



Risk based assessment applied to QA GLP audits

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RISK BASED ASSESSMENT FOR GLP AUDITS



INTRODUCTION

Since the origin of GLP the standard plan for QA inspections is based upon the concept of study and critical phases.

The concept of facility-based and process-based inspections emerges since a decade.

The “default standard” in the industry is still driven by the studies and the idea that facility-based and process-based should be performed quarterly.

The concept of processes, brought by the ISO standards, and the business need of optimizing the use of resources lead us toward a process based inspection concept, driven by the risks associated to the processes

This presentation is aimed to suggest to what extent this approach is GLP compatible



GLP inspections Authorities requirements



- **FDA: Inspect each non clinical laboratory study at intervals adequate** to assure the integrity of the study and maintain written and properly signed records of each periodic inspection showing the date of the inspection, the study inspected, the phase or segment of the study inspected, the person performing the inspection, findings and problems, action recommended and taken to resolve existing problems, and any scheduled date for reinspection. Any problems found during the course of an inspection which are likely to affect study integrity shall be brought the attention of the study director and management immediately.
- **OECD: conduct inspections to determine if all studies are conducted in compliance with these Principles** of Good Laboratory Practice.
Inspections should also determine that study plans and Standard Operating Procedures have been made available to study personnel and are being followed.
- Inspections can be of three types as specified by Quality Assurance Program Standard Operating Procedures:
 - Study-based inspections, Facility-based inspections, Process-based inspections.
- **Japan:** The quality assurance manager should implement by oneself, or designate a person in charge of study to implement the following:
 - (3) confirm that **inspections are conducted periodically at intervals appropriate to assure the reliability of study** in compliance with this ordinance; prepare records specifying the nature of inspection, inspection results, actions taken to solve problems, and the date when re-inspection is scheduled etc., then store them with signature or sign and seal;
 - **Ministry of Health and Welfare Ordinance No.21, 1997**



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CURRENT SITUATION IN THE GLP WORLD

- Still a lot of “critical phases approach”
- Process and facility based inspections design unclear
- Periodicity defined (often quarterly)
- “processes” are frequently periodic inspections of “phases”
- Frequent expectations by the authorities outside EU to maintain the status-quo



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Critical phases approach: Consequences

- Studies are comparable to products, QA inspections could be looked at as a QC of the product
- Many phases are audited again and again with very little to no added value
- Many interfaces between phases are rarely or never evaluated
- Information obtained is hardly useful for a CAPA or a continuous improvement process

BUT

- Studies are “clean” (product may be released)
- Compliance is granted



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What the processes risk based assessment can provide?

- A vision of the activity through processes regardless of the product (in this case the study)
- An inspection strategy based on actual risks
- An optimized and thorough use of QA resources
- The assurance of overseeing all activities and interfaces
- Information for continuous improvement



How to define processes



- Main challenge: find the right granularity of process mapping and design
 - Looking inside the processes:
 - Drives the content of the process inspection
 - Approach used for Quality risk assessment, process improvement and risk elimination and control
 - The areas of risk are identified and analyzed
 - The risk is controlled
 - Looking the processes as components of the system:
 - approach used for the purpose of the inspections planning
 - The risk is assessed and monitored
 - The 2 levels are complementary and sequential



Categories of processes



Categories

- Production Processes
- Support processes
- Management processes

Example toxicology study

- In vivo phase (dosing, clinical obs and exams, necropsy)
- Test item (synthesis, handling, formulation, analysis)
- Ex vivo phase (clinpath, anapath)
- Data management, statistics and reports)
- Animal husbandry
- Facilities management
- Metrology, IM
- SOPs
- Training and competencies



What is a risk?



- **RISK:** What are we talking about
 - Intuitively understand Risk as something harmful. In the GLP world it will be an undesirable event that put a study, a project or a facility in jeopardy
 - Three key components of Risk:
 - **Probability** that event will occur
 - **Severity** of the event
 - **“Detectability”** of the event
- To effectively assess risk, all components must be evaluated



Which risks are in the scope of GLP inspections



- Outside the scope
 - Risk of creating a harmful situation at the user level
 - Inappropriate safety assessment leading to false scientific conclusion
 - Inappropriate scientific study design
 - Workers safety (safety measures or inaccurate safety data)
 - Risk of inefficacy (inappropriate testing / misinterpretations)
- These risks are not addressed in this presentation



Which risks are in the scope of GLP inspections



– In Scope

- Risk of GLP non compliance (GLP principles, protocols or SOPs breaching or violation) with financial, regulatory or legal consequences
- Business risk (need for repeated studies, delays in registration / submission)
- Business risk (sites disqualification, image)
- Risk of creating a harmful situation for people or environment
 - Fraudulent activities that hide some characteristic of the test substance
 - Study misconduct that leads to wrong data thus bad conclusion
- These risks are the ones addressed in this presentation



How to assess risk



- The methods
 - Have very well defined processes that will be subjected to assessment and inspection (comparability)
 - Big variety of tools available for risk assessment
 - Basic Tools: the 5 steps approach, Preliminary Hazard Analysis, PHA Matrix and Risk Table
 - More sophisticated: FMEA, FMECA, HACCP, FTA
 - Select one; keep it for time (to ensure comparability of assessments with time)
 - Obtain a figure that will allow discrimination and prioritization
 - Reassess the risk after every process inspection (assessment update)



How to assess risk



- WHO does what? **PARTNERSHIP!**
 - Process mapping and processes design
 - QA (has the tool box)
 - Personnel (has the knowledge)
 - Risk Assessment
 - QA (has the knowledge)
 - Personnel (validate the assessment)
 - Risk based inspection plan
 - QA (knows the job)
 - Management (approve the plan)

The result belongs to the organization



How to assess risk



- Given the GLP nature of the risk, necessary information for a process risk assessment includes (but not limited to)
- Each topic may be associated with a number from a numeric scale
- Total of numbers contributes to overall assessment

Characteristic of the process
Novelty
operators awareness / competency
History of the process (last 12 months)
QA findings (number and grading)
Regulatory situation of the process
Regulatory inspection history (last inspection)
Process is on the authorities radar screen
Process scope
The process is a component of submitted studies
The process supports regulated / submitted studies
The process supports site Compliance
The process is outside the scope of compliance
The process contains Animal Welfare component
Criticality of the process
Failure of the process may negatively affect quality and / integrity of data
Failure of the process may invalidate studies
Failure of the process may impact site compliance



How to plan the process inspections



- Define frequencies and justify
 - Minimal (e.g. once a year)
 - Maximal (e.g. if a process needs to be inspected more than once a month, consider inspecting every activity of the process according to study specific critical phases plan)
- Prioritize according to risk level
- Adjust to available resources
- Revisit risk assessment and inspection plan after all inspections



Is RISK approach “GLP compliant”



- potential caveats from a regulatory standpoint.
 - Compatibility of risk approach with the GLP regulatory requirements
 - Not all studies will be “inspected”
 - To an extent, critical phases / study specific inspections could never happen (with the exception of protocols and reports)
 - How to demonstrate the GLP goals are fulfilled although the some of the GLP specific requirements may not be.
 - Provide the organization and the monitoring authorities with the assurance that all studies will meet the requirement
 - Means provide the assurance that the process will deliver what it was designed for.



Risk based inspection plan advantages:



- Formalizing QA decision making
 - Documentation
 - Data driven
- Improved process understanding
- Confronting key Quality questions
 - What is acceptable
 - What is most important
 - What is most value added
 - Consistency/ease of decision making when event occurs



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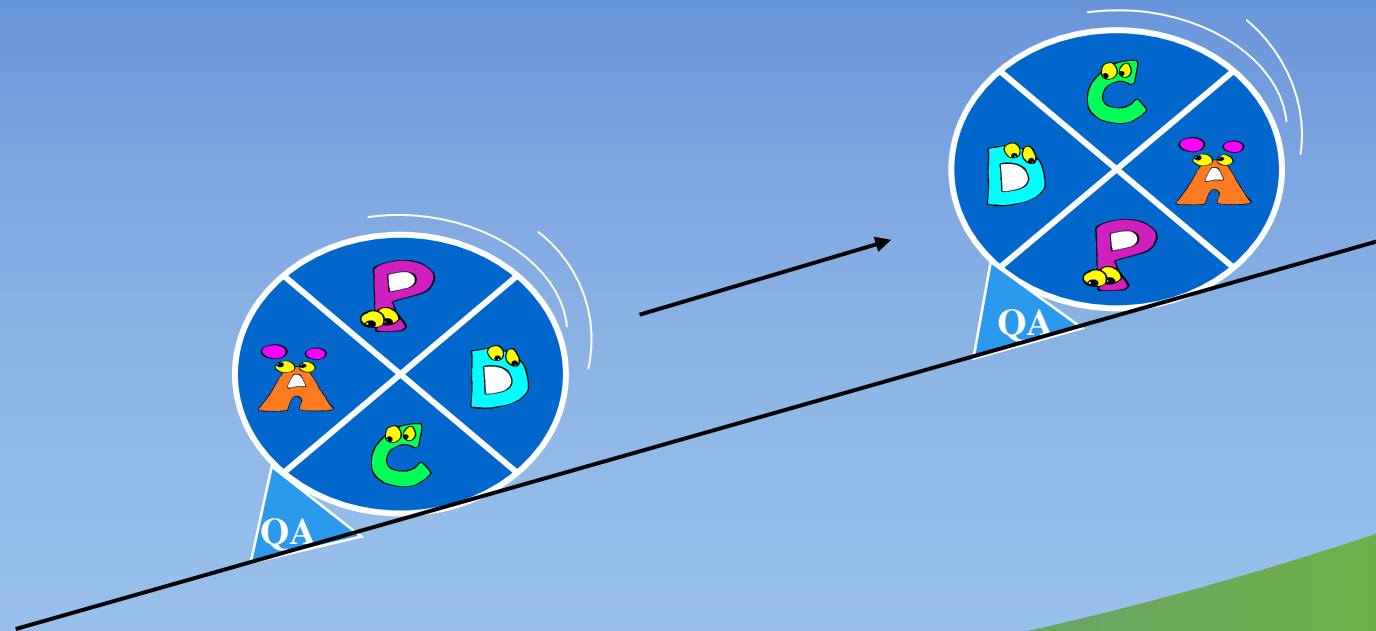


CONCLUSION

- This is my statement, please feel free to disagree
 - Inspecting processes based on a risk assessment provides valuable information while making the best use of QA common sense, knowledge, talents and resources
 - Such a plan, with the addition of each protocol being audited and each report being reviewed fulfills regulatory requirements



And finally, QA continuously improves its practices





- BACK-UP SLIDES



How does risk management compare to root cause analysis



- Risk Management looks at a dataset, and **what are the potential future consequences:**
 - Identifies potential risks
 - Analyzes potential risks
 - Evaluates potential risks
 - Controls potential risks
 - Actions are all focused on making decisions related to potential future events
- RCA is Retrospective, examining what **has already occurred** to:
 - Determine WHAT happened
 - Determine WHY it happened
 - Determine HOW it can be prevented from happening again



- **Selecting a Risk Assessment Method**
 - when the risk factors are more qualitative than quantitative. **Risk Ranking and Filtering (RRF), or Preliminary Hazards Analysis (PHA).**
 - When there is also an element of detectability chose to use **Failure Mode and Effects Analysis (FMEA).**

