DATA INTEGRITY WORKSHOP

Remediation plan: risk mitigation

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Pavia, 10th November, 2017

90 BRACCO anniversary

agenda

1. What is? Why? Who is involved (resources)? How long does it take?
2. How to do? Data Integrity assessment methodology
   a. Historical data
   b. IT Quality System
   c. Computerized Systems Compliance
      1. Computerized Systems Inventory
      2. GxP Impact Assessment
      3. GxP Risk Assessment
      4. Compliance Gap Analysis
      5. **REMEDIATION ACTION PLAN**
3. CONCLUSIONS

What is ?

A Data integrity risk mitigation plan should be developed to close the possible gaps identified during the risk assessment phase.

The scope of the assessment should be oriented to evaluate:

-The Integrity of historical data of QC Laboratory to verify the reliability and compliance of QC Regulated Processes and related Records collected within the Retention Period;

-Compliance of the IT Quality System against the provisions set forth by the EU cGMP Annex 11 (CSV) and 21 CFR Part 11 (ER/ES);

-Level of compliance of Computerized Systems operated in the Company (Production and QC departments) against the provisions and regulatory requirements set forth by the regulations above mentioned.

Why ?

Companies need to assess what are the areas of "vulnerability" within their business and compliance processes.
In other words the application of QRM !

-Demonstrate the level of compliance to the regulation aimed to improve a data Governance system.

-Confirm that all quality risk in the GMP processes of data handling are well known, controlled and kept to an acceptable level

-implement a mitigation plan can be considered an «opportunity» and a useful ongoing training tools for the local management involved in data governance

Who is involved (resources)?

Many contributors should be involved in the «project» such as:

- QU (QC and QA):
  Quality documentation (validation phase); new SOP/procedures, CSV protocols/reports, systems testing phase, change control system
- Special new technicians selected
- Production management (e.g. automation systems)
- IT services:
  mapping and inventory of all GxP Company computerized system; issuing of policy/procedure of access control and data security and backup/restore; infrastructure and HW qualification, SW changes or upgrading, periodic system review, testing of relevant IT-CSV activities

- Suppliers:
  interact and assist the local user/dept. to develop SW features or customization of report (e.g. audit trail report)

Who is involved? How long does it take?

- External consultant:
  give to the customer the best support on «how to do» and facilitate the planning and implementation of the tasks scheduled in the plan, in specific:
  - describe the assessment methodology
  - summarize the results of the assessment in terms of observed gaps
  - identify the Corrective Actions necessary to mitigate and/or solve the regulatory exposures determined by the observed gaps
  - propose a risk based strategy for the prioritization and execution of the remediation activities

- A remediation Plan may last some years (we've been dealing with it since 2016 and it is not yet completed)
- A periodic six months «state of the art» it is recommended (interim report) to monitor and demonstrate the improvement phase.

How to do ?
D.I. assessment methodology

Historical Data Assessment

is intended to verify if historical Records supporting QU release processes are complete, accurate and consistent.

Two batches have been randomly selected for the assessment.

For those selected batches, the verification has been executed on Electronic Records maintained by the LAS used in the QC Laboratory and on a consistent set of paper based Records (e.g. laboratory records related to the selected Batch Record).

The Records have been verified in regards to:

- the requirements set forth by the applicable regulations (21 CFR Part 11, EU cGMP Annex 11)
- the traceability needs
- evidence of controlled process

For each selected Batch, and for main LAS Systems used for the execution of the related QC analyses, the assessment includes the verification of the topics reported in the following table. A Regulatory Exposure is associated to each topic based on the impact that a possible non compliance may have on the data integrity.

HISTORICAL DATA ASSESSMENT

TOPIC	TEST ACTION	ACCEPTANCE CRITERIA	EXPOSURE IMPACT FACTOR
Audit Trail data	Verify availability of Audit Trail records related to the Analysis Ax	Records are available	MEDIUM
Audit Trail Review	Verify evidence that Audit Trail records have been reviewed or the presence of procedural controls which requires the Audit Trail review related to the Analysis Ax	Audit Trail Records have been reviewed	MEDIUM
Approved Analytical Method	Verify that the relevant paper Analytic Method was approved	Analytical parameters stored in the system match the value reported in the paper document	HIGH
Lab Notebook	Check the relevant Analyst Laboratory Notebook(s)	The records (instruments, standards, reagents) related to result Rx are reported in the Lab Notebook (LN) Date and other relevant values are consistent	HIGH

HISTORICAL DATA ASSESSMENT

TOPIC	TEST ACTION	ACCEPTANCE CRITERIA	EXPOSURE IMPACT FACTOR
Sample Receipt	Verify the availability of Sample receipt records	The Sample receipt record is available and the data and timestamps are consistent with Analysis Ax	MEDIUM
Analysis executor	In LN, Identify the Operator who has executed the analysis Ax. Compare against the relevant Audit Trail records	The operator matches with the Audit Trail record	HIGH
Operator Training	Verify the Training records of the Operator related to the Analytic Method	Training record of the operator is available	LOW
Naming Convention	Verify the naming convention of the results and associated records	The result has been named according to a predefined procedure and/or can be explicitly to predefined Lot/Sample ID	LOW

HISTORICAL DATA ASSESSMENT

TOPIC	TEST ACTION	ACCEPTANCE CRITERIA	EXPOSURE IMPACT FACTOR
Instrument Logbook	Verify the availability of the Instruments Logbook related to the period of the analysis execution	The Instruments Logbook related to the period of the analysis is available	MEDIUM
Instrument Qualification Status	Verify the qualification status of the Instruments in the Logbook related to the period of the analysis execution	The status of instrument in the analysis period is reported as qualified	MEDIUM
Calibration	Verify the availability of the Calibration Procedure and Logbook related to the instrument used for the analysis Ax	The Calibration procedure was in force. The instrument was correctly calibrated	MEDIUM
Stds & Reagents	Verify the availability of the records related the Standards and Reagents used in the Ax	The Standards and Reagents used for Ax was valid and correctly recorded	MEDIUM

HISTORICAL DATA ASSESSMENT

TOPIC	TEST ACTION	ACCEPTANCE CRITERIA	EXPOSURE IMPACT FACTOR
Suitability Test	In case a System suitability test(s) was required before the QC testing verify: • the availability of the relevant records in the system • the records in LN	The Suitability Test has been recorded in the LN. The records in Computerized System are available and the related timestamp is consistent	HIGH
Report Timestamp	Verify the Report Result for Rx and the related timestamp	Rx has been printed including the manual or automatic timestamp in the report. Dates are consistent with records in LN and Computerized System	HIGH
Automatic Timestamp	Verify the timestamp reported in the Report Result Rx	The timestamp has been generated automatically in the report and it was not modifiable by the user	LOW
Concurrent Analysis stored in System	Verify in System Audit Trail any analysis created in a temporal period equal to 3 times the analysis duration before the Result Rx (or before 24 hours)	No analysis can be associated to the selected Result Rx in System Audit Trail. If present, any associable analysis is properly documented and justified	HIGH (comparable data) MEDIUM (evident system failure)

HISTORICAL DATA ASSESSMENT

TOPIC	TEST ACTION	ACCEPTANCE CRITERIA	EXPOSURE IMPACT FACTOR
Concurrent Analysis reported in Lab Notebook	Verify in Laboratory Notebook any analysis created in a temporal period equal to 3 times the analysis duration before the Result Rx (or before 24 hours)	No analysis can be associated to the selected Result R in Lab Notebook If present, any associable analysis is properly documented and justified	HIGH (comparable data) MEDIUM (evident system failure)
Reprocessed data	In case data have been reprocessed, verify that results clearly allow to determine the reprocessing operations and relevant parameters	The reprocessing operations and relevant parameters are reported in the system records and LN	HIGH
External parameter(s) Reliability	In case analysis parameters are created from an external instrument (e.g. scale, pH meter), identified the used instrument(s) IN1:_____ IN2:_____ IN3:_____… ……	NA	NA

HISTORICAL DATA ASSESSMENT

TOPIC	TEST ACTION	ACCEPTANCE CRITERIA	EXPOSURE IMPACT FACTOR
External parameter(s) Reliability	In case analysis parameters are created from an external instrument (e.g. scale, pH meter), verify the output of instrument IN1 including the analytical determination. Repeat the check for all the external Instruments recorded in the previous point	The instrument IN1 output is attached to formal Batch documentation (e.g. Batch Record) or to the LN Timestamps (manual or automatic) are consistent with date of Analysis Ax The Instrument was calibrated when the analysis Ax was executed	HIGH
External parameter(s) Reliability	In case analysis parameters are created from an external instrument (e.g. scale, pH meter), verify the instrument output including the analytical determination. Repeat the check for all the external Instruments recorded in the previous point	The Timestamp is automatically printed by the instrument and it cannot be modified by the users	HIGH
Backup data	Verify the availability of Backup records for the Result and associated data	Backup records are available	LOW

D.I. assessment methodology

IT QUALITY SYSTEM ASSESSMENT

The assessment of IT Quality System has been oriented to evaluate the availability and adequacy of local (site specific) Procedures for the management and operation of Computerized Systems throughout their whole Life-Cycle.

The evaluation has been executed and documented through a dedicated **IT Quality System Checklist** based on the provisions set forth by the EU cGMP Annex 11 and 21 CFR Part 11

COMPUTERIZED SYSTEMS COMPLIANCE ASSESSMENT

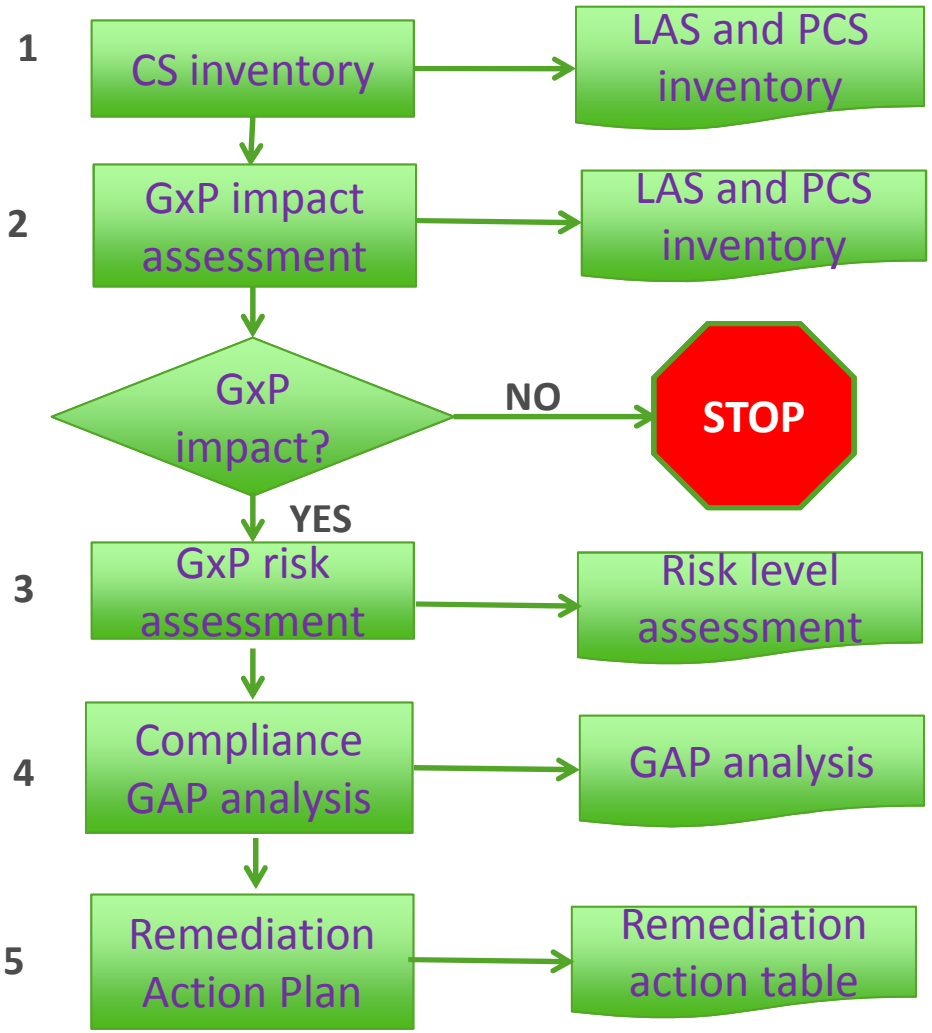
The Computerized Systems Compliance Assessment included the analysis of the following main items:

-LAS (Laboratory Application Systems)

-PCS (Process Control Systems)

The assessment has been executed according to the following methodology:

D.I. assessment methodology



PURPOSE

Identification and classification CS with GAMP SW category

GxP impact evaluation of the system

Determine the GxP risk level associated to the system

Determine the compliance status for systems vs. regulatory requirement (part11/annex11)

List the GAP and the relevant CAPA

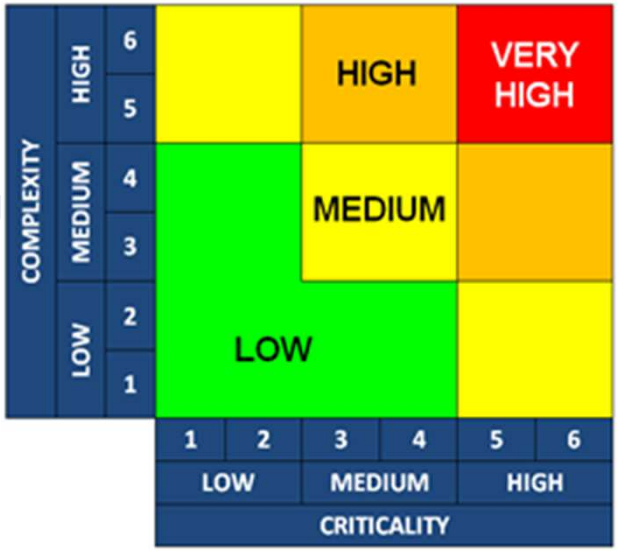
Computerized Systems Compliance Assessment

STEP 1 - Computerized Systems Inventory: listing the Computerized Systems in the scope of the assessment together with the required information, GAMP SW category, risk level, maintained Electronic Records (LAS) and PCS)

STEP 2 - GxP Impact Assessment: evaluation of GxP Impact of computerized systems in order to filter out those determined not to have any impact. Results are reported within the inventory list

STEP 3 - GxP Risk Assessment evaluation of the GxP Risk Assessment Level (Very High/High/Medium/Low) associated to those computerized systems determined to have a GxP impact within Step 2:

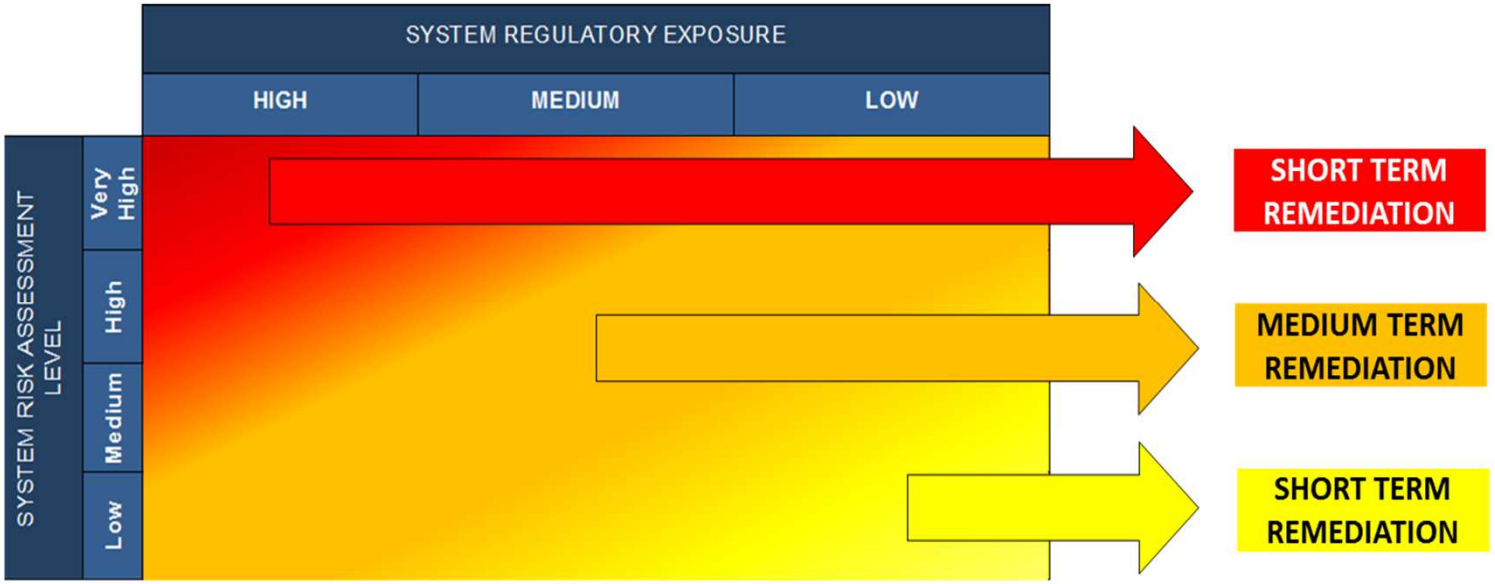
Criticality and the Complexity are combined to generate the System Risk Assessment Level according to the following matrix:



Computerized Systems Compliance Assessment

STEP 4 - Compliance Gap Analysis: execution of compliance assessment against the provisions of 21 CFR Part 11 and EU cGMP Guideline Annex 11 and available validation documentation.

STEP 5 - Remediation Action Plan: risk based classification of the assessed systems and relevant observed gaps will serve as an input to define and prioritize the implementation of remediation actions according to the following general matrix



Risk Based prioritization for Remediation

ASSESSMENT RESULTS

The phase of assessment is then converted in a SWOT analysis, taking in consideration: Strengths / Weaknesses / Opportunities / Threats.

W&O are the driver for a risk mitigation plan !

Weaknesses

- Lack of IT/Technical skills and support for QC LAS Administration
- Poor Quality System for the management of System Life-Cycle for local Systems
- Poor backup/restore process for LAS Systems
- Technical/Configuration Gaps (Data Protection/Systems Time Reference)
- Alarm management strategy and configuration for PCSs: not risk based or focused on Critical Parameters (e.g. presence of much “noise” for system alarms not quality related)
- Computer System Validation Gaps (Specifications and Testing) for Data Integrity related topics

Opportunities

- Ongoing global project of Data Integrity
- A compliance effort to establish at local level (e.g. since from the early stages for new CS projects)
- Implementation of ES for Master Recipe or implementation of Electronic Batch Record on PCS
- Upgrade HW/SW dated LAS or PCS systems to align them to the current “State-of-the-art” CS technology

CLOSE THE GAPS

Some gaps can be closed quickly (effort required to close the CAPA)

- Procedural Controls (e.g. update local procedures)
- Updates systems Configuration
- Needs for users training/retraining as necessary
- IT service supplier qualification/quality agreement with supplier services

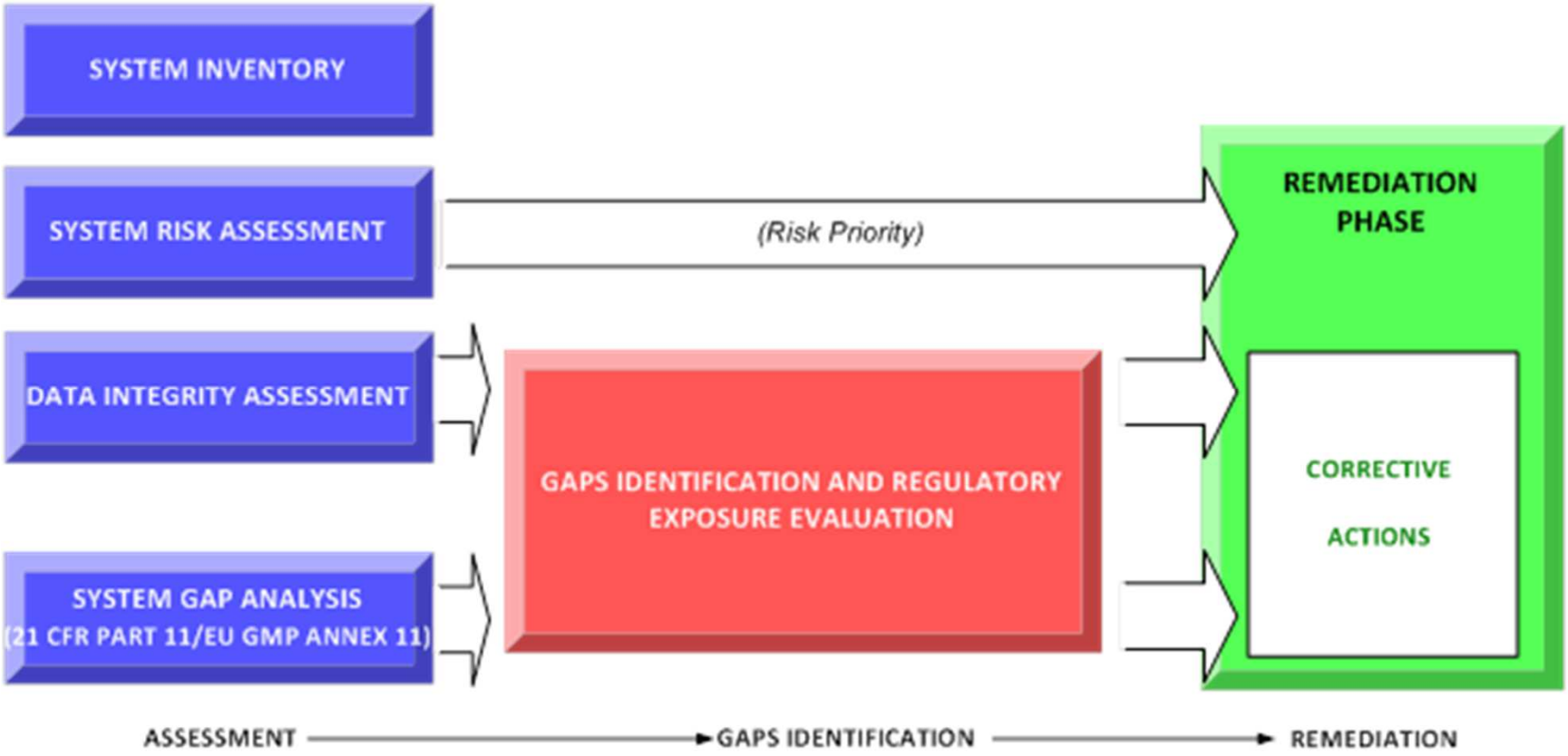
Others may require more time…

- New Equipment; New Software
- New hiring people (provide the Site with necessary resources)

Interim Control Strategy: Procedural Controls with Audit Oversight

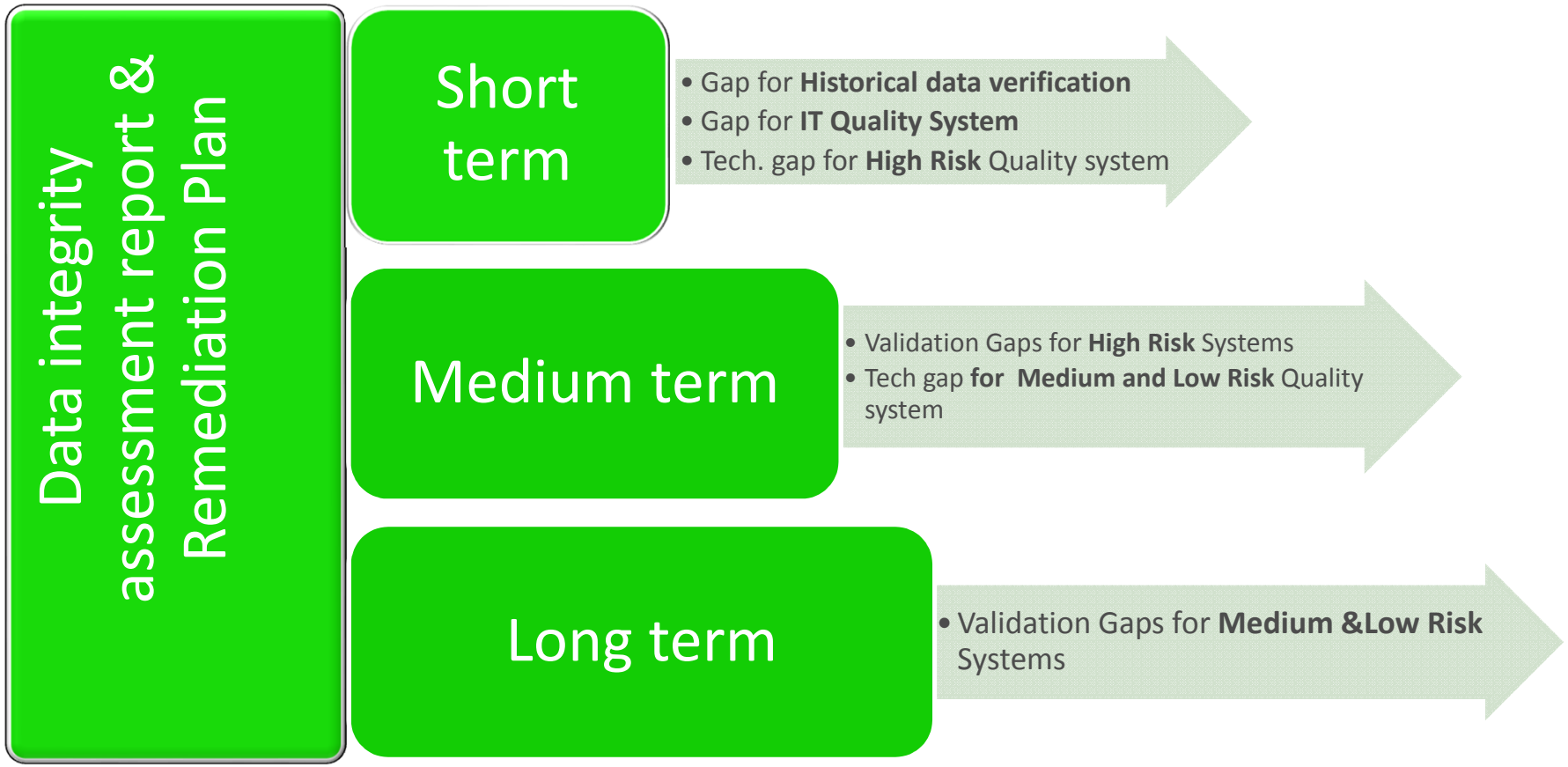
REMEDIATION PHASE

the ultimate target of the assessment is to define a risk based & priority driven corrective action plan to solve the observed gaps.



REMEDIATION PHASE

According to the previous scheme and based on the approach the following remediation phases are proposed to :



Some gaps from Historical Data Verification and relevant CAPA

TOPIC	Description	SEVERITY	CAPA
Stds & Reagents	The expiry date of the Reagent (or its dilution) used for a specific Analysis is not recorded. The expiry date of the Reagent used for a specific Analysis is not recorded on the Lab logbook and cannot be identified once the Reagent Bottle has been discarded	**H**	Update local procedures including provisions for recording the expiry date of the Reagents on the Lab logbooks
External parameters Reliability	For Balances with no paper based output, the weight values are only recorded on LIMS but date and time of data entry on LIMS do not match with the date of Analysis Ax (registration not contemporaneous)	**M**	Users retraining on Good Documentation Practices to enforce the contemporaneous recording of data: -The SOP "Allestimento scheda di laboratorio" has been upgrade to underline that all Raw data must be inserted to LIMS system in real-time -The lab. scales without printer were replaced with new ones equipped with printer on April 2016

Some gaps from IT Quality System Assessment and relevant CAPA

TOPIC	Description	SEVERITY	CAPA
Organization and Staff	Lack of IT/Technical skills and support for QC LAS Administration.	**H**	Provide the Site with necessary resources.
Audit Trail Periodic Review	AT review is not performed neither for LAB nor PCS applications. No SOP available to address this requirement	**H**	Implement and apply a risk based Procedure for a periodic review of Computer Systems Audit Trail oriented to ensure the GMP compliance of Analytical and Manufacturing processes: The SOP "Audit Trail Review" was issued on April 2016 Furthermore many other working instruction on specific LAS/PCS AT review have been issuing
Periodic Review	Periodic Review of Computerized Systems not performed. No SOP in Place to address the Periodic Review of Computerized Systems	**M**	Implement and apply a risk based Procedure for Periodic Review of Computer Systems oriented to verify and ensure that Computers Systems remain in a Validated status: The SOP "Revisione Periodica sistemi computerizzati" has been issued

Some gaps from Computerized systems compliance assessment and CAPA

TOPIC	Description	SEVERITY	CAPA
Computer System Validation (LAS & PCS)	CSV GAPs for Data Integrity related topics. System documentation (specification and testing) is only focused on the Equipment qualification. Adequate Specifications for Control SW are not established. IQ/OQ Testing for the Control SW is not complete and not properly documented	**H**	Integrate the current validation packages performing a GAMP5 V-model life-cycle including adequate specifications and testing on 21 CFR Part 11/EU GMP Annex 11 requirements as applicable, according to the current CSV procedure
Audit Trail (LAS & PCS)	Different Scenarios of Non Compliance have been observed for the Audit Trail: • Available but not activated • Not fully compliant, some information is missing (e.g. “reason for change” or “old and new values”) • Not available In general it could be slightly compromised by lack of protection of time reference	**H**	Implement Audit Trail mechanism (Automated or Manual). Paper based AT are temporarily permitted if different solutions are not possible

Some gaps from Computerized systems compliance assessment and CAPA

TOPIC	Description	SEVERITY	CAPA
Alarm Management (PCS)	Current approach and configuration of alarms does not allow an effective control on “critical alarms” (background noise)	**H**	Review and update the Alarm configurations as necessary assigning the high priority to the critical alarms only
Segregation of Duties (LAS)	Lack of measures to ensure the Segregation of Duties: • “Administration” Profiles include process related privileges • The person who is “Administrator” is also “Analyst”	**M**	Establish a general User Authorization Concept. Review the current Configuration of Computer Systems vs the required Authorization Concept and update it as necessary. System Administrator profiles should not include process related privileges. Where this is unavoidable in the organizational structure, the use of dual user accounts with different privileges should be enforced

CONCLUSIONS

Challenges and criticality in implementation of an effective risk mitigation plan :

1. Promote Quality Culture in D.I. and in all Data governance aspects:

   "A Strong Quality Culture is best indicated by what it is done when Nobody is Looking"

2. Strong commitment by the company management and willingness to sustain many resources demands

   - Significant economic investment for possible new IT infrastructures, HW and/or SW upgrade for both LAS and PCS (→ > 100k€)
   - Recruitments and empowerment of people in the organization (mainly in QU and production dept.)
   - required new professional skill in fields hybrid between traditional chemical/pharmaceutical knowledge and typical competence of IT people (e.g. CSV, security, data handling in computerized system)
   - Managing business change requires multi-level re-education:

     -From IT staff, prompted to learn new GMP skills quickly;

     -the QA department that needs to adapt the business philosophy to a sustainable perspective and bring real and practical benefits through periodic review of systems and the state of validation.

CONCLUSIONS

3. Establish a feasible timing for completion the planned tasks

-use project management tools

-guarantee the respect of time point s to implement changes to the systems involve d when required, reviewing in case the local projects priority

-periodic audit of systems and people behaviors

-integrate in the "ongoing" remediation plan any possible new CAPA derived from regulatory inspection (AIFA, FDA)

Risks and organization impacts to be considered

-significant increase of lead time to complete normal routine activities (e.g. batch release process) due to new time consuming activities (e.g. Audit Trail review to cover LAS systems)

-lack of continual system overview and people ongoing training


Thank you for attention !
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