THE AUDIT: A COAT OF MANY COLOURS

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PURPOSE OF THE AUDIT:

- Designed to be an independent examination of a quality system
- It measures the effectiveness of an organisation's quality management system.
- It is a documented and systematic tool
- It should be done periodically by qualified people

- "Audit" itself is **a checking system**, NOT **a quality system.**

- As a communication tool of management policies. All personnel have to understand and do their jobs well

WHY AUDITING OF THE SUPPLY CHAIN IS SO IMPORTANT:

- USA 1937 Sulfanilamide Elixir – 107 deaths
- South Africa 1969 Sedative formulated with DEG – 7 deaths (diethylene glycol)
- Italy 1985 DEG in wines from Austria – no known deaths India 1986 Medicinal glycerin laced with DEG – 14 deaths
- Nigeria 1990 Acetaminophen syrup containing DEG – 40 deaths (some sources say 200 deaths)
- Bangladesh 1990-2 Acetaminophen syrup containing DEG – 339 deaths
- Haiti 1995/6 Cough medicine containing DEG – 85 deaths
- Panama 2006 Cough and anti-allergy syrup containing DEG – 46 deaths
- USA 2006/7 Toothpaste containing DEG – no deaths
- Panama 2007 Toothpaste containing DEG – no deaths
- Nigeria 2008/9 Teething formula contaminated with DEG – 84 deaths

GOALS OF THE AUDIT:

- ✓ As a powerful tool to measure the effectiveness of quality management system
- ✓ Evaluates manufacturer's compliance with GMP in all aspects related production and quality control
- ✓ Detects any shortcomings in the implementation of GMP
- ✓ Recommends the necessary corrective and preventive actions

SCOPE OF AN AUDIT:

- Ensures quality in design, approval, monitoring and evaluation of products should comply GMP requirements
- Ensures quality in GMP implementation and its strategies
- Ensures quality in appointment, development and performance of staff and key personnel
- Ensures quality in obtaining and responding to the feedbacks from customers, consumers, employers, employees, government authority and other relevant institutions
- Includes all written quality documents, instructions and records
- Covering all elements of GMP including any corrective and preventive actions (CAPA) taken from past audits.

BENEFITS OF AUDITING:

- Provides a perspective on the health of the supplier's quality system
- Identifies any issues so a plan for corrective and preventive actions with timeline can be made jointly
- Makes it possible to avoid potentially big problems in the future
- Secures the supply line and future production between both parties
- Continuous improvement

THE PAPER AUDIT:

- To determine if a supplier is capable of meeting the GMP quality requirements to supply the starting material
- A questionnaire can be used as a way to gain information about the quality standards at the supplier's site.
- Questionnaires should contain questions that are applicable to the approval of a particular supplier.
- Sufficient information needs to be provided in order to determine that the supplier has an appropriate quality management system and there is satisfactory assurance that the starting material supplied will be of appropriate quality.
- The completed questionnaire and available documentation (as requested from the supplier) should be critically reviewed to determine the acceptability of the supplier.

SUITABILITY OF THE PAPER AUDIT:

A paper audit is satisfactory when:

- Performing the initial exploration of suppliers to determine which may be suitable at which point the next step would be an on-site audit
- In-between scheduled on-site audits to confirm the status of the Quality Agreement
- When risk is low as in the case of Category 3 materials.
- If an extensive on-site audit has been conducted by a 3rd party of a reputable supplier and acceptance of that audit has been justified.
- Some are now saying a paper audit is never acceptable.

SUITABILITY OF THE PAPER AUDIT CONT'D:

Is it necessary to perform a full audit of an active substance supplier if it has been inspected by an inspectorate from a European Economic Area (EEA) Member State and a valid GMP certificate is available along with the audit report?

- When inspection reports or GMP certificates issued by European Economic Area (EEA) mutual-recognition-agreement (MRA) partners or other recognized authorities are available, these can provide useful information but these cannot fulfil the statutory obligations of the manufacturer or the requirements of section 5.25 of the GMP Guideline. They can be used together with other supporting information in a risk-based approach by the manufacturer in establishing priorities for its own audit programme of active-substance suppliers. In other-words, 'No'.

SUITABILITY OF THE PAPER AUDIT CONT'D:

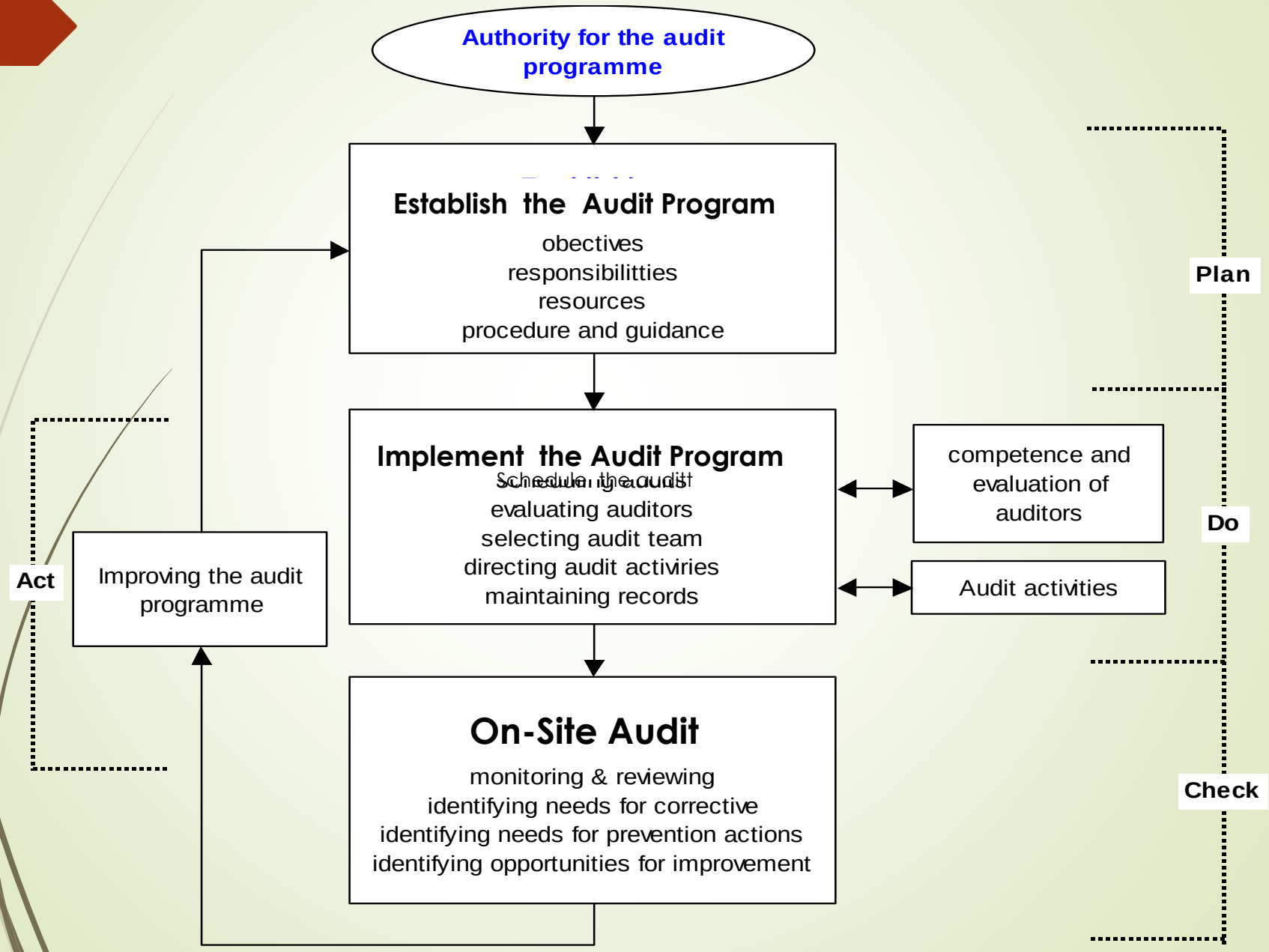
- The EEA inspectorates are not generally in favour of 'paper-based audits' *per se* as they do not provide the same level of assurance as on-site assessments, but do accept that they have a part to play in a risk-based strategy.
- They may be particularly applicable when recent positive inspection information is available and where satisfactory audits have been concluded in the past. They cannot replace on-site audits of active-substance suppliers but can be a useful interim and temporary measure within the manufacturer's audit programme.

THE ON-SITE AUDIT:

GUIDANCE WHEN CONDUCTING AN AUDIT:

- Auditing should be seen as a positive process not a fault finding
- Audits need to be documented
- Prior to the audit date, an auditor needs to review the quality system documentation, corrective and preventive actions, and past audit findings and develop a checklist
- During an audit, an auditor need to see evidences that the processes are being done in accordance to procedures and policies

FLOW CHART OF THE AUDIT



AUDITOR TRAINING:

HR needs to provide the Resource to achieve the following:

- ✓ Resources Internal or External
- ✓ Audit techniques
- ✓ Processes (SOPs)to achieve and maintain the competency of auditors and to improve their performance
- ✓ Competency and availability of auditors
- ✓ Available time for training

OVERVIEW OF ON-SITE AUDIT ACTIVITIES:

Planning and scheduling audit

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Conducting document review

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Preparing for on-site activities

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Conducting audit according to program

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Audit record review, Consolidation and audit report

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Conducting follow-up

PRE-AUDIT ACTIVITIES:

- **Forming an audit team and assign roles and responsibility and agreed on the scope**
- **Conducting document review**
  - ✓ Review documents (SOPs, audit findings, corrective action/preventive action, etc.), check the integrity of the quality system and various controls are effective
- **Preparing for the on-site audit activities**
  - ✓ Preparing audit plan
  - ✓ Assigning work to the audit team
  - ✓ Preparing work documents
    (eg. audit checklists, sampling plans, forms for recording information; questionnaires)

THE AUDIT AGENDA:

The Agenda has to be appropriate to the time provided by the supplier for the audit team to be on site. A full inspection and audit cannot be performed by a single auditor in several days. Nor can several auditors perform a full audit in a single day. With this in mind the agenda is prepared accordingly and send to the auditee in advance.

- **Opening Meeting**
- **The Audit**
  a) **Details on specific areas to be looked at**
  b) **Identification of the auditor looking at specific areas**
  c) **Identification of documentation to be reviewed**
- **Closing Meeting**

THE OPENING MEETING:

- Introductions of those in attendance
- Auditee presents a summary and history of the company
- Auditor reviews the objectives and scope of the audit
- Confirming of the agenda, scheduled visits to the workshops and laboratories
- Agreement on times for feed-back during the audit
- Review any outstanding issues

THE ACTUAL AUDIT:

- Compare what you see against what is written
- Checklists focus on the essential information
- Identify any non-conformities
- Point out Positive findings
- Record objective evidence
- Confirm with the auditee any non-conformity when it's found.
- Point out areas for improvement but which are not actual non-conformities
- Highlight issues of data integrity
- Assess the skills and competence of the personnel (be more objective than subjective.
- Identify errors in documentation
- Comment on condition of facilities and equipment

EXAMPLE OF AN AUDIT CHECKLIST:

CHECKING LIST FOR GMP ASSESSMENT

Date : **Location** : **Warehouse**
Auditor : **Auditee** :

DESCRIPTION	GMP.REF.	PARAMETER	AUDIT FINDING
Personnel	1.2.1 5.1.2 2.1.5	- Organization structure - Personnel hygiene - Training record	
Storage area	10.1.1 3.1 3.6 3.9 & 3.10 3.12.2	- Design and layout of defined area - Flow of personnel and goods - Structure of the storage area, based on GMP - HVAC system - Record of monitoring parameter	
Sanitation	3.1 5.3	- Pest record program - The map of bait - The cleanliness of weighing apparatus	
Documentation	4.3 10.2.2.3 10.2.2.1	- Record of maintenance and calibration of weighing apparatus - The effectiveness of label system - Inventory stock control	

REPORT THE AUDIT FINDINGS:

- **Type of findings:**

  1. Positives- Discuss the things the auditee does right.

  2. Negatives- Non-conformities (Critical, Major, Minor)

  3. Recommendations- Areas for improvement that should be undertaken by the auditee

  4. Comments- General observations that the auditee might wish to give consideration for improvement.

THE NON-CONFORMITIES:

- **Minor:**

  These represent smaller GMP deficiencies that may be raised during a regulatory inspection and represent breaches of current GMP standards. Several minor infractions within the same contextual sphere may result in a Major.

- **Major:**

  These represent GMP deficiencies which are either indicative of a general Quality Management System failure, or where there is potential to impact on the quality of the product or the testing data. They do not represent proven product deficiencies but require remediation before direct product impact occurs.

- **Critical:**

  These represent GMP deficiencies that directly impact on the safety, quality and efficacy of the product, or on the validity of test results.

ISOLATED VERSUS SYSTEMIC DEFICIENCY:

NON CONFORMANCE DEFICIENCIES	
ISOLATED	**SYSTEMIC**
Latex gloves rip	SOP contains an error on how to apply gloves.
Wrong expiration date written on a reagent bottle	Batch record is poorly written so instruction can be confusing as to dating of reagents.
Operator or lab technician spills a sample	Area management does not reinforce requirement to continually record information properly of lost samples.
Tables compression machine burns out	Preventive maintenance program does not include hydraulic units.

THE AUDIT REPORTING CYCLE:

- **The Closing Meeting:**
  1. Summarize the audit findings, positives and negatives
  2. Limited discussion on the findings
  3. Overall conclusions and recommendations
  4. Establish the timetable of final report and the expected response time from auditee.
- **The Audit Report:**
  1. A detailed outline of the findings with supporting evidence and references to the GMP violations where required.
- **The Auditee's Response:**
  1. Agree or disagree with the suggested corrective actions.
  2. Follow-up actions to be taken
  3. Scheduled revisit if required.

THE AUDIT TEAM:

The company should commission a permanent committee that includes personnel from purchasing, QC, QA, warehousing, and production. This core group is the primary audit team responsible for discussing tactical and strategic issues related to material sourcing, timing of audits, and ideally performing the audits as they will have the repeated expertise and knowledge of procedures. Additional auditors can serve as backup. A permanent team means that committee members are well aware of each department's requirements and issues. Too often companies hand out audit team memberships as perks to individuals, resulting in a team lacking unity, expertise, past-experience and fully understanding the requirements for an audit.

AUDIT FREQUENCY:

From the Guidance for Industry: Starting Material Supplier Management from PIC/S:

Pharmaceutical manufacturers are responsible for auditing all Category 1 (highest risk) suppliers of starting materials initially and on a follow-up basis.

Where audits are indicated, the supplier should be re-audited at a specified frequency to verify on-going performance. A rationale for the minimum audit frequencies for each supplier should be documented.

As examples only, the re-audit frequency for Category 1 suppliers may typically be 1 -3 years and for Category 2 suppliers may typically be 3-5 years. Audits of Category 3 suppliers (lowest risk) are not required other than the paper audit.

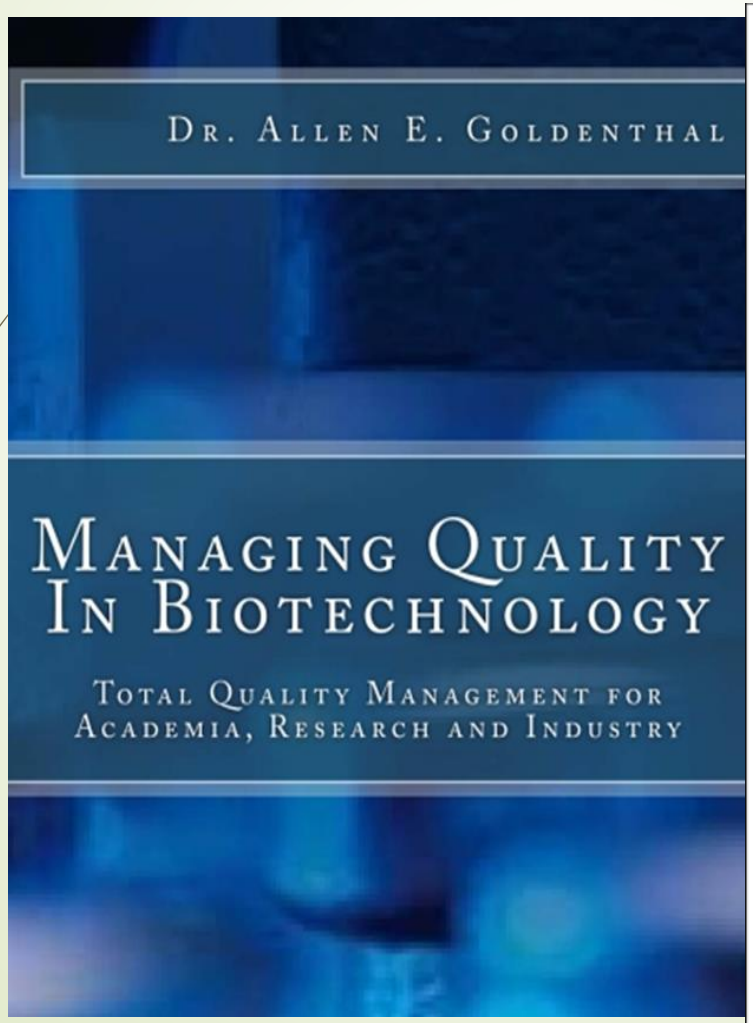
CONCLUSIONS:

Remember…

Nobody likes to be audited…….but…

It is a means to have continuous improvement

Read All 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 THREE COMPLETED

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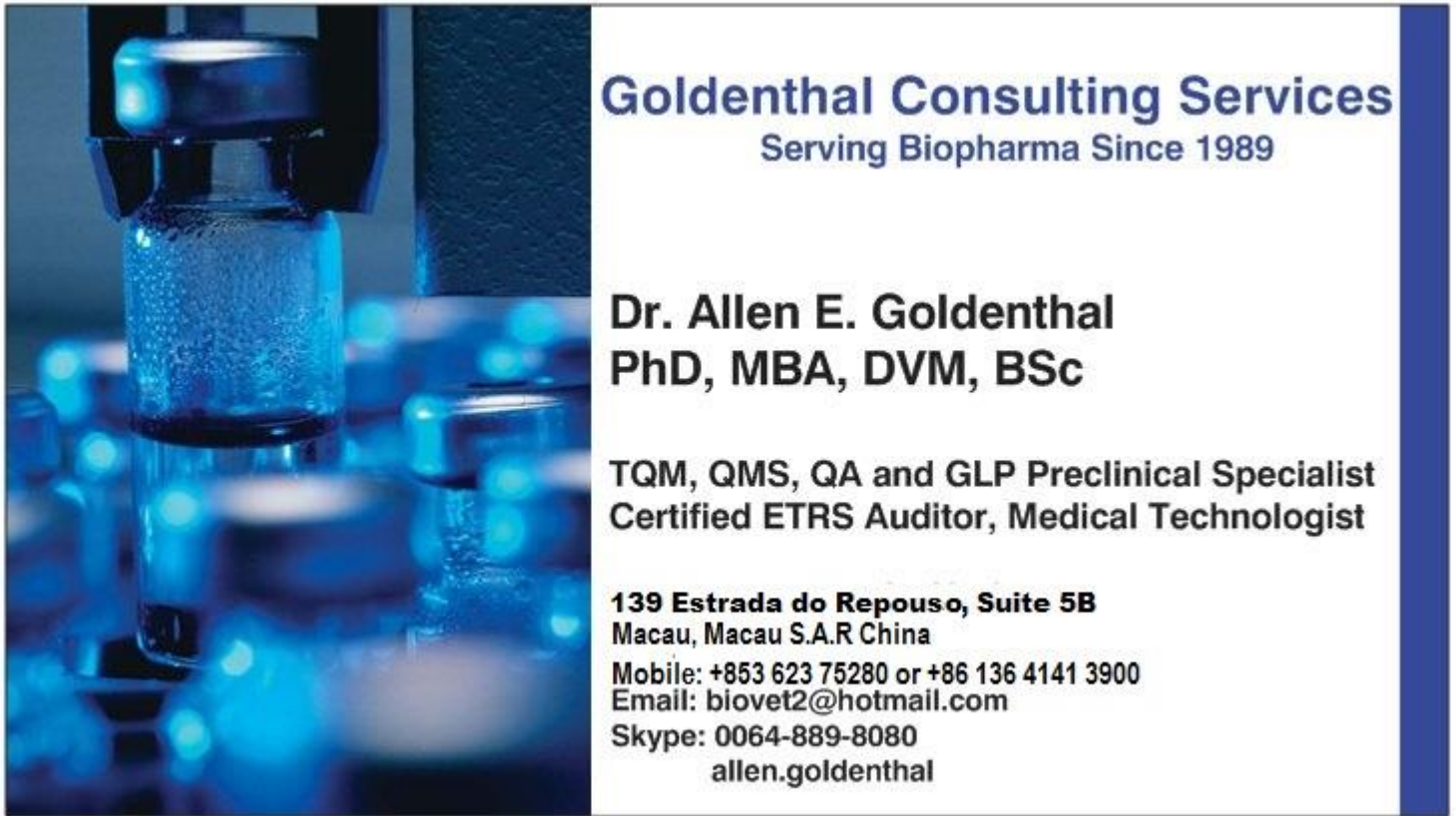

TIME FOR WORKSHOP #1

Divide yourselves into groups and one half of the groups will tackle problem 1 while the other half tackles problem 2. After half an hour of discussions, present your findings.

PROBLEM 1: You are an external auditor reviewing the QMS of the company. The company is always improving its testing capabilities and in order to perform its identity and protein content tests it has purchased a protein sequencer to replace the previous spectrophotometer based test. The vaccine is a bivalent product and using three different titrations of each monovalent product, providing one sample of each to be performed by the usual technician, the new sequencing unit produces linear results but is lower on average for Valent One by 13% on each reading and higher on average for Valent Two by 13% on each reading. As the slopes have a CI of greater than 80% and the validation only required a CV of less than or equal to 30%, on this basis the company has validated the new unit and entered it into the normal testing program.

As the auditor, what is your perspective on this?

TIME FOR WORKSHOP #1

Divide yourselves into groups and one half of the groups will tackle problem 1 while the other half tackles problem 2. After half an hour of discussions, present your findings.

PROBLEM 2: A vaccine manufacturer needs to audit the supplier of its foetal bovine serum. The supplier is located 400km away. A team of three people set out in the morning and return that evening. At some point in the evening the final report is written and signed off. There were no significant findings. There is no list of the documents reviewed or the operational areas seen. A good portion of the checklist is marked N/A.

In this case, you are a regulatory auditor reviewing this company's QMS system. Based on the conduct of this audit,, what is your impression and what will you write in your report to the company?