – Quality Management,
- **ICH Q10 - Pharmaceutical Quality System,**
- ICH Q8 – Pharmaceutical Product Development,
- ICH Q9 - Risk Management in Pharmaceuticals,
- FDA Quality Systems Approach to Pharmaceutical CGMP Regulations (9/2006),
- GHTF - GHTF/SG3/N15R8 - Implementation of risk management within a Quality Management System

# Major International Codes of GMP

- **PIC/S Guide to Good Manufacturing Practices - PE 009 - 2014**
- **EU Guide to Good Manufacturing Practices (Eudralex Ch 4)**
- **World Health Organisation (WHO) cGMPs**
- **United States - FDA CFRs Part 21**
  - CFR 210/211 for Drugs and Biologics - current GMPs
  - CFR 820 Quality Systems for Medical Devices - current GMPs
- ICH Q7 GMP for Active Pharmaceutical Ingredients
- Canadian cGMP (aligned with PICs)
- ISO 13485 : 2003 - Medical Devices
- ICH Guidance Documents – Technical Standards




# Conducting the Gap Analysis

- Brief the team on the focus of the gap analysis;
- Provide advance notice to the Department Heads of the coming gap analysis including the dates, the focus areas and likely documentation required;
- The Department Heads should brief their own teams as well as the supporting teams;
- There should be an emphasis of honestly answering the auditor questions and providing the requested information;
- The Department Head should put aside the necessary time to fully participate in the gap analysis (this is good training)

## Expectations of a Licenced GMP Manufacturer

- A robust Quality Management System which consistently supports the principles of QbD, (controls) defects to known and detectable levels and does not rely entirely on testing for detection of non conforming product,
- Releases Finished Products to the market which consistently meet their registered release specifications,
- Has well defined, documented and controlled manufacturing processes,
- Employs appropriately educated, experienced and competent staff,
- Maintains fit for purpose facility infrastructure and production/testing equipment,
- Uses defined risk based procedures which establish the elements of sampling, testing, validation and monitoring of direct and indirect systems of a manufacturing facility,
- Meets all of the required elements of the applicable codes of GMP as a minimum.



## Self Inspection, gap analysis. Why?

- Self regulation? This has not worked consistently across many decades
- Management should not see compliance as a cost-benefit exercise
- We prescribe to unwell patients with the aim of improving quality of life and potentially curing the illness.
- Finished products should always be suitable for their intended use, should do no harm and have no unintended effects,
- There should be no unknown side effects as a result of variation in product quality (e.g. variation in efficacy, purity, identity, safety).
- Use risk principles when assessing your manufacturing operations

## Utilising External Gap Analysis

- External “eyes” are unbiased and objective;
- Ability for Senior Management to pick an external specialist team to deliver a particular, targeted outcome;
- Supplement companies own self inspections;
- External Gap Analysis can focus on perceived “problem” areas;
- Objective final or interim reports are provided directly to the Senior Management Team;
- Can be very useful if the self inspection audits and CAPAs are not resolving ongoing GMP issues;
- Very useful in helping with the audit of external suppliers of raw materials, APIs, packaging – again if there are ongoing variability issues;



## The Purpose of the Gap Analysis

- Identify major and critical cGMP issues;
- Identify where capital $ are needed, or not;
- Identify time-frames / effort for any major gap remediations;
- Check “Hardware” status
  - HVAC, Water, Compressed Air, Steam
  - Facility and Cleanrooms
  - Steriliser validated status and build
  - Cross contamination potential and cleaning validation
  - GMP related computer systems and ERES** compliance

** Electronic Records and Electronic Signatures

# The Purpose of the Gap Analysis

- Check “Software” / Documentation
  - Evaluates the quality system – is it “robust” and “linked” ? And supported by records
  - Documentation and records systems
  - Process validation, sterilisation validation, EM program etc.
- Helps the company get focussed on what’s important;
- Evaluates PQ Audit readiness – are the managers organised and prepared for inspection ?
- What remediation teams would be needed.




# The Purpose of the Gap Analysis

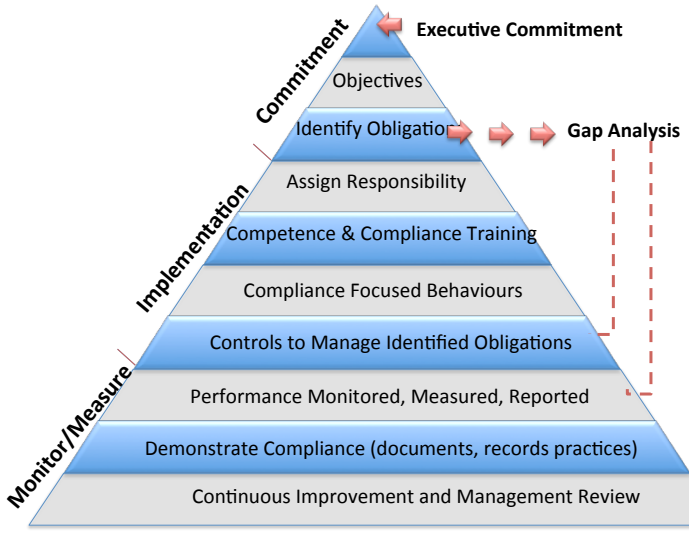
- Think about <u>why</u> and the purpose of the Gap Analysis (impending audit, ongoing unresolved deviations?),
- Is there are specific outcome required? Document it – provide the outcome in the form of an audit scope document;
- Regulatory inspectors – a quick walk through the facility? Have your teams on their best behaviour for the week? Give the place a lick of paint and a good clean up the week before? Is this enough of a gap analysis before a regulatory inspection?
- The second point is unlikely to deliver much value in understanding where the actual gaps in the QMS systems are.

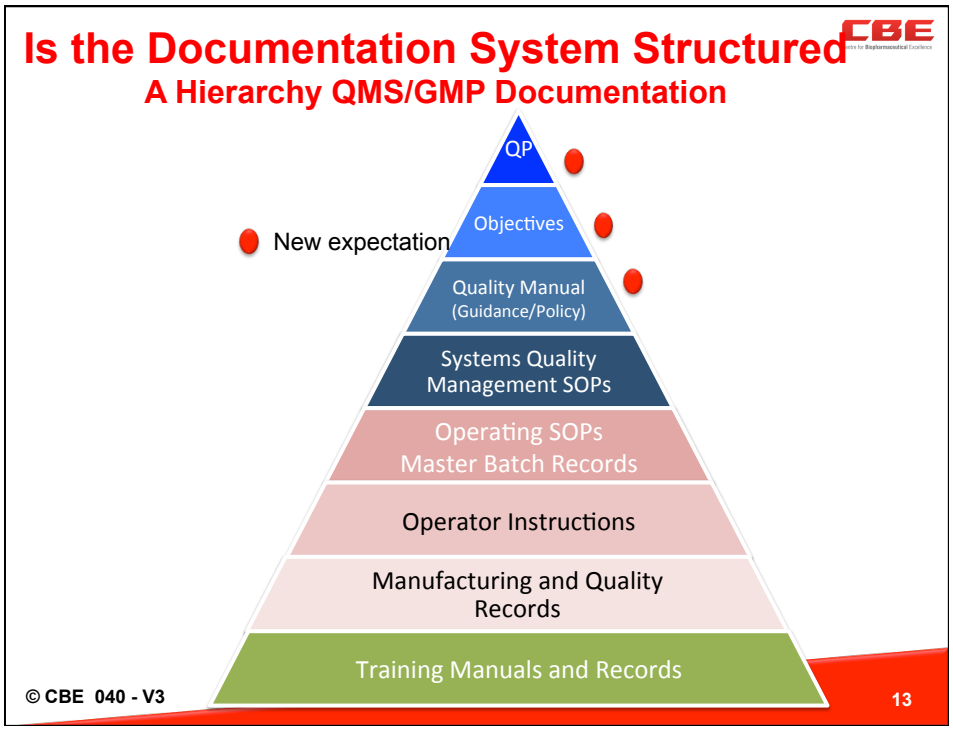
# Gold Mine of Information
## Deviation Systems – good place to start

- **Deviation Register**
  - How are the deviations rated? Too many low risk deviations?
- **CAPA System / Register** – this is a must when conducting gap analysis
  - How good and scientific are your investigations & conclusions?
  - How effective are the corrective actions in addressing problems?
  - Does the report stand up to your scrutiny? scrutiny of an inspector ?
- **Complaint Register** – what problems escaped to the market ?
- **PQRs** – quickly evaluate products of interest




# Compliance Programs




Is the Documentation System Structured
A Hierarchy QMS/GMP Documentation
QP
Objectives
New expectation
Quality Manual
(Guidance/Policy)
Systems Quality
Management SOPs
Operating SOPs
Master Batch Records
Operator Instructions
Manufacturing and Quality
Records
Training Manuals and Records
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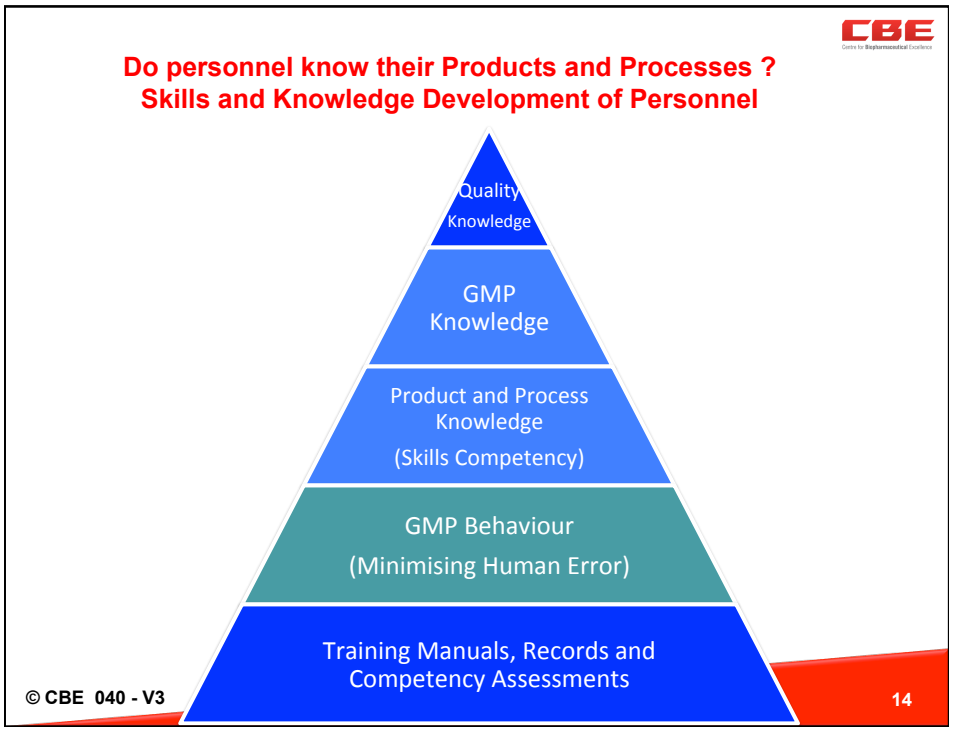
Do personnel know their Products and Processes ?
Skills and Knowledge Development of Personnel
Quality
Knowledge
GMP
Knowledge
Product and Process
Knowledge
(Skills Competency)
GMP Behaviour
(Minimising Human Error)
Training Manuals, Records and
Competency Assessments
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# Quality and Compliance

- **Quality refers to:**
  - **Product Quality** – meeting agreed specifications
  - **Quality Systems** – planned and deployed processes (systems) used to monitor, report and take corrective actions
- **GMP Compliance refers to:**
  - Identification, documentation and deployment of GMP obligations – Meeting cGMP intent
  - Verification that GMP obligations are being met, or not.



# So now into the elements of Gap Analysis

- We've outlined the Regulatory requirements,
- The main elements of a QMS,
- Management oversight and responsibility
- So how do we do the gap analysis?

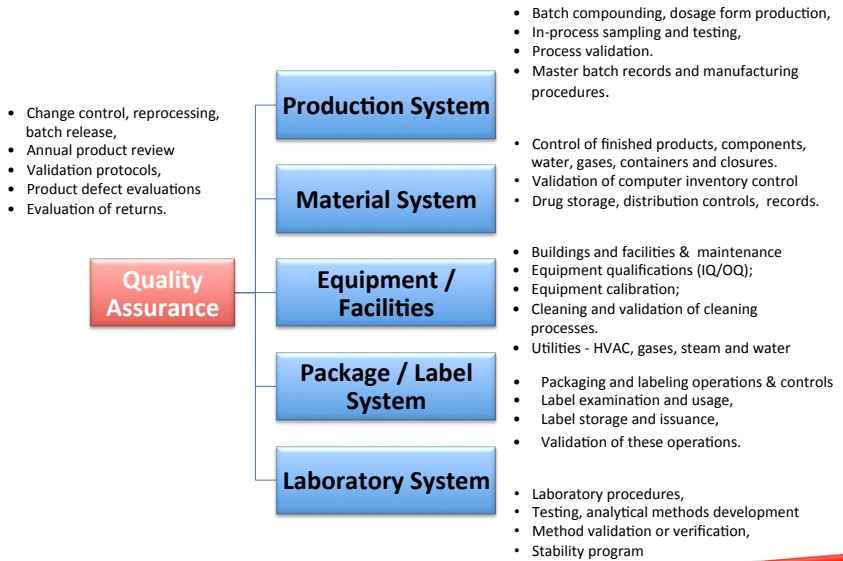
# Commitment to Quality by Management

- Governing Body and CEO are engaged
- The Quality Policy is aligned with business objectives
- Quality is shown to "add value" instead of being seen as just a cost
- Compliance and Quality obligations are embedded in Management position responsibilities
- Resources are allocated to Quality / Compliance
- Top level engagement in compliance/quality metrics and reviews



# Useful Gap Analysis Roadmap

## FDA Six Control Systems – Inspection 7356.002

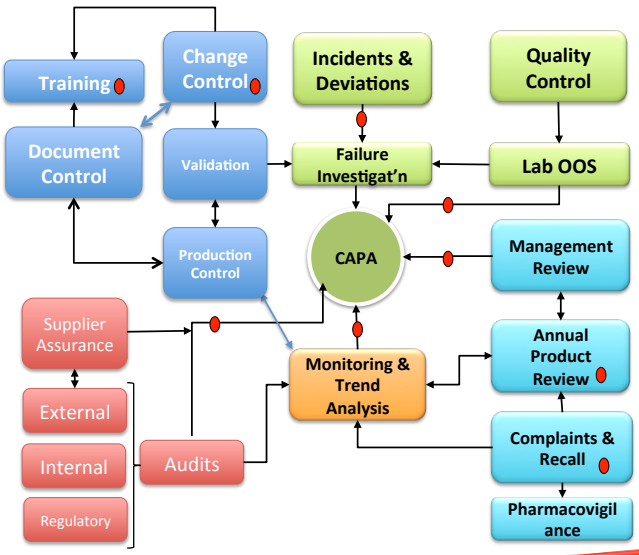


# Quality Systems – Gap Analysis

- Gap analysis of the QMS is looking at two main elements:-
  - Does the QMS cover all of the required elements of the cGMP?
  - How well does the company actually follow their own quality system?
- Together we're going to go into some of the key areas of a typical GMP regulated manufacturer's systems and take a look at some of the areas you must be totally across as Senior Managers and Leaders.



# Is the Quality System Integrated ?



# "Linkage" of the QMS system elements

- Each of the major elements are **inter - linked** to other elements
- Elements either drive or feed others or vice versa
- Linkage of related elements is critical to quality management oversight
  - Without strong linkage identification of problem root cause is difficult
  - With linkages, problems and root causes can be traced through the linked system
- Linkage enables "escalation" of significant issues




# Things to look for in the QA gap analysis

| Element/System | What to look for |
|---|---|
| Deviation, OOS System | The effectiveness of the failure investigations |
| CAPA System | Does the CAPA system look at root causes or just symptoms? |
| Audit Programs | Do the audits look at symptoms or root causes – are issues effectively resolved |
| Reviews, Trends and Reporting | Are management reviews and PQRs detailed enough and responsive |
| Training | Do training programs address compliance obligations |
| Management Responsibility | Is compliance a KPI within position descriptions of Managers and Supervisors? Metrics in place ? |
| Prioritisation and Resource Allocation | Is there a mechanism for resource prioritization e.g. risk based |
| Change Management | Does change management include compliance review |

## Are there Quality Metrics Available ?

| Indicator | Metric |
|---|---|
| **Lot Acceptance Rate** | Number of lots rejected in a year / number of lots produced |
| **Right First Time Rate** | Number of deviations / lot |
| **Complaint Rate** | Number valid complaints/number of lots released per year |
| **Invalidated (OOS) Rate** | Number of OOS test results invalidated /tests performed |
| **Annual Product Review (APR) on Time Rate** | Number of APRs generated within 30 days of annual due date |
| **Management Engagement** | Most senior manager that signed each annual product review |
| **Process capability or performance index** | Whether performed for each critical quality attribute as part of that product's APR. |
| **Corrective and Preventative Action (CAPA) Rate** | Number of CAPAs that were initiated due to an APR, divided by the total number of APRs generated. |



## Are Key QA SOPs available ?

- Internal Audit Program
- Document and Records Control
- Investigations and CAPA
- Deviation Management
- Change Management
- Product Quality Reviews (PQRs)
- Management Reviews and Quality Metrics
- Complaints and Recall Programs
- Rework and Reprocessing
- Quality Risk Management
- Release for Supply
- Contract Agreements
- Vendor/Supplier Management

## Laboratory and Materials Control Some Key SOPs to Review

- Inward Goods Sampling and Testing Programs
- Out of Specification (OOS) Procedure
- Management of Reference Standards
- Completion of Laboratory Records
- Data Integrity and Data Control, checking results
- Test Method Validation: Chemical, Sterility, Bioburden
- Stability Programs – present and meet ICH Q1
- Control of packaging (materials and process)



## Key Elements of Material Control Systems

- Walk through warehouses – look at temp. records
- Material warehousing – temperature / RH% controls
- Supplier Assurance – is risk assessment used. Audit schedule ?
- Material receipt and traceability in MRP systems
- Status and release for use controls
- Usage traceability/ tracking and reconciliation
- Control over Process Aids (filters, tubing etc…)
- MRP systems validated ?

## Environmental Monitoring of Cleanrooms Key Indicators

- SOP for EM (bacterial) testing for manufacturing rooms
- SOP for particle and room filter testing
- SOP for Purified Water Testing
- SOP for compressed gases testing
- Annual or periodic summary reports for the testing of these systems
- Risk Assessments for air flow patterns and sample locations
- Validation of EM methods



## Production System Gap Analysis Key Things to Review

- Physical walkthrough – start from inward goods and trace forward
- Master Batch Records (MBR) and control over changes
- Examine 1 - 2 completed batch records for:
  - Traceability and accountability of materials ?
  - Records complete signed and dated ?
  - Who 2nd checks the data integity ?
- Are formulae and unit operations consistent with registration details
- Manufacturing SOPs and processing logs present
- In-process sampling and testing programs recorded in records ?
- Process Validation – Examine example(s) - Protocol and Report

- **Potential for cross – contamination –** air , residues, personnel or mechanical transfer.

# Labeling and Packaging

- Master Packaging Records available ?
- Packaging records are complete ?
- Control over release of printed matter
- “Line side” controls – 100% verification of printed matter
- Reconcilliation of printed matter
- Adequate separation of packaging lines
- Adequate separation of stored printed matter
- Control over any returns to store ?



# Essential Validation Programs

- VMP in place and current – schedules for re-validation
- Focus on critical equipment / systems:
  - Sterilisation: Autoclaves, Hot Air Tunnels, SIP
  - Unit Operations equipment – tanks, chromatography etc…
- Focus on key processes:
  - vial washing
  - bulk mixing
  - Material transfers to Grades B and A
- Focus on Cleaning and Sanitation processes
  - Vital inactivation programs
  - CIP and manual cleaning – DEHT/ CEHT
  - Sanitant effectiveness programs (surfaces/organisms) kill

# Equipment / Facilities Review

- Critical review since any gap will involve $$ for remediation
- **Potential for cross – contamination ?**
- Cleanroom Finishes – Focus on Grades A and B
  - Positions of HEPAs and returns
- **Critical Pharmaceutical Services Review**
  1. Water System (WFI and purified water)
  2. HVAC
  3. Compressed Gases
  4. Clean Steam Supply
- Review testing program for Critical Services – check Annual Reports
- Review Drawings and whether they are ”as built”



# Equipment / Facilities Review (Key Decisions)

- Is any remediation needed ?
- If so is it Minor or Major ?
- Do any of the critical services need replacement ?
- If so how much $ and time needed ?
- Is the site capable of managing any remediation ?

## Scope of the Gap Analysis

- Desktop audit the key elements of the Quality System,
- Physical check of the Cleanroom areas of the Facility,
- Verification of data in all Logbooks including management review,
- Selection of BPS of the most complex products for a detailed review,
- Review of High and Medium level deviations and CAPA analysis and implementations – special focus on any repeat events,
- Desktop analysis of Environmental Monitoring results of all direct manufacturing zones,
- Review of all maintenance and testing data of complex systems. E.g. water
- Staff training – system and it's effectiveness
- Look at your last Inspection Report – it is a good start!



## PQS/Compliance Gap Analysis

- Identify and assess compliance obligations and potential failures - not just GMP
- Include external and internal obligations in gap analysis
- Prioritize gaps using use risk principles
- Establish a compliance register or database
- Develop a PQS remediation/ improvement plan
- Establish a system to monitor external changes in PQS & compliance obligations e.g Legislation, cGMP updates …

## PQS, Compliance and Quality Organisation

- Assign compliance and quality responsibilities to individual managers – set out in position descriptions
- Ensure all management and supervisors “walk the talk”
- Appoint a senior Compliance/ Quality executive:
  - direct access to the Board/CEO
  - Access to expert advice (internal and external)
  - Establish compliance/quality objectives and KPIs
- Ensure compliance/quality function has the authority to act



## Are there Continuous Improvement Programs Evident ?

- **Process performance and product quality monitoring system**:
  - Process control
  - Identification of improvement areas
- **Corrective action and Preventive action (CAPA) system**
  - In place and effectiveness evaluated
  - Focus on Continuous Improvement
- **Change management system**
  - QA oversight
  - Utilizes science and risk-based assessment
- **Management review of process performance and product quality**
  - Periodic reviews of performance against metrics
  - “Six sigma” understanding or programs

# PQ Audit Readiness Questions

- Is the company organised internally for PQ inspection
- Who will lead and host the Inspectors. Experience ?
- Are there “packages” of information being prepared and reviewed e.g water system package, HVAC package
- Have persons been assigned as subject matter experts ?
- Are the quality system indicators up to date – eg. past due CAPAs, unresolved major deviations or complaints etc.
- Are key personnel being coached in presentation to PQ Inspectors
- Has this been started 6 months in advance of PQ



# Rating of Gaps

**Significance Level** (Note this is NOT specifically related to GMP non-conformances but also the level of effort required to correct any issues.)

- **Significant Gap**
  - requires capital investment to correct the deficiency and / or major change to the quality system.
- **Major Gap**
  - no capital investment required but major change to the quality system/documentation needed
- **Minor Gap**
  - no capital investment required, only documentation updates to the quality system and/or limited revised testing needed
- **Validation Gap**
  - the validation is insufficient or absent
- **Recommendation**
  - not a significant GMP or quality systems gap but local health authorities may have “special” requirements that are different to cGMPs or the recommendation is likely to be a camp requirement in the future.

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