Clinical Quality Management System

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Quality is More than Compliance

Even 20 years after the issuing of the ICH GCP Guidelines (ICH E6), the principles of GCP are still sound, and little can be criticized about them. The updates of the Guidelines and especially its Addendum [ICH E6(R2)] that in Europe became effective in 2017 have not fundamentally changed the content of this Guideline but introduced technology and approaches that were unknown when the GCP Guideline got issued for the first time. Twenty years ago clinical development was largely a paper-based process, and the Internet and even more so the *Cloud* were technology and tools only known to a few *techies*.

The value of ICH E6 is also evidenced by the fact that ICH GCP successfully made its inroads even into new regions where public welfare priorities and medical practice differ from what is the norm in the original ICH regions: Western Europe, USA, and Japan. When these principles are so robust and still so sound, why is there then an ongoing debate about the inefficiencies of the clinical trial process, the growing disinterest of physicians in clinical trial activities, and an apparently dwindling quality of results generated through clinical trials which results in distrust by patients and the public at large into the clinical trials enterprise? What is causing this disenchantment? Could it be that we – sponsors, health

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F. J. Hock, M. R. Gralinski (eds.), *Drug Discovery and Evaluation: Methods in Clinical Pharmacology*,
https://doi.org/10.1007/978-3-319-56637-5_42-1

authorities, and also public health services – burdened the sound principles of GCP with bureaucratic requirements that at first seemed to be "good ideas" but as a matter of fact do not contribute to what are the two fundamental dimensions of GCP and quality: protecting patients' safety, right, and integrity as well as ensuring data integrity? Is the ICH GCP revision and especially its *Addendum*, which became effective this year, going to improve the way how GCP gets implemented? In fact, this *Addendum* stresses the importance of the sponsor's oversight on all stakeholders in a clinical trial, the **personal** responsibilities of the principal investigator, and the roles and responsibilities of a CRO. The *Addendum* also highlights the importance of a robust quality management system and calls for a structured risk assessment of protocols and processes applied to execute a trial protocol that are enablers of risk-based monitoring or what is a more accurate rendition of the concept: evidence-based trial quality management.

When implemented correctly *evidence-based trial quality management* allows:

1. Ensuring the protection of patients' safety, integrity, and rights.
2. As the flip side of the above, ensuring data integrity what is nothing else than the long-term dimension of the first requirement: avoid any false positive or negative conclusions because the data collected in a trial is faulty.

When this principle is recognized and correctly implemented – remember decisions should be data/evidence driven and not be based on opinions, even if decisions are reached by team consensus, as stated by Edwards Deming's *quality without data, is just another opinion* – then a liberating epiphany emerges: errors "that are understood" or "factored into the process," on the basis of the sound principles of a Quality by Design (QbD) methodology and approach, do not matter! In other terms, on this basis an isolated GCP non-compliance, such as an isolated transcription error, omission of a "minor" adverse event can be accepted as "forgivable sins." Conversely, system failures that do result or may result in a risk to the two fundamentals of GCP must be identified, proactively dealt with, and if they have materialized be corrected or at least mitigated swiftly.

Methodologies of Quality Risk Management (QRM) and Quality by Design are instrumental for a systematic quality management approach that allows focusing on the essentials of GCP.

Elements of a Pharma/Health-Care Quality Management System (QMS)

Any QMS should include the following elements:

A. **People**, i.e., those individuals who have a role and responsibility in a
B. **Process** related to the development of a new medicinal product/health-care activity. Processes are typically described in SOPs (standard operating procedures) and systems' (validation) documentation and are owned by the business units involved in these activities. A quality manual is a useful tool to summarize the quality principles and high-level processes of an organization.
C. **Controls**, i.e., those activities implemented by the business or process owner under the oversight of the independent quality assurance (QA) unit to identify and prevent process deviations and defective products. "Classical" control elements are review and approvals of essential documents, monitoring and co-monitoring of process and its deliverables, auditing, and inspections to verify and confirm compliance. Controls must include evidence (documentation) reviews and approvals that have been executed in a timely manner. In a Quality Risk Management, environment control needs to include KPIs (key performance indicator) and KRIs (key risk indicator) to allow for a continuous monitoring of the performance of systems and products or outputs meeting predetermined specifications.
D. **Documentation**, i.e., a transparent description of the systems and processes used allowing to reconstruct at any time the sequence of events as well as the body of evidence of compliance with stipulated checks and controls.

Quality by Design (QbD) Builds on Robust, Smart, and Well-Documented Processes

The classical approach to a QMS has its shortcomings as more and more the costs (for instance, for monitoring clinical trial centers) and resources needed for the management and controls of a clinical development process are not matched by a commensurate process efficiency and quality of the "product." From a QbD perspective, quality is best defined as *a product, service or process that meets customers' needs*, whereas the customer can be an independent third party such as a buyer, regulator, prescriber, etc. or an "internal" client, e.g., the next in the value chain. To define the process leading to a quality product or service, a concept known from the 6-Sigma methodology – SIPOC – has proven to be very effective. We prefer to refer to SIPOC^2:

- **S**upplier, a **named** individual who delivers a product or service – can also be an instruction – that enables the next individual in the value chain to execute a predefined task. It is good practice not to designate a *team* as the supplier; if a function is designated as the supplier in a process chart, then within the *supplier's* organization, a named individual needs to be identified.
- **I**nput, the (sometimes, semifinished) product or service – can also be a decision such as an approval – that serves as the building element for the next "production" step.
- **P**rocess, predefined, documented, and agreed sequence of activities that each meets predefined, documented, and agreed specifications. Critical process steps are linked to control steps.
- **O**utput, the deliverable – can be a product, service, or decision – of the above process.
- **C**ustomer, a **named** individual (exceptionally a functional entity) who receives the above output. The customer can be a third party or internal client.
- **C**ontrols, this is the C^2 in SIPOC and refers to all quality verification and governance activities as well as any corrective and preventive actions.

The purpose of the SIPOC^2 approach is to break down a complex (generally a multistep) process into discrete elements to drive transparency and accountabilities. Robust controls are defined and implemented at each supplier – customer interface and also specifications for input and output.

The SIPOC^2 concept can also be applied to the design of a protocol and the planning and implementation of a clinical trial. For instance, the protocol "designer" should not only define clear roles and responsibilities for all protocol tasks but as part of the *process* and *control* description also anticipate what could go wrong, build up-front contingency plans, define controls to identify early deviations from the design specifications, and include in the design of a new trial learnings from past, good, or bad experience.

Quality by Design and Quality Risk Management (QRM)

The QbD approach and QRM are intimately related. The smart implementation of a QRM strategy leverages operational or transactional data generated as a by-product of the clinical or pharmacovigilance processes to return inferences about process robustness and compliance with set specifications. Typically, QRM uses an array of so-called key risk indicators: a KRI is a measurable entity and is always associated with a threshold of acceptance/rejection. A KRI is comparable to a KPI but focuses on the quality rather than the efficiency aspect.

For instance, the audit trail generated for each change to a database entry (i.e., the GCP mandated tracking of the date of a change and the originator of a change) can be trended across all sites of a trial to determine whether an unexpected pattern in these changes emerges. The number of data entry changes is an example of a KRI. For example, investigators in a given country or clinical trial center may "produce" an above average

number of changes. QRM requires that the root cause and reason for this "aberration" are investigated and understood in order to take either corrective and preventive action (CAPA) or to accept the fact that there is such an "aberration" when this has a logical and justified reason. As shown in this example, QRM typically uses meta-data as drivers and input for KRIs and thus takes *QC and QA by sampling* to a seamless oversight of mission critical activities, processes, and deliverables.

6-Sigma, FMEA (failure mode and effect analysis), and Kaizen are established methods or models supporting a QbD and QRM approach.

Quality by Design in Other Domains and Industries

ICH had started the discussion about QbD (i.e., ICH Q8, Q9, and Q10 guidelines) in the GMP area, and the revision of ICH GCP and especially its *Addendum* has extended these concepts also to clinical trials. Nevertheless, compared to other industries, the health care and pharmaceutical sector are lagging behind in applying QbD and QRM approaches. Therefore, learning from other industries on how to successfully introduce QbD and QRM processes should become a priority.

The airplane engine manufacturer Pratt & Whitney is a good example for the successful shift from a *trial and error* approach in product development to a disciplined and process driven *engineering standard work* (ESW). In ESW process steps are documented and described in extensive but targeted *Workflow Maps* with a focus on the interdependencies between the successive process steps. This approach establishes *design criteria* with clear deliverables for each ESW step and demands for clear and unequivocal *ownership* of each ESW element. ESW also introduced the *practitioner proficiency assessments* to capture coaching needs as well as coaching capabilities of individuals involved in product development. ESW is a prime example for the application of Edwards Deming's principles of the PDCA cycle (**P**lan–**D**o–**C**heck–**A**ct).

Back in the early 1950s, the US Navy introduced under the leadership of Hyman Rickover a QbD methodology and mind-set that allowed to operate nuclear reactors on their ships without any radiation incident for more than 60 years. Rickover was a stern advocate of a process driven approach. One of his fundamental contributions was reinventing the methodology of testing. In a traditional approach, testing is seen as an enabler for discerning *good* from *bad*. Rickover redefined the purpose of testing as an enabler for discerning an *understood* from a *not understood* process or process step. This coupled with his non-tolerance of a work-around approach – a work-around being seen as evidence of a poorly understood or designed process – a data driven and disciplined (also in terms of detail) problem-solving approach, as well as a low threshold for what is counted as an incident resulted in an unprecedented reliability of a highly complex system such as a nuclear reactor on a submarine.

Quality Means Standardization

The pharmaceutical industry has failed to date to develop and implement common standards for its key activities. As a result of this deficiency and inefficiency, investigators are frustrated, quality of clinical trials is negatively impacted, and inefficiencies in the clinical trial process are the norm. This "state" is compounded by a silo mentality of this industry by which learnings of pre- or post-competitive nature around clinical trial activities are not shared or leveraged. The consequence is that the same errors are repeated again and again. From this follows that the successful implementation of QbD and QRM approaches will require that standards for routine processes get developed within the company and across companies. As demonstrated in other industries (e.g., airline industry), shared standards drive quality and eventually also efficiency as the need for retraining to different formats for an identical process becomes obsolete. Although TransCelerate – a cross-industry initiative – was established to streamline drug development processes, some of their achievements such as the publication of a template for a clinical protocol, a tool to conduct a risk assessment, etc., fall short

of a true standardization: What would truly streamline the clinical trial process was developing and implementing for each "common" indication a shared protocol, which would simplify the review by ethics committees and health authorities, the implementation of a trial by the investigators and their teams, training of all involved stakeholders such as monitors, and also the setting up of the database, the eCRF, by the sponsor.

Misconceptions Around the Building of a QMS

A common error in establishing a QMS is to build it as an afterthought rather than a strategic priority. Especially, start-up companies fall into this trap by focusing on their "science" and consider SOPs and other elements of the QMS as a nuisance rather than an asset. From experience a robust QMS should be in place no later than 6 months prior to starting entry into men trials. On one hand also inspectorates have moved to a *risk-based approach* and may inspect a trial as soon as phase 1 which is a significant change to past practices when inspections were triggered by a submission of a marketing authorization dossier. Moreover, thinking early about the scope and content of the QMS allows streamlining the procurement policy and aligning processes across the various functions of a company. Lack of processes and procedures inevitably lead to waste of time (rework because of errors caused by miscommunication) and money (bad contractual terms or even switching of service providers because of unsatisfactory performance). As a result unhappy or overworked staff members are a sad consequence which often exacerbates the compliance challenge.

Conclusive Remarks

The successful implementation of a modern QMS based on QbD and QRM approaches does not depend so much on the choice of the right methodology or tool kit but primarily requires a change in mind-set that must be initiated by the top management of the involved organizations. QbD needs a long-term commitment and is not a short-term measure to realize cost savings. It will eventually result in *operational excellence* if the process is applied consistently and in a disciplined manner. In this context Deming's profound observations are of significance: "in the 1970s, Dr. Deming's philosophy was summarized by some of his Japanese proponents with the following 'a'-versus-'b' comparison:

(a) When people and organizations focus primarily on quality, quality tends to increase and costs fall over time.
(b) However, when people and organizations focus primarily on costs, costs tend to rise and quality declines over time."[1]

Moreover, it should also be emphasized that the QMS must be owned by senior management and the process owner and that the QMS must be designed and implemented as an in-process and not an epi-process activity. To ensure a disciplined approach, senior management must ensure the true independence of the involved QA and QC functions.

References and Further Reading

Deming EW (1966) Some theory of sampling. Dover Publications, Mineola NY, USA
Imai M (1986) Kaizen: the key to Japanese competitive success. McGraw Hill, New York, USA
Lunau S et al (2006) Six sigma + lean toolset. Springer Verlag, Heidelberg, Germany
Spear SJ (2009) The high velocity edge. McGraw Hill, New York, USA

[1] Quote from Wikipedia