SECURITY OF THE SUPPLY CHAIN: RAW MATERIALS

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The Significance of Raw Material Suppliers:

- Usually, the auditing of suppliers and raw material testing is not considered scientifically challenging or exciting - until, of course, the supply chain is imperiled by a single failure.
- When that happens, there is suddenly a great deal of scientific and compliance information that must be made available and presented to a regulatory investigation team, resulting in both short-term and long-term actions being undertaken. Often the data is not readily accessible or transparent and requires the collaboration of subject matter experts to integrate and interpret.
- Therefore, selecting the appropriate supplier, qualifying them properly, and ensuring they provide a quality product is critical to the long term health of your product.

GMP Requirements of Material Suppliers:

- GMP regulations require that pharmaceutical raw materials and their suppliers be qualified both initially and periodically. Similar requirements can be found in the US Code of Federal Regulations, ICH guidance documents, European GMP regulations, and within ISO.

1. Materials deemed "critical" require testing of more supplier lots for more attributes and extensive supplier evaluation before qualification is achieved. The critical status of an RM is related directly to its intended use in the process and to the potential risk to adversely impact the product's identity, purity, potency, toxicity, or efficacy.
2. A material may be critical to one process but not to another. Each company must identify which materials are critical and justify the choice made and the additional oversight required.
3. Changing a material will meet regulatory hurdles and is therefore highly undesirable. By fully qualifying materials before use by audit and testing, then the quality program only needs to focus on monitoring of the qualified state.

What the Regulations Say:

Table 1. References to regulatory requirements

References to requirements	Major differences
21 CFR 210/211: Finished pharmaceuticals[1]	· Statistically justified sampling plan · Full testing periodically to monitor the raw material
21 CFR 820: Medical devices regulations[2]	Emphasis on design controls, change control, and device specifications
ICH Q7A, API guidance document[6]	· Active starting materials are distinct from other RMs or components, and should be more strictly controlled. · Represents the latest thinking from regulators on GMP
EU Guide to GMP: Finished pharmaceuticals[3]	Sampling for identity (each container) is a stated requirement for excipients
ISO 9000	Systems emphasis; supplier qualification
WHO Draft Guidance Document: Guideline for sampling of pharmaceutical and related materials.[20]	· Issued Fall 2003 as a draft · Appears to require every container be sampled and checked separately for identity, even for API starting material
ICH Q6A/6B, Specifications[11,12]	RMs should be suitable for their intended use as process ingredients, actives, or excipients

But then the EU Says:

EU GMPS Annex 8 Section 3 Under such a system, it is possible that a validated procedure exempting identity testing of each incoming container of starting material could be accepted for:

- Starting materials coming from a single product manufacturer or plant;
- Starting materials coming directly from a manufacturer or in the manufacturer's sealed container
- Where there is a history of reliability and regular audits of the manufacturer's Quality Assurance system are conducted by the purchaser (the manufacturer of the medicinal product) or by an officially accredited body.

Grading Classifications:

- Class 1 Materials
  1. In contact with the final product
  2. An excipient of the final product
  3. Animal derived materials
  4. Human sourced materials
- Class 2 Materials
  1. Ancillary materials used in manufacturing but not intended to remain in the final product.
  2. Critical Consumables
- Class 3 Materials
  1. No contact with the final product
  2. Suppliers of General Services
  3. Non Critical Consumables

Grading of Material Suppliers:

- For Category 1 and Category 2 suppliers requiring an audit, the audit report and supplier response to the report must be evaluated.
  1. All corrective actions arising from an onsite audit must be either closed or at a satisfactory stage of completion for the supplier to be approved.
  2. Where evidence of an audit by a third party has been accepted (e.g. GMP certificate, copy of audit report, response and closeout), this documentary evidence should be evaluated.
  3. If an audit report is obtained through a third party (wholly or in part), reasonable steps to ensure the validity of the report should be taken.
  4. Audits by other organizations may be considered on an exceptional case by case risk basis if it can demonstrate an equivalent level of quality assurance with documented justification.

Grading of Material Suppliers Cont'd:

- It should be noted that the risk of microbial contamination must be considered when deciding the risk category for a starting material. However, microbiological testing does not necessarily make the starting material high risk for supplier approval. How this material might come I contact with the product and what sterile processes are used in the manufacturing will determine the degree of risk.

Table 5 : Examples of materials defined as "critical" 10, 11

Example	Process Use	Criticality	Comments	References
NaCl USP	In-process RM; grade used may vary	Low	Low risk; well defined, known quality	USP; EP [17,18]
NaCl	Excipient in parenteral; USP/EP grade is specified	High	Direct injection into patient creates high potential risk	ICH Q6A6B (specs), EMEA Annex 13, EP, USP [12,5,17,18]
Serum albumin	In-process RM	High	Animal or human derived; major regulatory concerns and risks re: viral, BSE/TSE, and microbiological contaminations. Requirements include strict traceability, use from nonBSE countries, and RMs that have been treated to reduce risk are preferred	EMEA Note for Guidance on TSEs; CPMP Note for reducing viral risks [19,21]
Benzyl alcohol	Preservative	High	Evaluate stability and effectiveness as preservative	Consult USP [17]
Chromatography resin	Purification of product	Medium	Performance directly affects product purity, identity , stability, and possibly safety	Seely et al. [22]
"Active" materials	Support cell culture or expression of product (for example, insulin, methotrexate protein hydrolysates, anti-foams)	Medium to high	Process may set purity requirements on feed materials; if definable as an API or starting material, subject to ICH Q7A,	Consult ICH Q7A; EU GMP Guide: Annexes 1-20 [3-6]

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SUB-GRADING OF KEY MATERIALS BY RISK:

Supplier Classification	Examples of suppliers
Category 1 (High Risk)	Manufacturers of APIs and excipients used in sterile preparations or with known stability issue. Manufacturers of APIs in a country with poor or unknown GMP regulation. Brokers, distributors or agents where the supply chain from the manufacturer is complex, not fully known, or there is an increased possibility of counterfeit.
Category 2 (Moderate Risk)	Manufacturers of APIs and excipients used in non-sterile pharmaceutical products. Brokers, distributors or agents handling APIs requiring cold chain management.
Category 3 (Low Risk)	Manufacturers of excipients produced at a dedicated site (e.g. sugar).

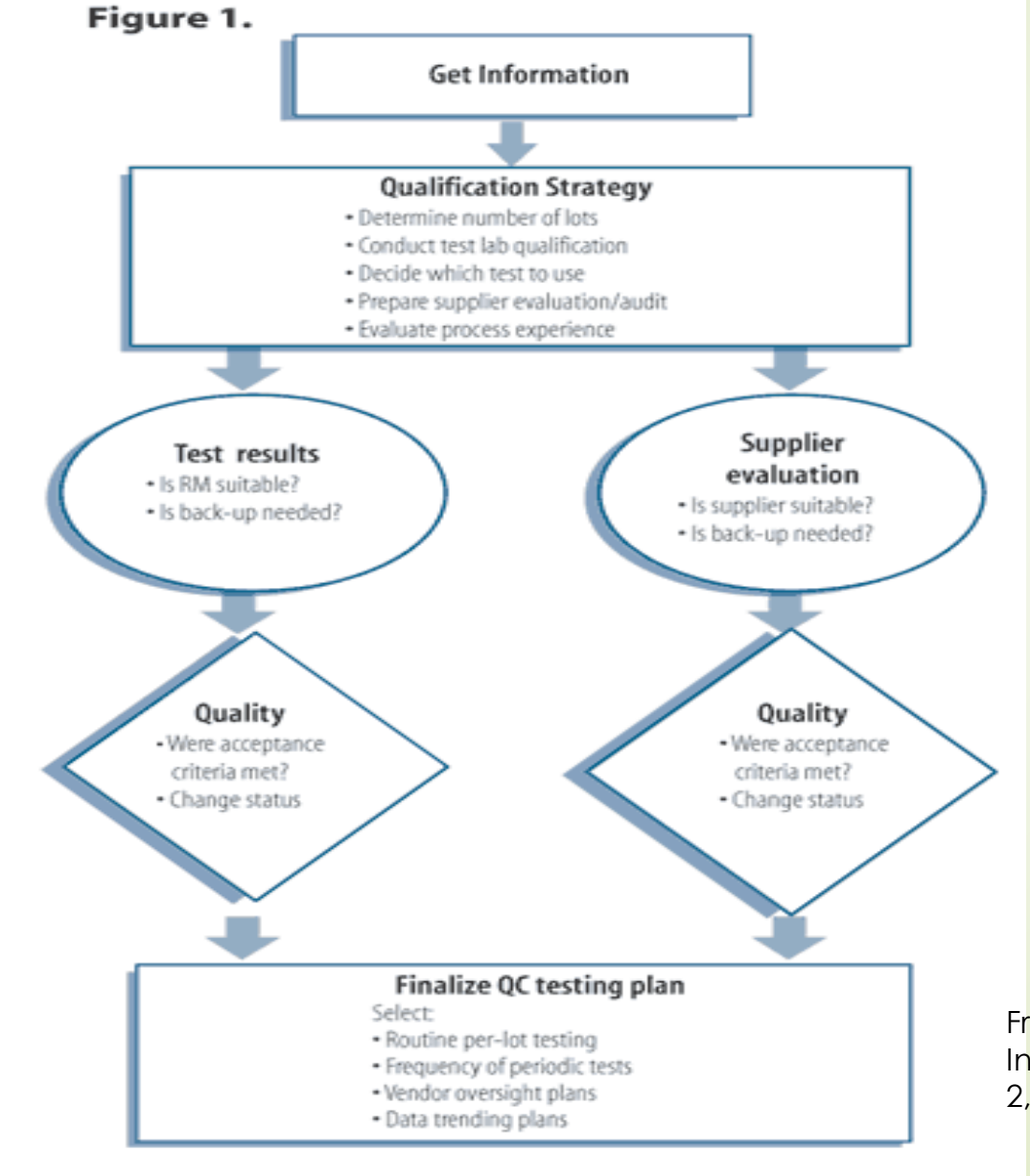
What QC Testing Should be Performed:

- Based on the determination of Risk Grade of the raw material, the panel of tests performed by QC for each incoming lot routinely is decided.
  1. Tests that do not provide useful information can be avoided.
  2. Certain tests are performed to confirm the accuracy of the CoA.
  3. The critical specifications stipulated for the Quality Agreement are performed for confirmation routinely.
  4. Regulatory authorities require the identity test be performed on the receipt of each raw material. The EU and WHO requirement for excipients is that each container in a lot be identity tested.
  5. Appearance testing is simple and should be done routinely.
  6. If aware of a potential problem in the manufacturing process then perform the appropriate test.

If the QC Test Results are not Satisfactory:

- If the data obtained is not satisfactory then several actions must be undertaken.
  1. Notify the vendor immediately of the test failure.
  2. Quarantine the lots that failed testing.
  3. Address the situation in a formal test report to aid the vendor in identifying the problem.
  4. Cooperate with the vendor in designing an investigation procedure..
  5. If a secondary supplier has not been identified then begin the search immediately.
  6. Establish a timetable during which the vendor must resolve the problem.

QC Testing of Materials:



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FDA WARNING CITATIONS:

- **November 18, 2011**

  For example, your firm accepts and relies upon **the Certificate of Analysis (CoA) from your stopper suppliers without conducting adequate vendor qualification** • b) Your firm does not sample incoming components/raw materials in a manner that represents the batch for the determination of acceptance or rejection of the material. Your firm fails to have a scientific justification for the sampling approach used for incoming materials. For example, you only sampled 3 (b)(4) of drums of a batch of (b)(4) received in February 2007 (less than (b)(4) samples). Your firm also lacks a written procedure describing the material sampling process.

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  There **is no assurance that your firm establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results** at appropriate intervals [21 C.F.R. § 211.84(d)(2)]. For example, your vendor qualification has not provided adequate evidence that the manufacturer can consistently supply raw materials that meet appropriate quality attributes. **Suppliers are not monitored and regularly scrutinized to ensure ongoing reliability.** Specifically, your firm has not adequately qualified the supplier of methyl salicylate API. There is no assurance that the API suppliers are in compliance with CGMPs, without supplier qualification by your firm and knowing how APIs have been manufactured, tested, and if quality is consistently assured. There is also no assurance that your firm has established the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

Testing of Materials Warning:

- Simply passing the QC test is not the full goal of assessing material suppliers. At the same time, QC must be investigating any negative patterns or trends in the testing of the product. The trend may show that even though the product passes, it is approaching the alert and alarm levels steadily over time which indicates that something has changed in the manufacturer's process.
    1. A follow-up audit will be necessary to see what may be causing the negative trend and therefore resolve an issue before it is a potential problem.
    2. Closer cooperation with the vendor to achieve maintenance and sustainability.

Stepwise Auditing:

1. Step One: Gathering the Facts:

- type of starting material – sterile/nonsterile, powder, liquid, highrisk excipient, lowrisk excipient, packaging, etc.
- type of supplier – manufacturer, broker, distributor, agent, etc.
- country of origin
- potential risks during supply chain and onsite storage
- history of the supplier (if known) – additional controls may be required for suppliers with questionable track records
- intended route of administration of the subsequent finished product – injectable, oral, transdermal, etc.

Stepwise Auditing Cont'd:

2. Step Two: Request the Information

- any relevant audits/inspections conducted in the last 3 years and available reports, responses and closeout;
- Quality Agreement
- supplier's current GMP certificates
- Site Master File
- supplier's third party certificates, if available (e.g. ISO 9001, etc.);
- any technical information, such as information received from Regulatory Affairs in the API Drug Master File;
- any testing history for related starting materials from the supplier already delivered on site
- any testing results for starting materials provided by the potential supplier
- changes, deviations or investigations communicated by the supplier.

Stepwise Auditing Cont'd:

3. Step Three: Request and Test Samples

- any testing history for related starting materials from the supplier already delivered on site;
- any testing results for starting materials provided by the potential supplier
- changes, deviations or investigations communicated by the supplier regarding the subject product that resulted from in-house or 3rd party testing.

Stepwise Auditing Cont'd:

4. Step Four: Ensure the Necessary SOPs are in Place at Your Company.

- SOPs need to describe the procedure to be followed during the vendor assessment and vendor evaluation for purchasing of raw materials, critical and non critical packaging components, laboratory supplies, engineering supplies and imported finished goods from the vendor as classified as A, B or C.
- These SOP instructions are essential for approving prospective vendor.
- Ensure that the SOP stipulates the critical components to be reviewed in order to certify a supplier as being approved

Stepwise Auditing Cont'd:

5. Step Five: Procedure to Deal with Problems

- Although this will be included in the Quality Agreement, it is best that there exists a written procedure that covers the receipt, logging, evaluation, investigation and reporting system of all samples or product received from a particular supplier.
- This SOP will contain step by step instruction to be followed by purchasing on how to approach the supplier and request that they undertake the determination of assignable cause for the deviation, and the follow-up implementation of subsequent corrective and preventive actions. It may be preferable to have this available to the supplier before they sign the quality agreement so they completely understand their role and responsibility.

Stepwise Auditing Cont'd:

6. Step Six: Repeated Evaluation of Product

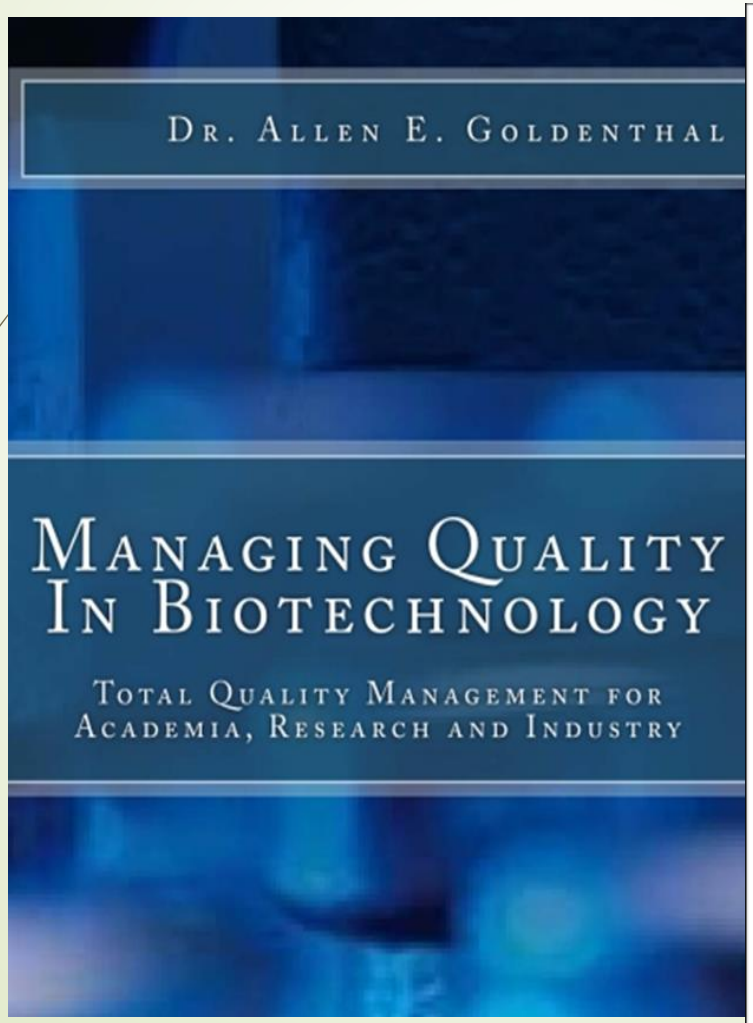
- The Customer establishes a procedure which provides a guideline for product review from suppliers by which repeated evaluation either through actual testing and/or trend evaluation a determination is made that there has been no change in the quality and performance of the product. . By this means, the Customer is assisting the Supplier in identifying any preventative or corrective action that should be implemented in order to sustain, maintain or improve product quality.

Stepwise Auditing Cont'd:

7. Step Seven: Uniformity of the Audit Performance

- This SOP describes the process of planning, performing, reporting and follow-up of different audits for your systems like Internal Quality audit, Vendor audit, Environmental Health and Safety (EHS) audit, etc.
- By having a detailed SOP on Preparing for an on-site audit, it ensures that the appropriate personnel are involved, the audit packages are complete and the audits are objective oriented and comprehensive.
- The SOP maintains the appropriate checklists and forms so that they remain uniform.

Read All About It in Chapters 9 and 11.



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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 TWO COMPLETED

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