CROs AND SERVICE PROVIDERS: A SPECIAL KIND OF AUDIT

Dr. Allen E. Goldenthal
BSc,DVM,PhD,MBA

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FDA WARNING LETTER:

This is what we want to avoid:

- *VENDOR QUALIFICATION – WARNING LETTER 30 Apr 2014*

You should note that CGMP requires the implementation of quality oversight and controls over the manufacture of drugs, including the safety of raw materials, materials used in drug manufacturing, and finished drug products. *See* FDCA, as amended by the Food and Drug Administration Safety and Innovation Act (Pub.L. 112-144, Title VII, section 711). We note that **you have chosen to hire a contract testing laboratory** to perform some of the required testing of your finished drug products. **FDA inspected this laboratory (b)(4) and observed deficiencies in its practices**. If you choose to contract with a laboratory to perform some functions required by CGMP, it is **essential that you select a qualified contractor** and that **you maintain sufficient oversight of the contractor's operations to ensure that it is fully CGMP compliant.** Regardless of whether you rely on a contract facility, you are responsible for assuring that drugs you introduce into interstate commerce are neither adulterated nor misbranded. *See* 21 CFR 210.1(b), 21 CFR 200.10(b).

OUTSOURCING: EXAMPLES

- Transfer of ownership/control of a process to a supplier in order to reduce overall costs and/or focus on core competencies (or)
- Buying from a provider those services that are not at the core of a organization’s competencies (or)
- The reliance on external sources for manufacturing components and other value-adding activities

OUTSOURCING IN PHARMA:

- An estimated 42% of pharmaceutical expenditure was committed to outsourcing in 2004
- A recent off shoot of outsourcing business known as Site Management Organizations (SMOs) have been rapidly evolving, capturing a growth rate of 43% /year
- Some estimated over 1200 organizations are involved in clinical research
- CROs, first organized as only outsourcing service companies, transformed into comprehensive service providers such as: management, complex drug trials, access to areas of expertise not available at client's site
- In some cases the CRO being used may also be a competitor.

IN A RECENT SURVEY:

- **When selecting service providers, according to a recent survey (2015), sponsoring pharma companies stated that they focus on the following criteria (listed in order of importance).**

1. Confidentiality (81%)
2. Quality (81%)
3. Consistency of performance (79%)
4. cGMP compliance (75%)
5. Regulatory inspection history (69%)
6. Ability to Work cooperatively (63%)
7. Experience in the Subject Area (61%)
8. Timeliness (60%)
9. Contract firm's financial stability (56%)
10. Project cost (54%)

As a result of this prioritization, they said 45.6% of the time, CROs contracted could not provide the quality of product or services that they promised.

OUTSOURCING IS A VIRTUAL OPERATION:

- **Virtual Operations outsource in any of the following areas:**

  Product Development
  Technical services
  Quality Control Testing
  Clinical Operations
  Clinical Trial Material Preparation
  Supply chain management
  Planning and Packaging

THE STRATEGY OF OUTSOURCING:

- Out source only non-core competencies
- Select regional to global preferred CRO
- Identify and consolidate short and long term objectives of ensured alignment between two companies
- Continuous flow of information between external and internal stakeholders
- Respect of competitive environment at both sites with fair and impartial treatment
- Relationship management via better communication, respect, face to face frequent visits, strengthen the sense of interdependency and common goals

AUDITING DIFFICULITES FOR CROs:

- **Important Selection Criteria are Required in Consideration of the Necessary Audits:**
  - Location and Language

    1. Within easy reach of a major air port and ideally in same time zone but 24/7 communication available.

    2. Accessible for periodic visits

    3. Communication in English at all levels is valuable

    4. All key documents in Chinese language and English
  - Quality approach

    1. Should have comparable approach to quality issues

    2. Practices are standardized for daily decision making

SPECIALIZED AUDITING SKILLS REQUIRED:

- Regulatory Compliance Status:
  1. Compliance to similar GMP standards
  2. National Regulatory Agency
  3. Audit history by the Regulatory Agencies
- Commitment to excellent supplier performance:
  1. Striving for quality, innovation and deliver timelines
  2. Passion for the product supply and safety
  3. Excelling flexibility and ability to turnaround at short notice
- Organizational structure:
  1. Consisting of similar core functions as the overseeing company with good site management and both clarity and responsibility for quality and compliance

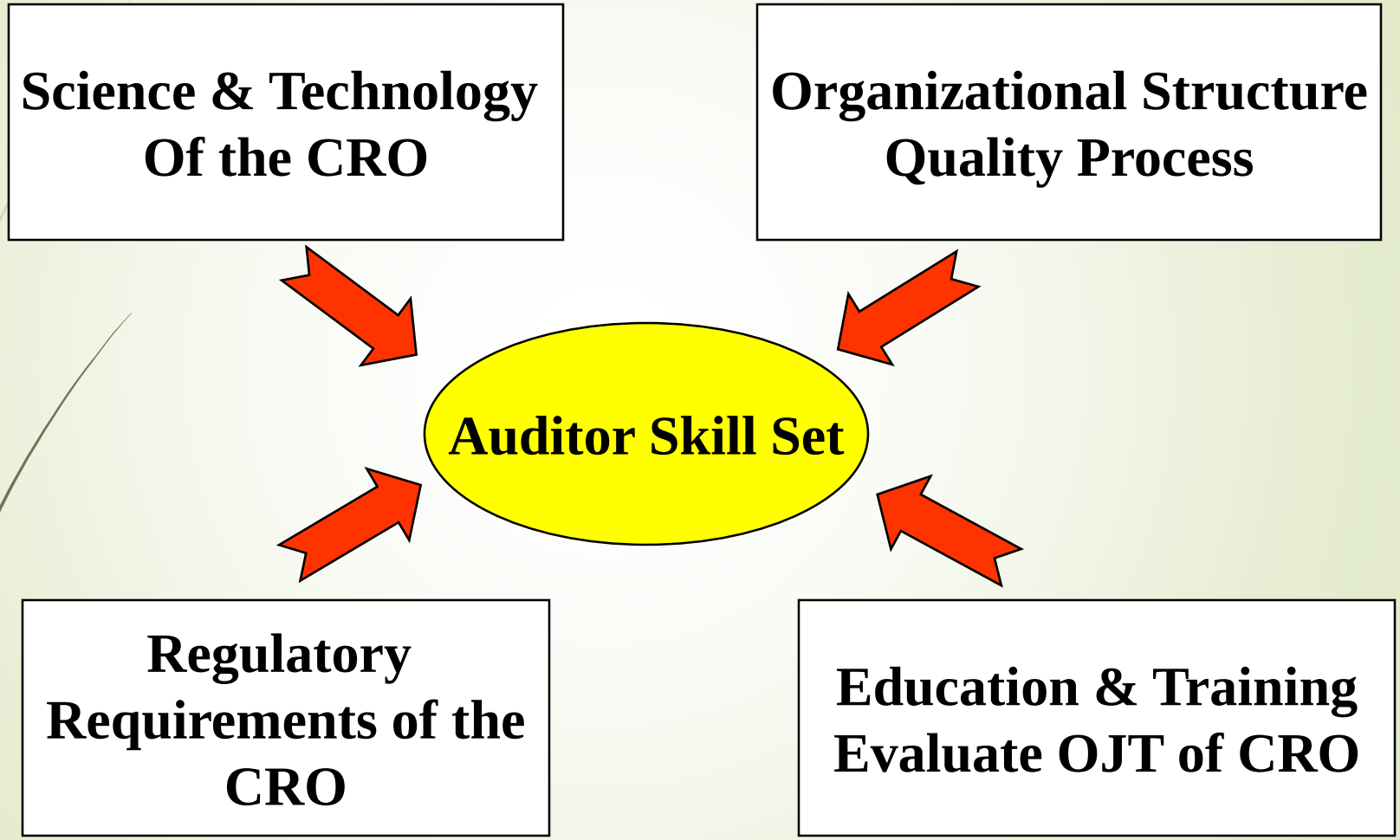
AUDITORS ALSO CHECK FOR:

- Processes and metrics used for day to day management
  - Change control, Quality agreements, complaint handling system
  - Periodic internal audits, trend reports for OOS and deviations
  - Master production schedule
  - It is almost as if performing an Internal Audit except it is not their own company

AUDITORS CHECK FOR QUALITY OF CONFORMANCE (QOC)

- QOC refers to product consistency
- QOC pertains to uniformity of product or service attributes
- QOC can be applied in:
  - Process design: Establishing design criteria
  - Process control: Quantifying quality
  - Sampling: Sampling plans
  - Product release: Testing, verification, audit, etc.
- Process Capability provides high degree of assurance for:
  - Process to conform to manufacturing limits
  - Product to conform to specification limits
  - Quantify performance during process validation
  - Can form the basis for process validation

SPECIALIZED AUDITORS FOR CROs:



CLINICAL TRIALS HAVE EVEN MORE OVERSIGHT:

Monitoring:

- Responsibility of the sponsor's clinical research department
- Part of the clinical research department
- Regular monitoring of each research center
- Monitoring reports to be circulated within the department

Auditing:

- Responsibility of the sponsor's Quality Assurance department
- Independent from the clinical research department
- Sample auditing of important clinical research centers
- Auditing reports to be submitted to high-level management

CLINICAL TRIALS REQUIRE A DIFFERENT KIND OF AUDITOR:

In general, these audits are performed by experienced quality management (QM) employees of the sponsor, who do not always have a profound background in data management (DM), biostatistics/statistical programming (BIO) or medical writing (MW).

As such, up to now, these fields, which are only a part of the tasks to be subcontracted, were to some extent neglected in such audits leaving big gaps in the reports.

MONITORING AND AUDITING OF CLINICAL TRIALS:

Purpose of the Routine Monitoring Visit

1. Review progress of a clinical study
2. Ensure protocol adherence
3. Assure accuracy of data
4. Assure safety of subjects
5. Regulatory Compliance (CFR & GCP)

Purpose of the Sponsor's Audits…

- Sponsor's QA department may chose to audit a site:
  1. as a preparation to filing the NDA/BLA.
  2. as a pre-audit before the FDA inspection
  3. as a result of monitoring findings
  4. to ensure source documentation is complete and that the site is well organized
  5. for review of monitoring practices (ie, QA of the monitor)
  6. aid in identifying and correcting problems
  7. provide suggestions to improve site

DIFFERENT OVERSIGHTS ON CLINICAL TRIALS:

- Audit refers to a systematic check-up, by people not directly involved in the trial, to evaluate whether the implementation, data recording and analysis of the trial are in accordance with the trial proposal, standard operation regulations and other regulations related to drug clinical trials. **THE SPONSOR'S RESPONSIBILITY**

- Inspection refers to drug supervision and management authorities' official evaluation of the documents, implementation, recording and other aspects of a clinical trial. Inspection can take place in the trial institute, location of the sponsor, or venue of the contract research organization (CRO). **THE REGULATORY AUTHORITY'S RESPONSIBILITY**

SERVICE PRODVIDERS MAY BE WORKING TO DIFFERENT REGULATIONS:

It is not only important when selecting a CRO to know which regulatory standards they are working under but also to appreciate the differences when performing the audit.
Expectations of the Sponsor may not always match the performance standards of the CRO.

WHAT ARE THESE REGULATIONS:

- **ISO 17020(5)**
  1. The new ISO 17025:2017 is the accreditation criteria for the competence of testing and calibration laboratories. It is designed for laboratories to improve their capability to consistently produce valid results. It specifies the general requirements to carry out sampling and testing using standard methods, non-standard methods, and laboratory developed methods. It applies to all laboratories where testing and/or calibration forms part of inspection and product certification.

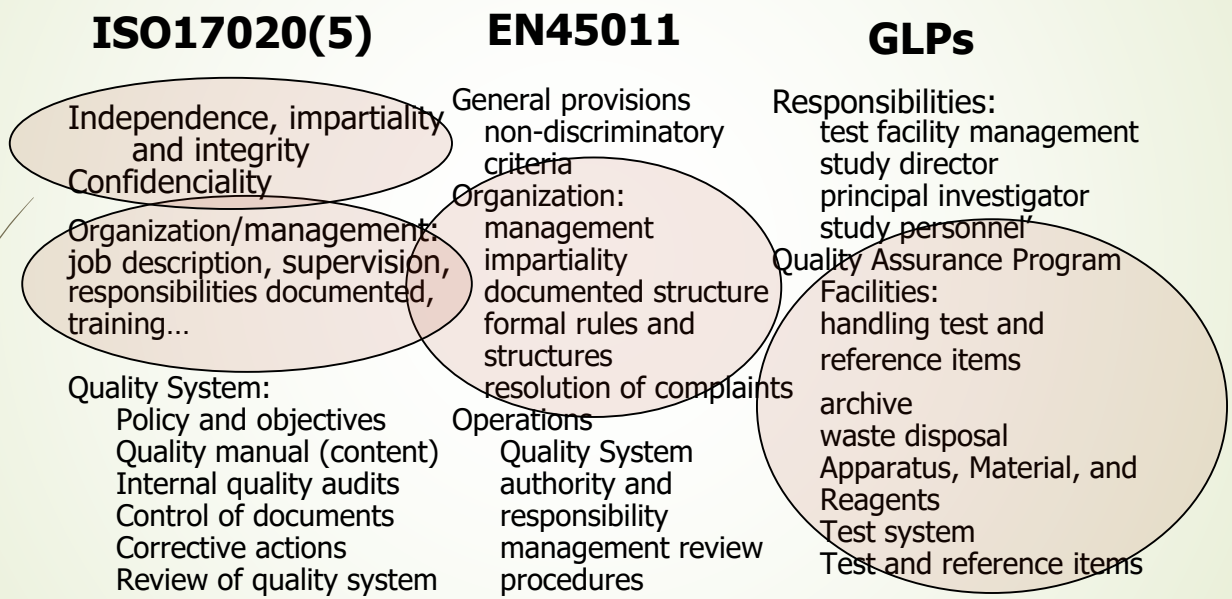
WHAT ARE THESE REGULATIONS:

- **EN45011**
  1. This European Standard specifies the general requirements that a 3rd party operating a product certification system needs to be compliant with in order to be competent and reliable.
  2. It contains specific requirements on the organization, quality system, subcontracting operations, documentation and internal auditing.
  3. It has defined confidentiality as part of its standard requirements.

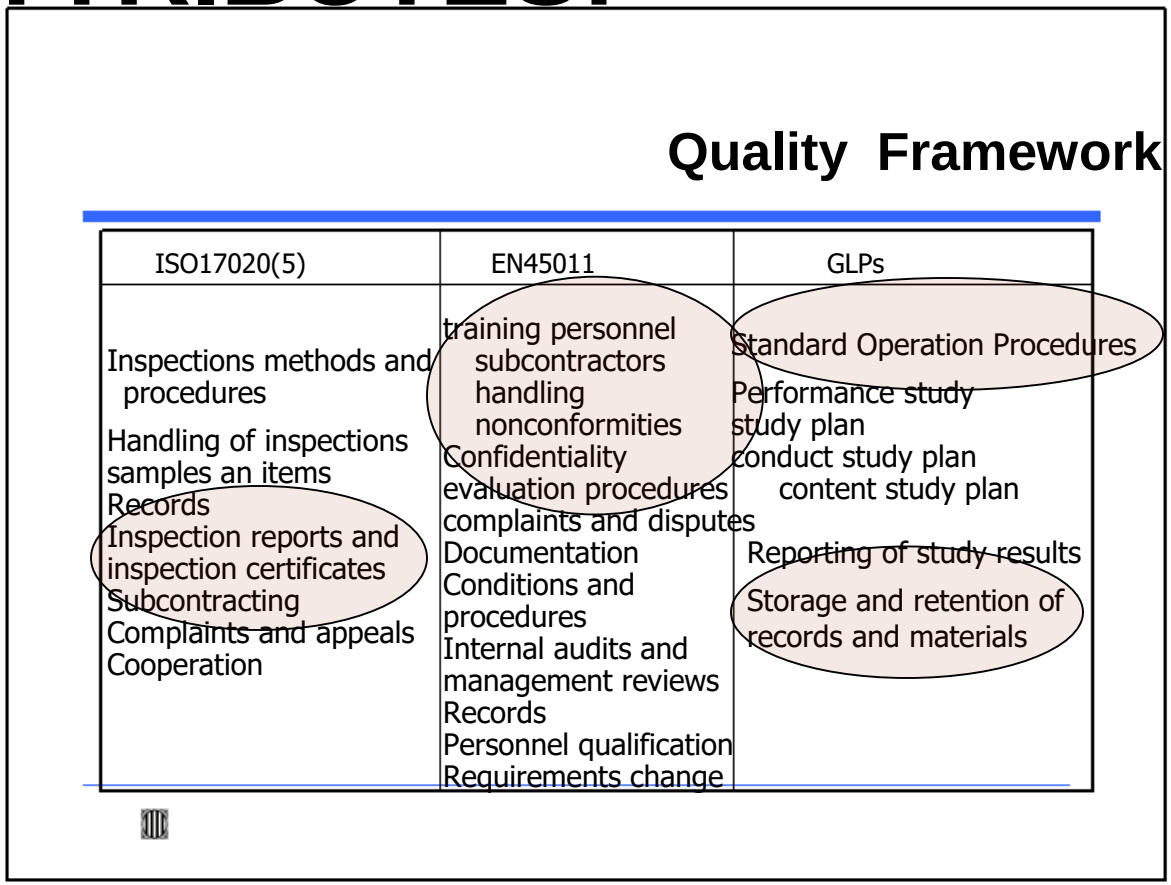
WHAT ARE THESE REGULATIONS:

- **GLP**
  1. The GOOD LABORATORY PRACTICES is the OECD Accreditation to ensure the generation of high quality and reliable test data.
  2. All testing is defined within the OECD 400 Series Guidelines.
  3. It is a managerial quality control system covering the organizational process and conditions under which non-clinical and environmental studies are planned, performed, monitored, recorded, reported and archived.

SOME QUALITY STANDARDS ARE STRONGER IN SOME AREAS THAN OTHERS:

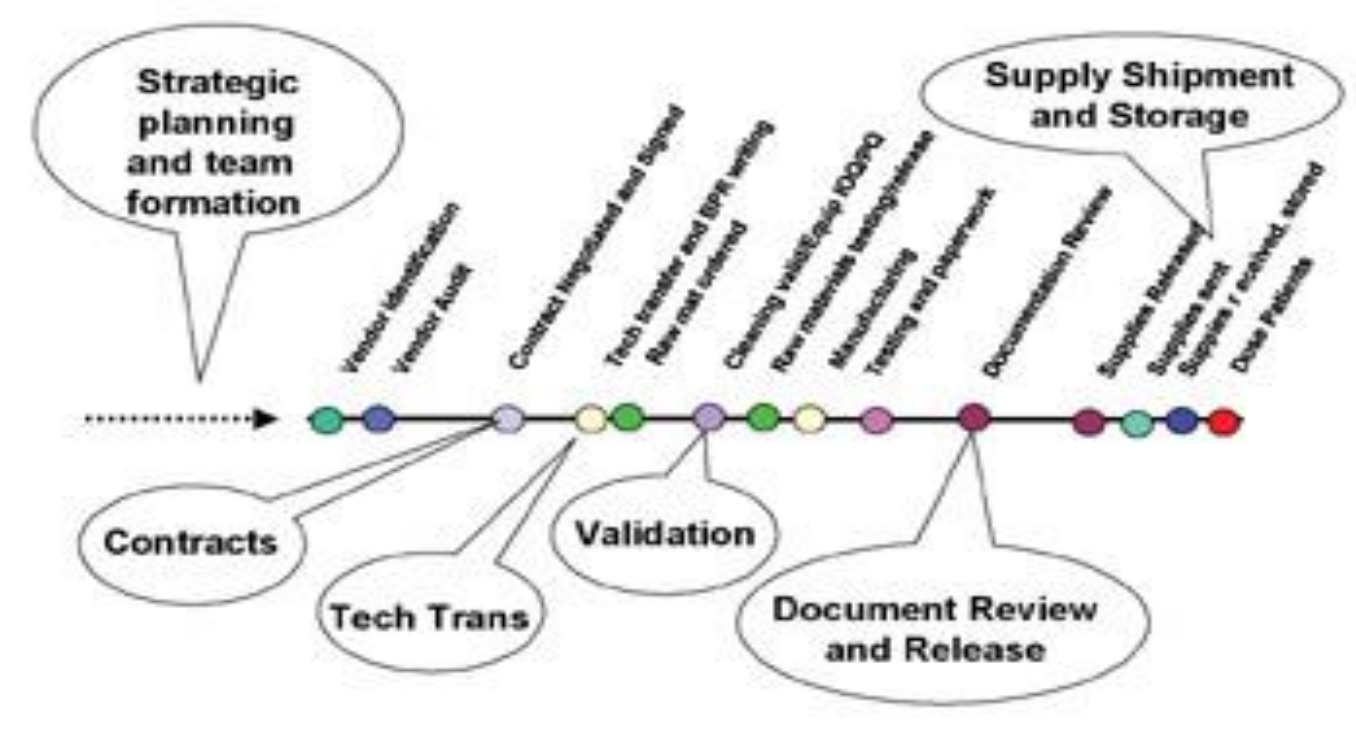


EACH HAS ITS MAJOR ATTRIBUTES:



CRITICAL AUDIT POINTS OF A CRO:

- The following six areas pose significant risks when using the services of a CRO and Auditors need to be knowledgeable in these areas to audit correctly.



- Adopted from:http://www.americanpharmaceuticaloutsourcing.com/static_past_issues/2002_3_May_Jun/Brownell_article.asp

CLOSER LOOK AT THE CRITICAL AUDIT POINTS:

- **POINT ONE: THE CRO TEAM COMPOSITION:**
  1. Who's on that team is critical to the success of your product. What are their qualifications, experience, understanding of your product needs. It is important that the auditor reviews their CV's, their history of performance and their personal work ethics.
- **POINT TWO: THE CONTRACT:**
  1. Like the Quality Agreement with a material supplier, the CRO contract needs to stipulate exactly what the expectations of provision are by the sponsor.
  2. The level of performance, regulatory standards to be met, the auditing and monitoring specifics need to be outlined.
  3. You cannot audit to a level that has not been agreed to within the contract.

CLOSER LOOK AT THE CRITICAL AUDIT POINTS Cont'd:

- **POINT THREE: TECH TRANSFER:**
  1. The NDA is a piece of paper. The level of comfort with the CRO is you only reassurance that the Intellectual Property you provide to the CRO does not get disseminated to a 3rd party. It must be remember that some CROs are not only service provider but are also direct competitors.
- **POINT FOUR: VALIDATION:**
  1. As within the sponsoring company, all procedures, methodologies, equipment and processes need to be validated.
  2. As the services provided are outside the normal sphere of production by the sponsoring company, the auditor will need to be familiar with these very different aspects in order to confirm their validation status.
  3. Often the sponsor will need to contract a 3rd party auditor to perform the assessment because of it own unfamiliarity with the services provided..

CLOSER LOOK AT THE CRITICAL AUDIT POINTS Cont'd:

- **POINT FIVE: DOCUMENT REVIEW AND RELEASE:**
  1. Data integrity is a critical part of the CRO audit. In order to audit properly, the auditor will be required to understand the testing performed by the CRO to ensure the accuracy and the Biostatistical evaluation.
  2. All documents will need to be handled according to an established QMS document system.
- **POINT SIX: SUPPLY SHIPMENT AND STORAGE:**
  1. The Sponsor needs to validate its own supply chain for shipping samples to the CRO. The Auditor needs to confirm that this supply chain performs properly without any errors.
  2. As with its own handling of incoming materials that would be evaluated on an internal audit, the Auditor must perform a similar evaluation of the CRO's capability of handling incoming samples and materials.
  3. Storage of the incoming samples and materials is a critical audit parameter that requires particular attention by the auditor.

THE AUDITOR'S DILEMMA:

- While the audit can demonstrate compliance, it is far more challenging to determine a successful and true outcome.
- Not all providers are willing to share details of adverse events or difficulties that may have occurred.
- An occasional visit/audit cannot automatically ensure that a provider will always be compliant.
- Facility general quality certifications (such as an ISO certification) do afford an additional comfort level, while more specific certifications by a regulatory authority/international body (such as GLP or GMP certifications) can increase the comfort level dramatically but they are not guarantees of proper conduct.
- When reviewing the provider's QA system, the auditor should authenticate the independence of the QA function, adequacy, and the experience of the QA headcount as well as the effectiveness of the QA system.
- While no project-related problems may exist at this early stage, problems could occur later, so QA needs to demonstrate the ability to anticipate where problems or deviations are likely to arise. The auditor should determine the provider's system for managing these anticipated issues

SOME STRATEGIC POINTERS FOR OUTSOURCING:

- Develop a Responsibility Matrix (RM): Defines accountabilities and responsibilities for key elements of the project so there is no confusion between the Company and the CRO or CSP. This is entered into the contract before startup.
- Escalation Tool: The ability to immediately red flag the CRO or CSP indicating issues requiring immediate attention. ie. A RED PHONE HOTLINE

REMEMBER THIS:

- A company can delegate its regulated tasks but not the legal responsibility
- Selection of a service provider needs to be an objective, inclusive, and balanced process using multiple criteria and a risk-based approach
- Oversight and governance of the relationship/partnership should be integrated at the inception of the partnership. Too late to add it later.
- Ensure that the contract with the service provider undergoes QA review.
- If the sponsor lacks the level of expertise and knowledge to conduct audits of the service provider then consider hiring an external auditor that has the capability.

A HISTORICAL PERSPECTIVE:

CONFUCIUS (K'UNG FU-TZU) SAID:

Learning without thinking is useless;
Thinking without learning is dangerous.

Is this all a magic bullet ? NO!!!!!!

What is the magic bullet ? None

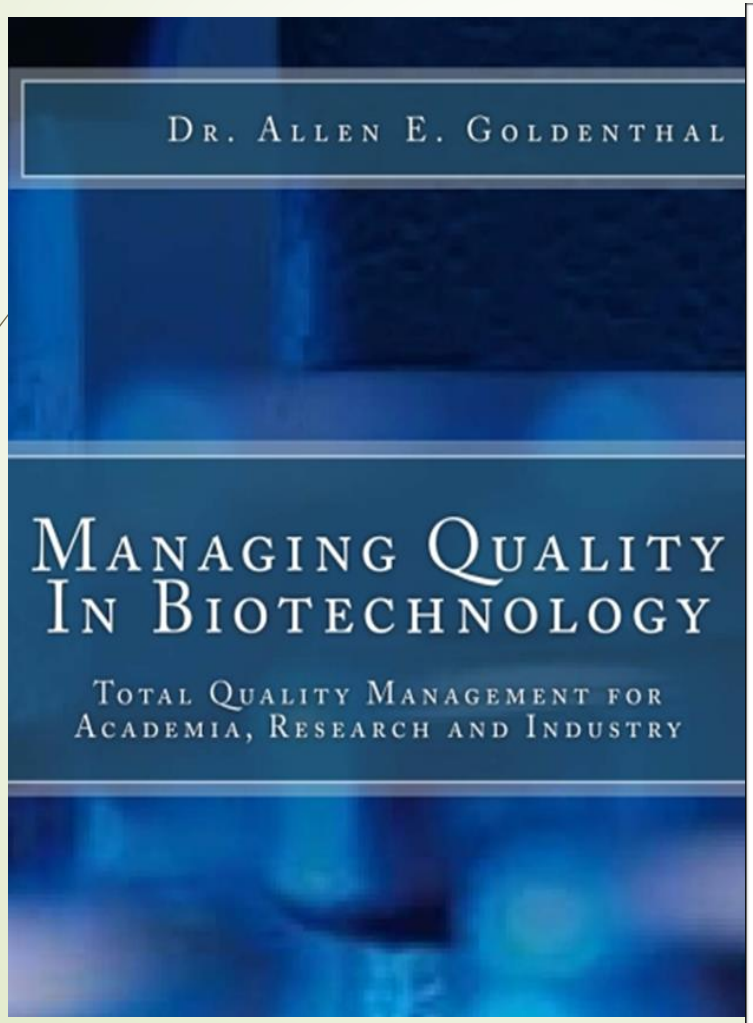
Knowledge, hard work, discipline, patience….

Only learning & practice in incremental and iterative steps.

CONFUCIOUS UNDERSTOOD CROs:

- Learning without thinking is useless; Thinking without learning is dangerous. **TRANSLATION:** If the CRO does not understand the principles of your project and the measured goals then they will not perform in your best interest. **Audit against a contract that ensured full comprehension.**
- Is this all a magic bullet ? NO!!!!!! **TRANSLATION:** The same training you provide to your own staff must exist at the CRO. There are no shortcuts. **Audit to confirm this is in place.**
- Knowledge, hard work, discipline, patience….Only learning & practice in incremental and iterative steps **TRANSLATION:** Confucius understood the QMS. An Auditor needs to exercise all of these in order to successfully audit CROs.

Read More About it in Chapter 18.



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Managing Quality in Biotechnology is unique in its approach to Total Quality Management (TQM) as it adopts an insider's view of what is crucial and important in the day-to-day operations of bio-related laboratories at both an academic research level as well as by a full production facility. Most reference books on TQM have been written specifically for the commercial production facility and have not addressed that quality must begin at inception of the initial concept and that relies on it being implemented all the way back to the primary investigator in his university or company laboratory. Though the research laboratory operates at a much smaller scale and modality, still all the essential requirements and expectations of TQM and Good Manufacturing Practices (GMP) apply. Ensuring that initial research and development meets the expectations of safety, efficacy and potency is why TQM is probably even more important within academic institutions. The absence of guidelines being applied to the university and developmental laboratory environments makes this book an essential part of any research library. It is a comprehensive reference book for university students, a hands-on manual for laboratory technicians, and a practical guide for biopharmaceutical managers.

SEMINAR FOUR COMPLETED

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