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Risk-based assessment applied to QA GLP audits. How to fulfill regulatory requirements while making the best use of our common sense, knowledge, talents, and resources?

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Summary. For ages the standard plan of internal good laboratory practice (GLP) audits has been designed according to the study critical phases concept. A decade ago the concept of facility-based and process-based audits was adopted, mostly under the influence of short-term and *in vitro* study design. For unclear reasons, the quarterly inspection scheme has been the prevailing rule. Nowadays, the emerging concept of risk management reaches the field of GLP. In this context, the following items are discussed: i) nature of risks associated with the GLP principles and GLP studies; ii) risk in a GLP environment and criteria used to characterize a risk in laboratory and in an environment of research and development; iii) quality and integrity of data, study results and scientific conclusions; iv) risks associated to the processes and those associated to the products; v) workers safety; vi) consumers safety; vii) variety of tools available for the assessment of the above specific risks; viii) principles of risk assessment (the five-step approach); ix) standard and specific risk assessment tools; x) required level of accuracy; xi) use of risk assessment results for the elaboration of audit plans; xi) nature of information obtained; xii) prioritization; xiii) intrinsic risk versus available resources; xiv) potential caveats from a regulatory standpoint; xv) compatibility of risk approach with the GLP regulatory requirements; xvi) how to demonstrate the GLP goals are fulfilled although some of the GLP specific requirements may not be; xvii) benefits of this approach for the audits efficiency and the quality systems improvement; xviii) what the risk approach provides to the organization; xix) how does risk approach efficiency compare to standard efficacy; xx) use of metrics for continuous improvement.

Key words: quality, good laboratory practice, audit, risk assessment, compliance.

Riassunto *(Valutazione delle audizioni di BPL della AQ basate sulla definizione del rischio. Come soddisfare i requisiti regolatori facendo al tempo stesso il miglior uso del buon senso, conoscenze, competenze e risorse)*. Per molto tempo l'impostazione convenzionale delle audizioni di buona pratica di laboratorio (BPL) si è basata sul concetto delle fasi critiche di uno studio. Successivamente, circa dieci anni or sono, soprattutto in considerazione delle caratteristiche degli studi a breve termine e degli studi *in vitro*, è stato sviluppato il concetto dell'audizione dedicata alle strutture e di quella dedicata ai processi. Fino ad allora, per ragioni non del tutto chiare, lo schema ispettivo prevalente era stato quello trimestrale. Al giorno d'oggi il concetto innovativo della gestione del rischio permea anche i principi di BPL e gli studi relativi. In quest'ambito vengono esaminati i seguenti argomenti: i) natura del rischio associato ai principi di BPL e con gli studi effettuati conformemente a tali principi; ii) rischio in un ambiente BPL e criteri impiegati per analizzare il rischio in laboratorio ed in un ambiente di ricerca e sviluppo; iii) qualità ed integrità dei dati, risultati degli studi e conclusioni scientifiche; iv) rischi inerenti ai processi e rischi inerenti ai prodotti; v) sicurezza del lavoratore; vi) sicurezza del consumatore; vii) varietà di strumenti utilizzabili per la definizione dei suddetti rischi specifici; viii) principi per la definizione del rischio (impostazione a cinque fasi); ix) strumenti per la definizione di rischi standard e rischi specifici; x) livello di accuratezza richiesto; xi) uso dei risultati della definizione del rischio ai fini della elaborazione di schemi per le audizioni; xi) natura dell'informazione conseguita; xii) esame delle priorità; xiii) rischi intrinseci e risorse disponibili; xiv) divieti potenziali da un punto di vista regolatorio; xv) compatibilità dell'impostazione della valutazione del rischio con le necessità regolatorie; xvi) come dimostrare che gli obiettivi del sistema BPL sono stati conseguiti anche nel caso che alcune specifiche richieste dei principi di BPL non siano state rispettate; xvii) vantaggi della impostazione suddetta per l'efficienza delle audizioni ed il miglioramento del sistema di qualità; xviii) che cosa deriva all'organizzazione dall'adozione del concetto di rischio; xix) confronto tra l'efficienza conseguente alla adozione del concetto di rischio e l'efficienza standard; xx) impiego dei sistemi di misurazione per il miglioramento continuo.

Parole chiave: qualità, buona pratica di laboratorio, audizione, definizione del rischio, conformità.

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INTRODUCTION

Since the launch of good laboratory practice (GLP) principles in the late seventies, the standard plan of internal audits has been designed according the study critical phases' concept [1]. A decade ago, the concept of facility-based and process-based audits came into force, mostly under the influence of short-term and *in vitro* study design [2, 3]. For unclear reasons, probably dictated by an unchanged interpretation of the Food and Drug Administration (FDA) principles of GLP, 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. Nowadays, the emerging concept of risk management reaches the field of GLP.

The concept of processes is mainly brought by the ISO standards and the business need of optimizing the use of resources lead us towards a process-based inspection concept, driven by the risks associated to the processes [4]. However, many foot traps will pave the way to implementation, among which determining to what extent this approach is GLP-compatible is not the least.

NATURE OF THE REGULATORY REQUIREMENTS

Three major GLP systems are quite consistent in their requirements regarding the nature of QA inspections for ensuring GLP compliance of a study or a site, namely:

i) OECD. Inspections are conducted to determine whether all studies are performed in compliance with the principles of GLP. Inspections should also determine that study plans and standard operating procedures (SOPs) have been made available to study personnel and are being followed. Inspections can be of three types as specified by the quality assurance (QA) programme SOPs: study-based inspections; facility-based inspections; process-based inspections.

ii) Japan. The QA manager should implement personally or by designating a person to implement the following: confirm that inspections are conducted periodically at intervals appropriate to assure the reliability of study in compliance with what is prescribed: prepare records specifying the nature of inspection, inspection results, actions taken to solve problems, and the date when re-inspection is scheduled; store documents after signing and sealing.

iii) FDA. Each non-clinical laboratory study is inspected at intervals adequate to assure the integrity of the study and written and properly signed records of each periodic inspection are kept 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 solve existing problems, and any scheduled date for re-inspection. Any problems found during the course of an inspection which are likely to affect study integrity shall be brought immediately to the attention of the study director (SD) and management.

THE CURRENT SITUATION

The requirements summarized in the former section, with the exception of the OECD principles of GLP are not very incentive to move toward a different audit scheme. In addition, the GLP monitoring authorities (MAs), already facing the difficulty of harmonizing their requirements based upon the long lasting principles, are sometimes reluctant to consider different or innovative approaches of the GLP audit plan. Last, but not least, the strict adherence to the GLP principles is in itself seen as a valuable option by contract research organizations (CROs) and by the industry to mitigate the risk of findings during a client audit or a regulatory inspection. This is particularly true for those organizations that deal with multiple MAs (human pharmacy, animal health, chemistry, etc.) and for those handling international multisite studies.

This creates a situation where all partners, although very conscious of the need for change, still stick to a risk adverse and conservative way of running internal GLP audits and strive to maintain the *status-quo*.

The scenario in the vast majority of test facilities (TFs) is as follow:

- many studies are individually inspected according to the criteria of critical phase inspections;
- the design of process- and facility-based inspections is unclear. It is common practice to run process inspections identical to those for critical phases, although less frequently and not for all studies. There is here a conceptual confusion between processes and the activities which compose the processes;
- the inspection frequency is predefined (often quarterly as this is what the industry thinks will please the authorities), regardless of the outcome of past inspections and the seriousness of potential activity misconduct;
- the review of study reports often includes a significant amount of quality control (QC).

As side effects of this approach, studies are considered like products. Therefore, QA inspections could be looked at as a QC of the product. By missing the information related to the process, corrective actions are less efficient to identify root causes of failures, to manage a corrective action/preventive action plan (CAPA) or a continuous improvement process. Many phases are audited over and over again with very little or no added value, waste of QA resources and disruption of the operations. Many interfaces between phases are rarely or never evaluated, either within the process or across processes. On the other hand, there are obviously positive outcomes as the studies are

formally correct (products may be released) and compliance is granted.

It is therefore legitimate to ask the question: what can be provided by the risk-based assessment of processes? The major advantages are listed below:

- a vision of the activity through processes regardless of the product (in this case the study). This vision permits confidence to be gained in the fact that the processes, when operated according to robust and validated specifications, will deliver what is expected. When confidence is obtained, the need for subsequent QC is decreased, both at the operational level and at the QA one;
- an optimized and thorough use of QA resources. Time not spent in useless inspections can be devoted, *e.g.*, to training, internal consulting, process mapping, risk assessment, continuous improvement, change control and validation;
- an inspection strategy based on actual risks. Identifying metrics to characterize the risk of processes failures permits resources to be focused where the risk is higher. A robust risk assessment method is not only beneficial to the organization, but also well received by MAs to justify the audit programs;
- the assurance of overseeing all activities and interfaces. When the risk assessment is based on a comprehensive process mapping, all activities, including the hidden ones that contribute to meeting the requirements, will be subjected to evaluation. This is very different from the activity audit that often disregards the interrelations and interdependences between them;
- information for continuous improvement. The design of processes permits the risks associated to basic activities to be evaluated and improvement plans to be in place. Similarly, the non value-added activities are identified and eliminated, so that efficiency increases.

HOW TO DEFINE AND MAP ROCESSES

There are numerous publications available to assist in the methodology for process mapping [5-7]. However, there are some pitfalls that must be known in advance. The first challenge when implementing this type of approach is the definition of the right granularity, (*i.e.*, the resolution of the process) of mapping and design. The processes can be seen at a very high level such as producing safety information on a new chemical entity (NCE) or a very detailed one, such as transforming a tissue sample into a stained histological slide. If the vision is too broad, the mapping is meaningless, the risk analysis useless and the audit plan unmanageable. If the vision is too much detailed, the chances to revert to the activity inspection scheme are very high. In addition, the granularity of all processes must be identical to guarantee the correct evaluation of interdependences and interrelations.

It is commonly accepted to categorize the processes according to what they can deliver. Those processes that deliver a quantifiable entity are called production processes. The ones that deliver intangible entities needed to run the production processes are called support processes. Lastly, the ones that operate systems needed to run the organization are called management processes.

Listed below are some examples of processes for a toxicology laboratory with the same level of granularity. These examples are to be taken as such, since the categorization and the definition of processes is primarily specific to each organization according to its size, structure, status and stage of development of this approach.

Production processes

- *In vivo* phase (dosing, clinical observations and examinations, necropsy);
- test item (synthesis, handling, formulation, analysis);
- *ex vivo* phase (clinical pathology, anatomical pathology, bioanalysis);
- data management (statistics and reports).

Support processes

- Animal husbandry;
- facilities management;
- metrology, informatics;
- contracts and procurement;
- audit plan.

Management processes

- QA system;
- quality documents system (manuals and policies, SOPs, operating modes, instructions, forms);
- training and competencies.

RISK IN A GLP ENVIRONMENT

What is risk? Common sense and intuition attach to risk the meaning of something harmful. In the GLP world it is understood to be an undesirable event that jeopardizes a study, a project, or a facility. To effectively assess risk, two components must be known, *i.e.*, the probability that the event will occur and the severity of the event. More sophisticated approaches in addition to this evaluate also the detectability of the event. The probability can be predicted using history or intuition, or can also remain unknown. This is the criterion that is mostly discussed as it is the least measurable. Severity of the event is an easy concept: it consists of listing the consequences of the event in the case it actually occurs. Detectability, in turn, may sometimes be a tough concept. Examples may be found in the literature on bugs or viruses in complex IT systems or in highly automated analytical chains, where malfunctions may happen several days before being detected.

Not all risks are in the scope of designing and planning QA audits and inspections in a GLP environment. However, when the audit program is designed to cover an integrated approach in terms

of quality, safety and environment, they might be assessed in order to design a comprehensive audit system covering also the following items that do not belong to the scope of GLP principles: *i)* risk of creating a harmful situation at the user level by misevaluating the characteristics of a new biological or chemical entity; *ii)* inappropriate safety assessment leading to false scientific conclusions: *iii)* inappropriate scientific study design. These three types of risks belong to the technical and scientific capabilities of the study designers, Safety measures or inaccurate safety data, in turn, may well impact workers safety.

The risks that should be assessed to put in place a risk-based audit program comprise (but are not limited to) the following: *i)* risk of non GLP-compliance (breaching or violation of the GLP principles, protocols or SOPs) with financial, regulatory or legal consequences; *ii)* business risk (need for repetition of studies, delays in registration and submission); *iii)* business risk (sites disqualification, image); *iv)* risk of creating a harmful situation for individuals or the environment; *v)* fraudulent activities to conceal some characteristics of the test substance; *vi)* study misconduct that leads to wrong data and the ensuing erroneous conclusions.

HOW TO ASSESS THE RISK

Risk assessment, like many other metrics, is founded on processes. Risk should be assessed at two consecutive and complementary levels, namely: *i)* looking at the processes as components of the system. This consists in the assessment of the risk associated with the process failure (performance metrics) without examining the real cause of the failure. This assessment can be used for the calculation of the frequency at which the process should be subjected to audit, *i.e.*, the audit plan design. This approach is aimed at evaluating and monitoring the risk. In addition to the risk evaluated according to the methods indicated below, some metrics such as novelty of the process, training of personnel, etc., may be used to assess the probability of failure; *ii)* looking inside the processes. This consists in the detailed assessment of the sequence of activities inside the process, thus identifying at what step and for what reason the process could fail (diagnostic metrics). This approach is used for quality risk assessment, process improvement and risk elimination and control. It is not meant for setting up audit plans. It serves the purpose of determining what should be given priority when auditing the process, thus focusing resources in the areas where risks are identified and analyzed.

From a general viewpoint, risk management looks at a given dataset and takes into account potential future consequences in terms of identification, analysis and assessment and control of potential risks. Actions are all focused on making decisions related to potential future events. Root cause analysis (RCA) is retrospective and examines what has already occurred in order to determine what happened, why it happened and how it can be prevented from happening again.

As regards risk assessment methodologies, it is of paramount importance to have very well defined processes that will be subjected to assessment and inspection (comparability). This is a lesson learned from the ISO approaches: robust and detailed process design and process mapping are the backbone for many activities, such as continuous improvement, change control, business continuity planning, disaster recovery planning, and, obviously, risk assessment. As far as the risk assessment itself is concerned, the literature offers a big variety of tools. Some are basic, some more complex and sophisticated. Among the basic tools, worth mentioning are the five-step approach and the (matrix and risk table). When the risk factors are more qualitative than quantitative, the risk ranking and filtering (RRF) or the preliminary hazards analysis (PHA) should be resorted to [8]. When there is also an element of detectability more sophisticated tools such as failure mode and effects analysis (FMEA), hazard analysis and control of critical points (HACCP), or fault tree analysis (FTA) should be used [9-11].

When selecting a tool, it should be kept in mind that it will be used for some time to ensure comparability of assessment and to measure the efficacy of preventive actions. Generally, the basic methods end up with risk classification such as low, medium, and high. Although it may be enough for other uses of risk assessment, it may lack discriminative power when used for audit program design, especially when the key factor is prioritization. Obtaining figures that will allow for a better discrimination (*e.g.*, numerical scale from 1 to 20) will help setting priorities. The history of records is one of the most important inputs, especially for the evaluation of the probability that the event will occur. Therefore, in order to use updated information, the risk must be reassessed after every process audit.

The nature of the risk assessment activity makes it an obvious candidate for a full partnership approach.

In terms of process mapping and process design, QA has the knowledge of methodologies whereas personnel have the knowledge of operations and activities. In other words, personnel provide the raw material and the QA supplies the recipe. The QA has the expertise, whereas the personnel must review and confirm the validity and relevance of the assessment. A strict theoretical approach may miss obvious basic components, with a probability of over- or underestimate the risks. For the risk-based inspection plan, the design comes from the QA and then the management must approve the plan. The results of the assessment and the audit plans themselves belong to the organization.

PLANNING THE PROCESS AUDITS

Before moving to the risk-based planning, the QA group must establish with documented evidence the upper and lower limits of confidence of the risk assessment. These limits are defined according to numerous criteria: *i)* the maximum acceptance of risk, *ii)* what is the lowest frequency monitoring authorities are likely to accept, *iii)* how much the organization management feels comfortable with this approach, etc. The minimum frequency generally accepted is once a year. On the other hand, the maximum frequency is harder to define as it is essentially based on the type of activities performed by the GLP-compliant TF. It seems reasonable to say that, if a process needs to be inspected more than once a month, it would rather be inspected according to the study specific critical phase plan. The first step of the plan must be based on the risk level only, assuming that unlimited resources are available. Then the plan needs to be adjusted to take into account the really available resources as an audit always causes a work overload both in terms of QA activity and TF operations. As already mentioned, as soon as an audit is completed, audit results will be used to update the risk assessment and the audit plan.

RISK-BASED AUDITS AND GLP COMPLIANCE

Considering the current requirements and positions of GLP MAs worldwide, this approach is still highly controversial. As discussed above, there is much reluctance, both on the side of the industry as well as of the authorities, to move towards a new scheme. This resistance to change is somehow justified by potential caveats from a regulatory standpoint. When considering the compatibility of the risk approach with the GLP regulatory requirements, several facts stand out, *i.e.*: *i)* not all studies will be audited; *ii)* to a certain extent, critical phases and study specific inspections could never take place (with the exception of protocols and reports). Hence, the most serious questions are: *i)* how to demonstrate that the GLP goals are fulfilled although some of the GLP specific requirements may not be complied with; *ii)* how to provide the organization and the MAs with the assurance that all studies will meet the requirements.

Looking at the problem with a pair of "ISO" eyes, the question turn to be what are the means that we need to provide evidence that the processes deliver what they were designed for? It is expected that studies are acceptable as far as data quality, integrity, repeatability and reproducibility of results, personnel competence, protocols, SOPs, and follow-up instructions are concerned. Auditing processes will provide this assurance if: *i)* the processes contain the necessary QC steps; *ii)* the processes are well designed; *iii)* the audit plan covers all processes at an appropriate frequency. In addition, the review of the final outcome of a study – the study report – will permit to ascertain that the processes produce the expected products.

ADVANTAGES OF A RISK-BASED INSPECTION PLAN

The very first advantage is to finalize the QA decision making. This means that the QA Unit (QAU) does not do things "because it has always be the way to do it", but makes decisions based on motivated reasons, justified and discussed or agreed upon with the whole organization.

A second advantage is to create documentation to support the decision made, to demonstrate now and in the future the way decisions were made, the criteria for decision making and the data used for creating the plan.

The third advantage is that the audit plan is data driven. Therefore, only the criteria may be challenged, either by the authorities of by internal partners. Data used for the audit design are generated by the organization and therefore not suspected of being partial or distorted.

A fourth advantage is that the continuous improvement process is easily understood as it is based on a risk evaluation that tends to diminish when the control of the processes increases.

The fifth advantage is that the QAU and the partners must reach an agreement on key quality questions, in particular regarding what is acceptable in term of deviations, what is most important and what is the key value added. It always reminds the QAU that their work is just a component of all activities that are needed to produce good science, good technique, good business, and good practices. This minimizes the tendency the QAU may show to work in isolation for the sake of ideal compliance and quality achievements.

By providing clear, shared, and well-known ways of assessing, measuring, and acting, the consistency of decisions is assured along with an ease decision making when unexpected events occur.

Finally, by focusing QA resources on major aspects and eliminating non-value added activities, time is saved for QA people to handle the best valued part of their job, thus partnering with operations for continuous improvement, training, and advising.

CONCLUSIONS

Inspecting processes based on a risk assessment model provides valuable information while making the best use of the QA common sense, knowledge, characteristics, and resources. Such a plan, with the addition of each protocol being audited and each report being reviewed, fulfills regulatory requirements. Assessing risk drives the organization to firstly map and design its processes, an activity that has numerous positive side effects. Among these, of primary importance is the possibility of fostering a continuous improvement process that can be used by all personnel in general and by the QAU in particular.

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