Conducting a GAP Analysis of your Validation Program

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GAP Analysis - Process Control

Agenda

• Defining “GAP Analysis”
  – How does it differ from an audit?
  – What is it beneficial?
• Preparing for a GAP Analysis
  – Understanding the shareholders and their requirements
  – Defining standards
  – Tools for conducting a GAP Analysis
• During the GAP Analysis
  – Communications
  – Define Expectations
  – What to look for
• After the GAP Analysis
  – Metrics
  – Final Report
  – Implementing Improvements and Remedial Action Plans
  – Conclusions/Review:
  – The “DO’s and “DON’TS of a GAP Analysis

Defining Scope Of A
“GAP Analysis”

Part 1:
Planning is Key
<table>
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<tr>
<th>What is a GAP Analysis?</th>
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<td>• Evaluation of a specific program or process to determine how it compares to a pre-defined set of objectives, goals, or standards.</td>
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<td>• Defining the specific objectives or expectations to be met is the most difficult part of the GAP Analysis.</td>
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<th>GAP Analysis</th>
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<td>• Identify GAPs between the documentation and the shareholders requirements.</td>
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<td>• Who are the shareholders?:</td>
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<td>– Regulatory Bodies (e.g., FDA, EU, HPFBI)</td>
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<td>– The people who use the program and systems on a day-to-day basis in order to get their jobs done (employees).</td>
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<td>– Other departments who depend on information that are deliverables from the documents or process analyzed.</td>
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<td>– Those responsible for routine review, assessment of the documentation, and its output.</td>
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GAP Analysis - Process Control

GAP vs. Audit

GAP
• Do not confuse a GAP Analysis with an Audit (They are different)
• They are generally highly focused on one specific process or program.
• Very thorough assessment of that program (typically looking at many documents.)
• The approach and interaction between the GAP Analyst and the company is more open, less protective, and defensive. (“Open Book Policy”)
• Depending on the standards agreed upon, it may look beyond what is in the regulation.
• Defines improvements, as well as deficiencies.
• Helps developed corrective action plan and minimize regulatory exposure.

Audit
• Scope is greater—e.g., are we complying with GMP for Product XYZ.
  – A broader scope will mean that an audit will look at only a few processes, pieces of equipment, or products, using these as examples to ascertain whether or not the entire system/company is in compliance.
**GAP vs. Audit**

**Audit, Continued…**

- Standards that must be met are typically derived from regulation, as opposed to current industry standard practice.
- Focus on examples of deficiencies relative to compliance.
- Can put persons being audited in a defensive position. Environment during an audit is sometimes seen as “adversarial” or “judgmental”

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**When should you consider a GAP Analysis?**

- FDA inspection or company audit has identified process control problems that may be systemic.
  - GAP Analysis will help to identify *systemic* problem and risks with systems and processes that might not have been examined in the inspection/audit. – Proactive Approach
- Prior to developing a new program
  - For example, in the case that you know your program is not where you want it to be, but aren’t sure where ALL the GAPs are.
- Introduction of new process or system
  - When bring a new system or process into a facility its important to determine what complexities could arise during the introduction phase
When is a Problem Systemic?

• It affects or can be seen in multiple product types, product batches, types of equipment, departments, or procedures.
• May be indicated by a rash or trend in errors, deficiencies, or events over a period.
• It is not an intermittent problem or isolated error.

Preparing for the GAP Analysis

Part 2
How Do We Get Started?
Requirements for a Successful GAP Analysis

- Management must agree in advance on the scope of the GAP, as well as the specific standards/requirements to be met (benchmarks)
- Preparation of tools to be used to perform the GAP Analysis
- All personnel involved understand the process, expectations and goals.
- Development of report containing results and recommended remedial action.

Defining Scope of the GAP Analysis

- For a GAP Analysis to be effective, it must focus on a specific areas or functions.
- Defining what will and won’t be covered in the GAP is more difficult than it may seem, since all elements of the quality system link together, and are often closely related.
- Starting requires detail planning and focus.
- Good-Start can lead to a successful beneficial report.
Scope of GAP Analysis

- A GAP Analysis Covering **Systems, Documentation, Product & Process Controls** would include:
  - Process Control Procedures
  - Process monitoring
  - Training Programs
  - Document Control
  - Deviations
  - Equipment
  - Environmental Controls
  - Personnel
  - Critical Utility Systems
  - Contamination Controls/Environmental Controls
  - Facilities
  - Control of Manufacturing Materials (charge in of component, time limits on manufacture)
  - Yield Reprocessing/rework Procedures
- **AS WELL AS**…
  - Automated Processes
  - Process Validation

A process control GAP Analysis could easily extend to many supporting systems and related program areas

- For example, the process control program GAP could include:
  - Software Control and Validation
  - Change Control
  - Part 11 Compliance
  - CAPA
  - Calibration and Maintenance
- And the GAP might cover very specific validation requirements, such as those for:
  - Sterilization Validation
  - Depyrogenation Validation
  - Aseptic Filling Processes
  - Cleaning Validation
  - Lyophilization, process H2O
  - Analytical Method Validation

Must be careful not to let the scope get out of hand- A GAP Analysis covering all of this could take a month!
Limiting the Scope

- Different Options might include:
  - Looking only at the Policies and Procedures to identify procedural GAPs (Focus on the program, not whether or not it has been implemented correctly).
  - Excluding certain systems in order to narrow the focus (e.g., utilities, sterilization process—these might be covered in their own separate GAP Analysis.)
  - Limiting documentation to be reviewed to those documents generated after a specified date. (What’s the risk in this?)

How do you get the scope under control?

- Have a pre-approved plan for the GAP Analysis and/or agreement upfront on the method to be used.
- Use a pre-approved matrix indicating the data to be reviewed.
- Have management agree on all standards to be applied.
- Don’t get side-tracked during the actual GAP Analysis.
- Focus only of the systems or process that was apart of the GAP strategy.
Everyone must agree on the requirements:

- What Guidance Documents should be used?
- What Reference documents must be reviewed?
- What current standards are available?
- What do the internal shareholders need? (QA, Regulatory, Manufacturing)

What are the benchmarks?

- Must Compare Current System or Process with Expected Systems. For example:
  - International Regulations.
  - Government Standards (e.g., ISO)
  - Industry Standards
  - Guidance Documents
  - Professional Trade Groups or Technical Journals.
  - Information from 483s, Warning Letters (what is FDA finding?)
  - Other programs/Previous Experience.
Preparing a GAP Analysis Matrix

- Matrix provides a way to document results against very specific requirements or objectives.
- Matrix can be developed to quantities and qualities results.
- Matrix will be reviewed/approve before initiating the GAP. (cross departmental agreement relative to the requirements to be met.)
- Also provides a means of quantifying results.

Organizing information in the Matrix

- Helpful to break it down into subsections:
- For example,
  - DQs
  - IQs
  - OQs
  - PQs
  - Process Unit Operations
  - Process Monitoring
  - Training
  - Calibration and Maintenance
  - Software
Resource allocation…

- Developing a very thorough matrix requires line-by-line review of every standard, corporate reference document, regulation to be met.
- May actually take longer than performing the GAP Analysis. (Resource intensive.)
- May be a good investment; once developed, can be used for many future analyses, suppliers, other divisions of company.
- Excellent training and communication tool for management and employees.
- Helps to define the company approach, philosophy; provides a framework for the program or process.
- Must allocate time for interviewing shareholders and employees.

Matrix should include:

- Each requirement to be met
- Reference (where did the requirement come from?)
- Documents reviewed during GAP Analysis to evaluate each requirement.
- Comments/Observations
- Decision regarding extent to which the requirement has been met.

All requirements should be numbered to facilitate cross reference
Matrix might also include:

- A classification of the significance of each requirement (critical, major, minor, incidental) so that a “weight” can be assigned to each requirement.
- Place to score each requirement.

Who should approve the GAP Analysis Matrix for a Process Control GAP.

- Production/Manufacturing
- Engineering – Facilities, Utility and Equipment
- QA
- Regulatory
- IT (if software is to be included)
- QC Microbiology (If sterilization is to be included.)
- QC Testing (If analytical methods are involved)
Training the Participants

- The personnel involved (those who will provide documents, answer questions, etc.) must understand the objective, and the company’s reason for conducting a GAP Analysis.

During The GAP Analysis

Part 3
What Do We Look For?
The “Developing the Environment”

- Management needs to explain the “Open communication” concept.
  - Approach/communication is different than an "audit"
  - Why is this so important?
- Those participating will need to share their opinions, concerns, in order to assure that all the problems and Gaps are identified.
- Should be a positive experience for everyone. No one should feel defensive. (This is not finger pointing event) “Facts nothing but the facts”
- A “learning” experience for all shareholders.

Using your matrix

- Requirements to be met by the validation program and process control program have been defined.
- Management agrees on the requirements.
- The GAP Analysis is simply a comparison of the current system, its supporting documenting, and the people/resources against the defined requirements.
To determine if requirements have been met...

- Read documentation carefully
- Ask Questions if you do not understand an issue.
- Use your knowledge, not your emotions
- Once you have determined that a requirement has not been met, move on.
- Get on the manufacturing floor! (Not virtual active – leg work is involved)

What to look for...

Three General Areas to Assess for each defined “Requirement”

1. Do the Procedures, Policies, Forms, and Templates for the Process Control and Process Validation program meet the defined requirements? *(establish)*
2. Have the requirements been met in actual practice? *(implement)*
3. Do employees understand the program, expectations, etc? Are they trained? Are resources necessary to support the program appropriate *(support)*?
1. The Procedures/Policies

- What has been established procedurally?
- Are there any inconsistencies between one procedure and the next?
- Do procedures define terminology correctly?
- Can you understand the procedures?
- Do the procedures meet the defined requirements.

2. Implementation of Procedures and Policies

- The number of examples to be reviewed will depend on the scope.
- Do documents exist to support the requirements for all systems, products, or processes that are within the scope of the GAP Analysis. (e.g., is there a protocol? is there a report?)
- Are the executed documents (protocols, reports) consistent with what is in the established procedures? Are they consistent with the defined requirements?
- Do the executed documents demonstrate that validations are technically and scientifically accurate and appropriate.
3. Are employees trained.

- Do employees understand the terminology defined in the procedures? Do they apply it correctly in discussion?
- Do they demonstrate knowledge of the program that exists (regardless of whether or not the program meets requirements)?
- Does management provide appropriate resources to support the program (personnel with the right skill set, tools, technology).
- Is training documented?
- What does the evidence show (deviations from the program)?

Part 4
Are Your Validation Documents Compliant?
Are the right procedures in place?

- Procedures need to cover:
  - Requirements for validation (who, what, when, how)
  - Purchase and acquisition of Equipment
  - User requirement specification
  - Commissioning
  - FATs, SATs, DQs, IQs, OQs, PQs
  - Process development
  - Process Monitoring requirements
  - Revalidation requirements
  - Equipment Control (identification, approval for use, calibration, PM)

Do procedures specify document content for

- Equipment Design Requirements
- Equipment Specifications
- Protocols
- Final Reports
Evaluating the Protocols for Equipment Qualification/Process Validation

- Must be approved before executed.
- Must have a well-defined purpose/scope.
- Must specify (in detail) what is to be done
- Must specify measurement tools to be used.
- Must define and justify statistical sampling methods, sample sizes.
- Must explain how results are to be documented.
- Must provide guidance for handling/documenting/evaluating deviations, should they occur.
- Must specify data analysis methods.

Are process specifications appropriate?

- Ranges of acceptable operation, not the target mid-point should be defined.
- Where Proven Acceptable Ranges (PARs) developed
- Many systems cannot hold a single set value, but oscillate around a target point. Failure to establish an appropriate “range” will guarantee failure during execution of the protocols.
Specifications

- Defines the process or equipment in terms of the unique application in which it will be used by the company
- Identifies the full range of operating parameters - (identifies parameters to be challenged in validation)
- Defines all critical characteristics of the process/equipment

Evaluating the Final Report

- Just the facts; no opinions
- Must accurately reflect the data collected
- Full explanations for any outliers
- Full explanations for any deviations
- Document disposition of validation test materials
- Review the content and verify the information is factual
Are processes Controlled After they are validated?

- Process Controls include:
  - Documented instructions, SOPs, and methods that define and control production.
  - Monitoring and control of process parameters and product characteristics during production.
  - In-process testing
  - Compliance with reference standards or codes.
  - The approval of processes and process equipment
  - Criteria for workmanship.

Are processes Controlled After they are validated?

- Must monitor your processes to detect trends through techniques such as:
  - Statistical Process Control
  - In-process testing
  - Evaluating adjustments to process operating parameters that occur over the course of the production run.

- Attempt to detect a trend that may lead to a process deviation BEFORE it occurs.
Are processes Controlled After they are validated?

Why trend?

- The purpose of trending is to identify a potential problem as quickly as possible. The more quickly an unexpected product performance trend can be identified, the more effective and thorough corrective action can be.
- Timely and effective corrective action minimizes negative effect upon business.

By evaluating changes in output (product performance), we can detect possible problems in:

- Equipment Performance
- Process Control
- Workmanship
- Sample handling and processing
- Personnel training,
- Test Methods
- Material deficiencies (either raw materials or test materials).
Are resources for validation appropriately allocated?

- Key indicators include:
  - Ability to adhere to project schedules
  - Timeliness of investigations
  - Excessive product or process deviations that may indicate lack of validation or uncontrolled processes.
  - Need for excessive product reworks, reprocessing
  - Inability to follow established validation program.
  - Number of GAPs identified?

Are the employees trained?

- Key indicators
  - Adherence to defined process control parameters, validated operating ranges
  - Familiarity with validation program, ability to describe policies, procedures.
  - Documentation inconsistent with procedural requirements.
  - Following established validation program.
  - Training documentation
  - Number of GAPs identified?
Part 5
Are Your Validation Documents in a State of Control?

Investigator Expects to See

- Defined development processes
- Written validation plan
- Documented requirements
- Documented design specifications
- Documented functional specifications
- Documented testing protocols and proof/test results
- Documented evidence of installation protocols and proof of test results
- Complete traceability
Things FDA Looks For:

- Process is well-defined and includes:
  - Product development data
  - Component specifications
  - Critical process steps
  - Operating parameters and limits
  - Worst-case scenarios
  - In-process limits
  - Product specifications
  - Sampling plans
  - Support documentation
  - Sign-offs

Things FDA Looks For:

- All data must be reviewed and approved by the quality unit
- The completed validation study must have a summary report, and the completed validation protocol and summary report should be reviewed and approved by the entire validation team
- Validation batches should be put on Hold until the validation studies are successfully completed
Things FDA Looks For:

- Validated analytical methods
- Validation Master Plan and procedures
- Individual validation protocols for each drug product
- Pre-approval of protocols
- Specific number of runs
- Consecutive batches
- The data should be within the statistical limits of analysis

Things FDA Looks For:

- Pre-approval inspections assess the ability of a mfg process to produce a drug within its quality and safety specifications
- Personnel are trained
Documentation RED FLAGS

• No approved specification.
• Atypical data points.
• Failure to challenge full range of intended operating parameters.

Documentation RED FLAGS

• Inadequate sample size.
• Sample not randomly chosen from throughout the validation run.
• Samples sizes not justified.
Documentation RED FLAGS

- Referenced procedures, manuals, guidelines, or industry standards not available on site.

- Inconsistencies between one Process Validation run and the next.
- Failure to provide clear and complete instructions in the protocol.
- Changing specifications as you go.
Documentation RED FLAGS

- No documentation for calibration of tools used in validation
- Failure to clearly show calculations used in analyzing data.

- Unexplained deviations from protocol.
- Inconsistencies between final report and data recording forms, lab books, etc…
• Failure to ensure Implementation of Validated Parameters. Current batches of production records reflect the use of different equipment or different process operating parameters or procedures than those validated.

• Repeatedly allowing same deviation instead of fixing the cause of the problem
• Pre-approved deviations without an expiration.
• Pre-approved deviations without proper justification.
Documentation **RED FLAGS**

- Failure to react in a timely manner when process trends, which may lead to a deviation, are identified through process monitoring programs.

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**After the GAP Analysis**

**Part 6**

**Summarizing Your Findings?**
Final Report

- Should be objective
- Should make it very clear if there are potential risks (business, compliance, product safety).
- Should provide recommendations for corrective actions.
- Should recommend improvements
- Clarify which recommendations are intended to correct GMP deviations vs. those that represent opportunities for improvement.

To Quantify Results or Not?

- Metrics can be helpful, but it does take time, resources to apply them.
- Must determine in advance how the results will be scored.
- May not be “value added,” especially if you already know the program is in pretty bad shape.
- Many means of quantifying results:
  - % of requirement met
Risk Based Assessment

- GAP Analysis Report should discuss the business and product safety risks that may exist based on the results of GAP Analysis
  - How serious are the problems?
  - Is product safety or effectiveness potentially compromised.
- Corrective Actions and recommendations must take risk into consideration.

How serious is it?
Identifying Systemic vs. Intermittent Problems

- Intermittent events may not necessarily be indicative of a systemic quality problem,
- A steady increase in the reported events over time, or a rash of deviations within a specific period indicate a systemic problem.
**Systemic vs. Intermittent Problems**

- GAP analysis reports should specify whether or not deviations identified are **intermittent or systemic** in nature.
- Corrective actions should be appropriate, and based on whether or not the problems identified were systemic.

**If potential product risk are identified:**

- Investigate to assure the full scope of the problem is identified so that it can be corrected.
  - What product is affected (what lines, what batches)?
  - What is the root cause of the deviations (is it procedural, training, etc.)
  - Do you know the cause, or THINK you know the cause?
Corrective Action Program:

- Identify the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems.

Remedial Action Plan - FDA expects manufacturers to

- Implement and record changes in methods and procedures needed to correct and prevent identified quality problems.
Corrective Actions

• Put a plan in place.
• Correct at the “Systems” Level.
• Justification for corrective actions must be scientifically sound, logical, and thorough.
• Corrective actions must be commensurate with the problem.

Any Questions???