Abstract
Drug industry is currently the second largest global industrial sector by market value. Healthcare products marketed to a specific country should comply with the regulations of Good Manufacturing Practices (GMP) of that country and hence the need to meet the current GMP regulations is crucial in the pharmaceutical industry. Unfortunately GMPs vary to some extent from country to country. On the other hand global pharmaceutical players are interested to market their products to different countries to leverage high development costs. It is just therefore a good understanding of common requirements is important. Material is one of the key aspect amongst 4 M’s of Quality (Man, Material, Machinery and Methods), yet it is being given reduced importance. Product variability is major quality concern now a days and variability in raw material (Active Pharmaceutical Ingredients (API) and excipients) is significant impact factors. In the light of above facts an attempt has been made to review different GMP requirements associated with “Material Management” and suggest an approach for its compliance by manufacturers of API.

Keywords: Material Management, Good Manufacturing Practices, Quality Assurance, 4 M’s of Quality, Approach for Compliance.

Introduction
Any system or regulation is event driven and GMP regulations also evolved through sequences of tragic events.

Between 1986 and 1998 in India and Bangladesh, paracetamol syrup contaminated with diethylene glycol resulted in 236 reported deaths, while a similar case of diethylene glycol poisoning led to 88 reported deaths in Haiti in 1996. [1]
2006 Panamanian case, a Chinese factory was found to have exported diethylene glycol mislabeled as the glycerol suitable for use in medicines. The result was some 100 fatal poisonings.\textsuperscript{[1,2]}

At a first sight, above incidents reveal that there might be poor material management system at the end of formulation manufacturer or reduced control over the distribution channel of raw material manufacturers. Regulatory requirements in the pharmaceutical industry became advanced over the time to reduce such events.

**Good Manufacturing Practices (GMP)**

Good Manufacturing Practices (GMP) is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use. GMP are aimed primarily at diminishing the risk inherent in any pharmaceutical production. Such risks are essentially of two types: cross contamination (in particular of unexpected contaminants) and mix-ups for examples false labeling.\textsuperscript{[3]}

Worldwide, there are different official regulatory statements and guidelines, national and international, on GMP (or “drug” or “medicinal”) products. They may be regulations (as in the US, Japan or Korea), directives (as in the EU), guides (as in the UK), codes (as in Australia), or WHO code (as in many Southeast Asia Countries). Out of them, following stands out as being the most influential and most frequently referenced:

- The US Current Good Manufacturing Practices for Finished Pharmaceuticals regulations (the “US cGMPs”).\textsuperscript{[4]}
- The Guide to Good Manufacturing Practice for Medicinal Products of the European Union (the “EC GMP Guide”).\textsuperscript{[5]}
- ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients.\textsuperscript{[6]}
- WHO good manufacturing practices.\textsuperscript{[7]}

The other guidelines and regulation referred by the pharmaceutical manufacturers are as under
• Schedule M “Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products” The Drugs And Cosmetics Act And Rules, India.\(^8\)
• PIC/S Guide to Good Manufacturing Practice for Medicinal Products.\(^9\)
• Centre for Drug Evaluation and Research (CDER); Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients.\(^10\)

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body is known as API.\(^6\)

Figure 1 indicates that variability in API contribute about 25% probability to in product variability.

\[
\sigma_{Product}^2 = \sigma_{API}^2 + \sigma_{Excipients}^2 + \sigma_{Process}^2 + \sigma_{Interaction}^2
\]

**Figure 1**
Factor affecting the variability in product\(^11\)

Following observation from a 2008 warning letter is indicative of regulatory focus on material management system.
Observation from 2008 warning letter\textsuperscript{[12]}

“Your vendor qualification program should provide adequate evidence that the manufacturer can consistently provide reliable and safe materials. Suppliers should be monitored and regularly scrutinized to assure ongoing reliability. It is your responsibility to ensure that raw materials received are suitable and approved by the quality unit prior to use.”

COMPREHENSIVE REQUIREMENT:

Note: The comprehensive requirement prepared by referring above mentioned guidance documents / regulatory requirements\textsuperscript{[4-10]}

General controls

- No materials used for operations such as cleaning, lubrication of equipment and pest control, should come into direct contact with the product. Where possible, such materials should be of a suitable grade (e.g. food grade) to minimize health risks.
- There should be written procedures describing the receipt, identification, quarantine, labelling, storage, handling, sampling, testing, approval or rejection and dispensing of materials.
- Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials.
- The purchase of starting materials is an important operation that should involve staff who have a particular and thorough knowledge of the products and suppliers.
- Starting materials should only be purchased from approved suppliers named in the relevant specification and, where possible, directly from the producer. It is recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that all aspects of the production and control of the starting material in question, including handling, labelling and packaging requirements, as well as complaints and rejection procedures are discussed with the manufacturer and the supplier.
- Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.
- Highly active materials or products should be stored in safe and secure areas.
• Highly hazardous, poisonous and explosive materials such as narcotics, psychotropic drugs and substances presenting potential risks of abuse, fire or explosion shall be stored in safe and secure areas. Adequate fire protection measures shall be provided in conformity with the rules of the concerned civic authority.

• Raw materials that are stored outdoors should be in suitable containers. Identifying labels should remain legible and containers should be appropriately cleaned before opening to prevent contamination.

• All incoming materials shall be quarantined immediately after receipt or processing. All materials shall be stored under appropriate conditions and in an orderly fashion to permit batch segregation and stock rotation by a ‘first in/first expiry’ – ‘first-out’ principle. All incoming materials shall be checked to ensure that the consignment corresponds to the order placed.

• Rejected raw materials should be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

• If the supplier of a critical material is not the manufacturer of that material, the name and address of that manufacturer should be known by the intermediate and/or API manufacturer.

• Changing the source of supply of critical raw materials should be routed through change control procedure.

• For solvents or reagents delivered in bulk vessels (e.g., tanker trucks), a procedural or physical system, such as valve locking or unique couplings, should be used to prevent accidental discharge of the solvent into the wrong storage tank.

• Regular checks shall be made to ensure adequate steps are taken against spillage, breakage and leakage of containers

Receipt and quarantine

All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled, if required, with the prescribed information. Where additional labels are attached to containers, the original information should not be lost.
Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labelling (including correlation between the name used by the supplier and the in-house name, if these are different), container damage, broken seals and evidence of tampering or contamination. Materials should be held under quarantine until they have been sampled, examined or tested as appropriate, and released for use.

Damage to containers and any other problem that might adversely affect the quality of a material should be recorded and reported to the QC department and investigated.

Before incoming materials are mixed with existing stocks (e.g., solvents or stocks in silos), they should be identified as correct, tested, if appropriate, and released. Procedures should be available to prevent discharging incoming materials wrongly into the existing stock.

If bulk deliveries are made in non-dedicated tankers, there should be assurance of no cross-contamination from the tanker. Means of providing this assurance could include one or more of the following:

- Certificate of cleaning
- Testing for trace impurities
- Audit of the supplier.

Large storage containers, and their attendant manifolds, filling and discharge lines should be appropriately identified.

Each container or grouping of containers (batches) of materials should be assigned and identified with a distinctive code, batch, or receipt number. This number should be used in recording the disposition of each batch. A system should be in place to identify the status of each batch.

**Sampling and testing of incoming production materials**

Sampling is an important operation in which only a small fraction of a batch is taken. Valid conclusions on the whole cannot be based on tests which have been carried out on non representative samples. Correct sampling is thus an essential part of a system of Quality Assurance.

If a single delivery of material is made up of different batches, each batch shall be considered as a separate batch for sampling, testing and release.
Starting materials in the storage area should be appropriately labelled. Labels should bear at least the following information:

- The designated name of the product and the internal code reference where applicable;
- The batch number given by the supplier and, on receipt, the control or batch number given by the manufacturer, if any, documented so as to ensure traceability;
- The status of the contents (e.g. On quarantine, on test, released, rejected, returned, recalled);
- Where appropriate, an expiry date or a date beyond which retesting is necessary.

The sample taking should be done in accordance with approved written procedures that describe:

- The method of sampling;
- The equipment to be used;
- The amount of the sample to be taken;
- Instructions for any required sub-division of the sample;
- The type and condition of the sample container to be used;
- The identification of containers sampled;
- Any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials;
- The storage conditions;
- Instructions for the cleaning and storage of sampling equipment.

Starting materials should be dispensed only by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.

Each dispensed material and its weight or volume should be independently checked and the checks recorded.

Materials dispensed for each batch of the final product should be kept together and conspicuously labelled as such.
An identity test should be conducted on a sample from each container of key starting material.

In lieu of testing by the manufacturer, a certificate of analysis (COA) may be accepted from the supplier, provided that the manufacturer establishes the reliability of the supplier’s analysis through appropriate periodic validation of the supplier’s test results and through on-site audits of the supplier’s capabilities. Certificates must be originals (not photocopies) or otherwise have their authenticity assured. Certificates must contain at least the following information:

- Identification (name and address) of the issuing supplier;
- Signature of the competent official, and statement of his or her qualifications;
- The name of the material tested;
- The batch number of the material tested;
- The specifications and methods used;
- The test results obtained;
- The date of testing.

Supplier validation should take account of at least the following aspects:

- The nature and status of the manufacturer and of the supplier and their understanding of the GMP;
- The QA system of the manufacturer of the starting material;
- The manufacturing conditions under which the starting material is produced and controlled;
- The nature of the starting material and the medicinal products in which it will be used.

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 QA system are conducted by the purchaser/other authorized body.
However, as a minimum, a full analysis should be performed at appropriate intervals and compared with the Certificates of Analysis. Reliability of Certificates of Analysis should be checked at regular intervals.

Processing aids, hazardous or highly toxic raw materials, other special materials, or materials transferred to another unit within the company’s control do not need to be tested if the manufacturer’s COA is obtained, showing that these raw materials conform to established specifications. Visual examination of containers, labels, and recording of batch numbers should help in establishing the identity of these materials. The lack of on-site testing for these materials should be justified and documented.

Samples should be representative of the batch of material from which they are taken. Sampling methods should specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The number of containers to sample and the sample size should be based upon a sampling plan that takes into consideration the criticality of the material, material variability, past quality history of the supplier, and the quantity needed for analysis.

Sampling should be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.

Containers from which samples are withdrawn should be opened carefully and subsequently reclosed. They should be marked to indicate that a sample has been taken.

Sampling equipment should be cleaned and, if necessary, sterilized before and after each use and stored separately from other laboratory equipment.

Each sample container should bear a label indicating:

- The name of the sampled material;
- The batch or lot number;
- The number of the container from which the sample has been taken;
- The signature of the person who has taken the sample; and
- The date of sampling.

Any lot of components, drug product containers, or closures that meets the appropriate written specifications of identity, strength, quality, and purity and related
tests may be approved and released for use. Any lot of such material that does not meet such specifications shall be rejected.

- Raw materials should be handled and stored in a manner to prevent contamination and cross contamination. Bagged and boxed raw materials should be stored off the floor and suitably spaced to permit cleaning and inspection. Raw materials that are stored outdoors should be in suitable containers. Identifying labels should remain legible and containers should be appropriately cleaned before opening to prevent contamination.

**Re-evaluation**

- Raw materials should be reevaluated, as necessary, to determine their suitability for use (e.g., after prolonged storage or after exposure to heat or high humidity).

- Written procedures should be established and followed that describe the sampling methods for in process materials, intermediates, and APIs. Sampling plans and procedures should be based on valid data and scientifically sound sampling practices.

**APPROACH FOR COMPLIANCE:**

The following approach pertaining to “Material Management” may be helpful for pharmaceutical manufacturers to implement the expectations of different regulatory agencies

- There should be a system in place for qualification of suppliers. Suppliers may be approved on the basis of one or more factors such as historical experience, quality audit, third party certification based on the nature of the material to be purchased and its impact on the final product quality.

  List of approved suppliers should be supported by appropriate records.

- There shall be a written and approved contract between supplier and manufacturer, which clearly states the responsibilities of each party.

- Purchasing documents should be reviewed and approved for accuracy of specified requirements prior to use.

- Identify special storage requirements of incoming materials. List of the raw material against its storage conditions shall be made available to personnel working in the warehouse.
Analyze special shipment requirement of incoming materials and finished products to be supplied.

Describe potential sources of mix-up and identify methods to minimize their risk, including material segregation, labeling, special storage of rejects, control of material returns, lot-control methods, material codification system etc..

Incoming stock should be released before mixing them with the existing stock. After mixing the new stock with existing stock, the combined bulk shall also be analysed. This new stock should get a new code.

Non-dedicated tankers should be released for use to prevent cross-contamination. Cleaning certificate should be provided with each supply. If no such certificate can be provided, an audit of the cleaning procedure of the suppliers and/or transport company is required.

Identity test should be done on each incoming batch of material except in cases where testing can negatively influence the safety or health of the person responsible. In that case, a visual check of the containers and a certificate of analysis should be available and recorded.

Change in source of material should be treated through change control procedure and vendor qualification programme.

The impact of new source of material on final product to be manufactured should be studied w.r.t. manufacturing process and stability data evaluation.

Damaged container or container received with other problem that might adversely affect the quality is recorded, reported to Quality Assurance. The damaged container shall be considered for separate sampling and appropriate precaution should be taken to prevent contamination of other materials.

Identify the requirements for using weighing equipment and handling utensils for sampling and dispensing of materials, including proper cleaning, labeling and environmental controls based on the type of materials and manufacturing process being used.

Following SOPs should available and followed

- Vendor Selection and Qualification
- Sampling of Incoming materials covering statistical approach for sampling of different types of materials
- Purchase agreement: Roles and Responsibilities of suppliers
- Physical verification of incoming material
- Status labeling at warehouse
- Cleaning of Dispensing utensils
- Dispensing of materials
- Rejection of materials
- Storage of Different Materials
- Calibration and Preventive Maintenance of Sampling and Dispensing booth and balances
- Control of materials
- Environmental monitoring at warehouse

CHECKLIST FOR COMPLIANCE ASSESSMENT:

Following checkpoints/checklist may help to assess the compliance of material management system.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Checklist / Checkpoints</th>
<th>Y/N/NA</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Is SOP for receipt, identification, quarantine, storage, approval of material available?</td>
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<td>2.</td>
<td>Are appropriate Specifications available for all Raw materials?</td>
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<td>3.</td>
<td>Is there system to audit the manufacturer supplier of Critical material?</td>
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<td>4.</td>
<td>Is there a system to make Purchasing agreements for quality critical materials?</td>
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<td>5.</td>
<td>Are materials purchased against an agreed specification?</td>
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<td>6.</td>
<td>Is approved vendor list specific to site of manufacturing?</td>
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<td>7.</td>
<td>Is there a system to ensure that quality critical materials are only purchased from approved suppliers which are qualified for capability to consistently meet agreed-upon requirements?</td>
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<td>Sr. No.</td>
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<td>8.</td>
<td>Is there segregated area for Quarantine, Under-test, Approved and Rejected materials?</td>
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<td>9.</td>
<td>Is there separate sampling area with laminar air flow booth available for prevention of cross-contamination?</td>
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<td>10.</td>
<td>Is Receiving bay available at warehouse?</td>
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<td>11.</td>
<td>Is there separate storage for hazardous &amp; toxic material available?</td>
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<td>12.</td>
<td>Are control measures defined for dispensing of toxic material?</td>
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<td>13.</td>
<td>Is there procedure available for cleaning of utensils utilized for dispensing and record maintained?</td>
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<td>14.</td>
<td>Is sampling and dispensing tools covered under the cleaning validation plan?</td>
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<td>15.</td>
<td>Is appropriate system available for stock rotation? (e.g. First in First out; First expired First out)?</td>
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<td>16.</td>
<td>Is there SOP available to follow controls for bulk deliveries?</td>
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<td>17.</td>
<td>Is there a system to analyse the bulk material before and after mixing/unloading with existing material?</td>
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<td>18.</td>
<td>Are dedicated tanks available for storage of solvents received in bulk?</td>
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<td>19.</td>
<td>Is there a system to verify cleaning certificate of tanker supplying bulk solvents?</td>
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<td>20.</td>
<td>If quality critical materials are accepted on certificate of analysis (COA), is at least an identification test performed (when it is safe) on every batch and receipt?</td>
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<td>21.</td>
<td>Are all material stored in approved area according to storage classification?</td>
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<td>Sr. No.</td>
<td>Checklist / Checkpoints</td>
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<td>condition? Is the storage permits easy cleaning of area?</td>
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<td>22.</td>
<td>Is the mapping study carried out at warehouse to identify worst case location? (Required for material storage which demands controlled condition)</td>
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<td>23.</td>
<td>Is temperature mapping study at warehouse carried out with full load of material?</td>
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<td>24.</td>
<td>Is there system for recording of maximum temperature &amp; humidity observed throughout the day?</td>
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<td>25.</td>
<td>Is temperature and humidity monitoring device located at identified worst case location?</td>
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<td>26.</td>
<td>Is there a system for trend analysis and its evaluation for environmental conditions observed at warehouse?</td>
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<td>27.</td>
<td>Is there any procedure for re-testing of material? Is rationale/stability data available to support the assigned re-test period?</td>
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<td>28.</td>
<td>Is there procedure for retention of each lot of critical material?</td>
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<td>29.</td>
<td>Is procedure defined for periodic training of personnel involved in Sampling and Dispensing activities?</td>
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<td>30.</td>
<td>Is there procedure to maintain log of sampling and dispensing activities?</td>
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<td>31.</td>
<td>Are clear job responsibilities available for personnel involved in the warehouse and personnel responsible for sampling activity?</td>
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<td>32.</td>
<td>Is statistical sampling approach adopted is justified based on the material and scientific rationale?</td>
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<tr>
<td>33.</td>
<td>Is any computerized system adopted for material management? If yes, appropriate qualification record available for its intended use?</td>
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CONCLUSION:

Pharmaceutical manufacture and regulation is clearly an international business. With the increasing emphasis on harmonization efforts and standard setting along with mutual recognition agreements, knowledge of foreign regulations is a necessity for both understanding the future direction of these efforts as well as for international supply of drug products. Legally its responsibility of pharmaceutical manufacturers to ensure quality of purchased materials, its control and management for uses in a cGMP manufacturing process. Compliance to material management requirement make sure that an organisation’s quality system is well defined and controlled. It is anticipated that the mentioned approach would be a useful reference work for those personnel preparing and using documents for pharmaceutical manufacture, tool for training staff and may be useful for quality assurance professionals for assessment of compliance during self inspection.

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