REVIEW

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Vendor qualification for pharmaceutical excipients – GMP requirements and approach

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Excipients are, in the large majority of cases, not made specifically for pharmaceutical use. Most pharmaceutical excipient manufacturers supply less than 10% of the total production of that particular material for pharmaceutical use. Excipient product portfolio consists of hundreds of products differing in chemistry, origin and functionality and they are used in many different applications. The days of treating excipients like commodities and buying them without fully qualifying the source and the entire distribution chain have gone by as GMP regulations demands to ensure quality of other materials used in the manufacturing process. The paradigm that exists in some pharmaceutical companies today where excipients are sourced from distributors without knowing the actual manufacturer, manufacturing site and full distribution lifecycle chain to be changed. The present contribution gives an overview about the current moves on GMP requirements for pharmaceutical excipient and approach for qualification of pharmaceutical excipient manufacturers.

1. Introduction

Drug industry is currently the second largest global industrial sector by market value (Freemantle and Hill 2004). Drug quality has become an issue of growing concern in developing countries (Taylor et al. 2001). It may lead to adverse clinical results both in terms of low efficacy and by inducing drug resistance or serious damage to patients' health (Ogoh 1994; Roy 1994; Menkes 1997). In several countries, there is great concern that the prevalence of low quality drugs is high (Syhakhang 2002). In addition, the manufacturing of substandard medicines remains a global concern (WHO 2003). In drug industry, quality more accurately reflects adherence to the rules as Good Manufacturing Practice (GMP) (Volsen et al. 2004).

Good Manufacturing Practice (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 example false labeling.

Excipients are those materials that when combined with the Active Pharmaceutical Ingredients (API) result in a drug product. Whereas an API has only one function-albeit an extremely important one, that of providing a therapeutic effect – the excipients contained in a drug product play a multitude of roles. Excipient ingredients enable an APIs to be compounded into a stable drug dosage form that can be safely stored and administered with assurance of a consistent bioavailability profile (Silverstein 2002).

Most formulations (70–80%) contain excipients at a higher concentration than active drug. Consequently, the excipients contribute significantly to a formulation's functionality and processability (Nachaegari and Bansal 2004). Now a days purity, safety and standardization become extremely important, as excipients are critical to delivering drug actives. In the past, excipients were merely regarded as the inactive part of formulations and relatively unimportant from a specification perspective. It has recently become obvious that controlling the quality and consistency of excipients will have a major impact on dosage form development. They are a key aspect of product Quality by Design (QbD) (Larner et al. 2006). Excipients are an intrinsic part of nearly all medicinal products and therefore they have an impact upon the quality, safety and efficacy of drug products.

In the past three decades, the pharmaceutical industry has seen the development of drugs that actually cure diseases rather than just offer symptomatic relief. During these years, the concepts of improving efficacy and GMPs have grown in importance. In addition, many new concepts and terms had come into common usage. For example, the concept that a dosage form must act to release the active ingredient has become generally accepted. Words like disintegration, dissolution, and bioavailability also have gained prominence and meaning. Accompanying these terms and concept was the realization that inactive ingredients frequently are critical to ensure storage stability, safety and efficacy of drug dosage forms. The transition from excipients being perceived as inactive, inert ingredients to the present status of pharmaceutical excipients is well on its way (Steinberg et al. 2001).

Under current GMP rules and regulations, it is the pharmaceutical manufacturer who is responsible for overall operations including the quality of components: the active ingredient(s), the excipients and the packaging materials.

2. Tragic incident

It is a truism that it takes a disaster to happen for people, and especially regulators, to wake up and review the accepted way of doing things. So, too, with the question of drug safety and drug quality (Globepharm).

- In the 2006 Panamanian case, a Chinese factory was found to have exported diethylene glycol mislabeled as glycerol suitable for use in medicines. The result was some 100 fatal poisonings (Taylor 2008; Eisele 2007).
- 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 (Taylor 2008).
- In September 2008, FDA received a report from China about food articles contaminated with melamine, which have resulted in thousands of hospitalizations for kidney problems and at least three fatalities. Before that FDA was not aware of any pharmaceuticals that have been contaminated with melamine. In August 2009, Centre for Drug Evaluation and Research Food and Drug Administration, United States has issued a Guidance for Industry "Pharmaceutical Components at Risk for Melamine Contamination" and by that FDA has made mandatory to test the component for melamine content for those which can be derived from source material that might be contaminated with melamine (CDER 2009).

3. Current status of GMP for pharmaceutical excipients

Many regulatory agencies provided GMP guidelines for APIs. Unlike APIs, excipients receive least oversight from regulatory authorities. In the United States, FDA is responsible for enforcing the requirements of 21 CFR Parts 210 and 211 for the manufacture of drug products from APIs, excipients, and other components. Over the years, the agency has issued numerous guidance documents concerning the manufacture of drug products. In the past several years the agency has also focused on the manufacture of APIs, which has led to an additional series of guidance documents. However, to date, no FDA guidance exists that deals solely with the requirements of the excipient quality system (Silverstein 2002). The Drugs and Cosmetics Act, India has not provided a discrete GMP guideline for manufacture of excipients (Schedule M 2005).

The World Health Organization (WHO) published GMP Guidelines specifically for excipient manufacturers in 1999 and industry bodies have evolved GMP guidelines previously over many years (WHO 2004). In the UK, the Pharmaceutical Quality Group (PQG) developed "PS 9100:2002 Pharmaceutical Excipients" which includes both a GMP guide and an audit standard based on ISO 9001:2000 (PQG 2007). In 2006, the International Pharmaceutical Excipient Council (IPEC) of Europe and America jointly published "Good Manufacturing Practices Guide for Pharmaceutical Excipients"(IPEC 2006). U. S. Pharmacopeia 31-NF 26 also mentioned discrete chapter for GMP for Bulk Pharmaceutical Excipients (USP 2008).

The regulatory environment for excipients is subject to change in Europe as part of the new legislation amending the existing pharmaceutical laws that was introduced in 2005. This new legislation requires from API manufacturer to adhere to GMP requirements. Directive 2004/27/EC specifically mandated the implementation of GMP for "certain excipients" including (Taylor 2008):

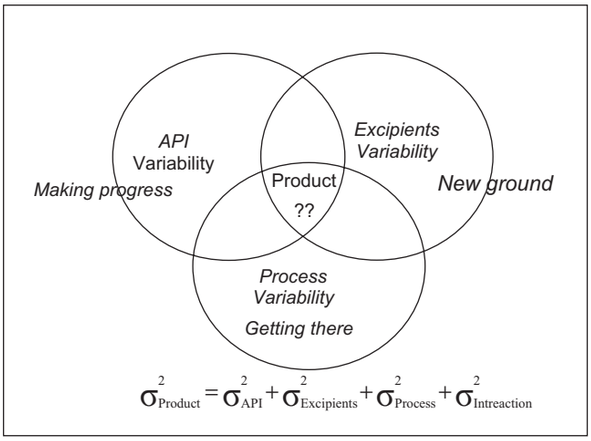

Fig. 1: Factor affecting the variability in product

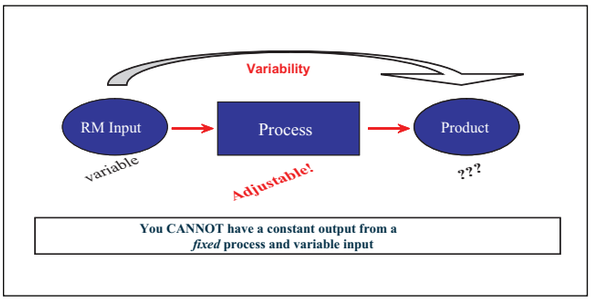

Fig. 2: Product variability with variable RM and fixed process

- Excipients prepared from materials derived from a Transmissible Spongiform Encephalopathy (TSE) relevant animal species, with the notable exception of lactose
- Excipients derived from human/animal material with potential viral contamination risk
- Excipients claimed to be sterile (or sold as sterile) and used without further sterilization
- Excipients with the specification or claim that they are endotoxin/pyrogen controlled; or
- Specific excipients, namely propylene glycol and glycerol.

4. Why excipient vendor qualification is required

In addition to GMP regulatory expectations and requirements mentioned above, the excipient vendor qualification is particularly important

- in the product approval process, where bioequivalence comparisons are made between clinical bioequivalence (biobatch) production and commercial scale-up batches.
- to provide adequate assurance of drug product performance in vivo, the excipient used in commercial batches should not differ significantly from that used in biobatches and in case of significant differences, additional testing is required to establish the bioequivalence of the product.
- to avoid the potential risks mentioned below
  - Presence of extraneous matter e.g., metal, paper, particles
  - Cross contamination with other chemicals (either excipients or APIs or breakdown products)
  - Contamination with TSE & melamine risk materials which is not permitted by legislation

- Inconsistent manufacture such that the quality of final products cannot be assured
- mis-labelling of containers leading to product mix-up

- Concept of Quality by Design (QbD) involves understanding of product variability in which contribution of excipient also needs special consideration

Product variability (Morris 2006): Current requirement of GMP, Quality by Design and Process Analytical Techniques demands thorough understanding of a process and the impact on that process of all the input variables and their effect on that process. Following variables affect the consistency of the product:

- Variable Manufacturing Techniques
- Manufacturing Equipment Variables
- Manufacturing Process Conditions
- Environmental Conditions
- Formulation (API and Excipient) chemical & Physical property Variation

Figures 1 and 2 indicate that variation in excipient manufacturing/supply/quality has a significant effect on consistency of drug product manufacturing.

5. Approach for excipient vendor qualifiation

The qualification process is defined by the American Society for Quality Control (ASQC) as "the process of demonstrating whether an entity is capable of fulfilling the specified requirement." Vendor qualification is the process by which a vendor is evaluated to determine if it can provide the necessary goods or services to the standards that the purchasing company requires (Cafmeyer and Lewis 2009).
Quality systems are defined as "the processes, organizational structure, procedures and resources that are used to control variables associated with producing a product of consistent quality and that meets predefined specifications." In simpler words, an organization's entire operation is a measure of a product s quality and not simply the testing of its finished product (Cafmeyer and Lewis 2009).
For effectiveness of the quality systems and to assure continual quality of excipient to be used for drug product manufacturing, following approach may be helpful.
Design the SOP for "Excipient Vendor Qualification" which includes following

- Excipient vendor selection criteria
- Procedure for evaluation of criticality of excipient for consistent out put of drug product
- Procedure for Qualifying Non-Critical Excipients
- Procedure for Qualifying Critical Excipients
- Onsite audit requirement and frequency of periodic audit for assurance of consistent supply
- Procedure for preparation of audit report and verification of observations made during audit
- Procedure for pre-shipment sample analysis
- Procedure for manufacturing trial batches and evaluation of stability data for preliminary screen
- Procedure for alternate vendor development
- Procedure for Trend analysis
- Criteria for Rejection of approved vendor
- Agreement with vendor

Q.U.E.S.T. approach (Cafmeyer and Lewis 2009)
Q = Question phase:
What type of excipient is required for the drug product manufacturing to fulfill the drug product characteristics, safety and efficacy of the product. The defined specification for raw material required should be prepared with scientific rationale behind its proposed usage.
U = Understanding phase:
The specific requirement related to particle size, special functionality. Based on the preliminary trials taken at laboratory scale and outcome of compatibility, stability and development activity, the requirement of excipient can be finalized. Scientific rationale shall be available in form of the laboratory trials or through published literature
E = Evaluation phase: Identification of the best potential vendor
Based on the requirement, the potential vendor can be identified.
S = Site audit phase: Onsite and offsite verifications
Based on the criticality of excipient, the onsite audit shall be carried out.
T = Track phase: Monitor and requalify
The vendor's performance must be monitored on a continuous basis. The monitoring process involves a review of any problems associated with the good or service supplied by the vendor. A schedule is determined so that each qualified vendor is requalified on a periodic basis.

6. Checklist for onsite audit of pharmaceutial excipient manufacturer

Following checkpoints / checklist may help to assess the GMP compliance during vendor audit of pharmaceutical excipient manufacturer.

S.No.	Checkpoints
General Information of the firm	
1.	Name of the organization
2.	Address of manufacturing site
3.	How long has the company been manufacturing pharmaceutical excipients?
4.	No of Products and range being manufactured by the organisation
5.	% of supply to the pharmaceutical industries
6.	Approximate turn over
7.	Strength of the organization
8.	Approximate area of the manufacturing facility
9.	Type of pharmaceutical formulation in which the excipients being used
10.	Details of National/international accreditations
Quality Management System	
11.	Is Quality manual available?
12.	Is Quality policy in place?

S.No.	Checkpoints
13.	Is system for documentation control available to include following? • Indexing • Document numbering • File numbering • Storage of documents
14.	Are all documents pass through appropriate review and approval procedure?
15.	Is distribution records maintained for all documents?
16.	Is there any procedure for assurance of current version of documents being used?
17.	Are all documents impacting quality of final product reviewed by quality units? e.g., specification, Batch Records. . .
18.	Is responsibility assigned for issuance and control of documents?
19.	Is history of changes made in documents are maintained?
20.	Is electronic signature being used?
21.	Is procedure available for "correction of entries"?
22.	Is retention period of documents defined in procedure? Is it appropriate?
23.	Is procedure available for change control management?
24.	Is independent unit like QA/RA responsible for review and approval of changes?
25.	Is there any procedure to inform customers for process related changes?
26.	Is independent quality unit available?
27.	Is a defined job responsibility available for all personnel?
28.	Is approved organization chart is available?
Management Responsibilities	
29.	Is there a defined programme for review of quality objectives?
30.	Is there procedure to permit customer audits and records are maintained?
31.	Is there procedure for upgradation of system based on customer demand?
32.	Is there system for periodic review of quality systems? (Internal audit)
33.	Is there system in place for periodic management review? If yes, following details covered under the scope? • Results of internal and external audits • Customer feedback • Customer complaints • Status of CAPA • Changes that affect the quality
Resource Management	
34.	Are sufficient personnel with appropriate qualification available to carry out assigned responsibilities?
35.	List of personnel available with their experience and qualification status?
36.	Is there system to maintain personnel file which includes • Job description • CV • SOP training record • Record of external training and certificates
37.	Is record of consultants maintained? which includes • Name • Address • Qualification of consultants • Type of service they provided
38.	Is there procedure for periodic training?
39.	Is the appropriate documents available for training of the personnel?
40.	Is there a system to train person on job-specific task before allocation of job? Documents available for the same?
41.	Is the training SOP covers the training on GMP and health and hygiene on periodic basis?
42.	Is appropriate gowning procedure available and followed?
43.	Are protective wears available in the applicable locations?
44.	Is there any policy available for periodic health-check up for employee?
45.	Is there procedure to re-evaluate health condition of the personnel suffering from an infectious disease before re-assigning task?
46.	Is premises situated in appropriate location to prevent cross contamination?
47.	Is toxic/sensitizing material being produced in the premises?
48.	Is facility permits easy cleaning?
49.	Is SOP for cleaning available?
50.	Is record of cleaning maintained with type of disinfectant / sanitizing agent used?
51.	SOP for pest control available?

S.No.	Checkpoints
52.	Is list of equipment available with • Capacity • Id. No. • Preventive maintenance frequency • Material of construction
53.	Are SOPs available for operation, cleaning and preventive maintenance of equipment?
54.	Is there a system to maintain equipment file containing all details of equipment containing IQ,OQ,PQ, Preventive maintenance, details of breakdown and re-qualification?
55.	Are Equipment logs maintained properly?
56.	Is any equipment attached with computerized system? If yes, • Record available for proper functioning of software? • Periodic check up procedure for proper functioning? • Retention at suitable location for back up? • Change control system for programme?
57.	Is there procedure for checking quality of utilities? (Compressed Air, Steam, Nitrogen gas used in production are certified for its quality?)
58.	Is water being used in the production? If yes, • Is type of water appropriate for its intended use? • is there procedure for periodic testing of bore-well water? • Are specification of bore-well water and process water available and followed? • Is facility for water testing is appropriate?/ Is contract available for testing of water? • Is microbial control is part of specification?
59.	Is purification of excipient is carried out in controlled environment?
60.	Is there system for qualification of AHU/HVAC? Collect the following details. • Type of filter • % of Recirculation Is the type of filter and system for recirculation of air is justifiable for its intended use?
61.	Are pipework identified with its content and flow direction?
62.	Is the location of piping/ducts appropriate for minimizing contamination?
63.	Is there adequate lighting available?
64.	Are drain provided with an air break to prevent back-siphoning?
65.	Washing & toilet facilities are adequate and equipped with following? • Hot & cold water • Soap or detergent • Air dryers • Single service towels • Clean toilet facility • Showering/changing cloths
Product Realisation	
66.	Is there a system for purchasing agreements for quality critical materials? It shall include: ■ The name, type, class, style, grade, item code number or other identification and packaging specifications ■ Drawings, process requirements, inspection instructions and other technical data along with procedures, process equipment and personnel. ■ A statement to notify the excipient manufacturer of significant changes in quality critical raw material
67.	Is there SOP for receipt, identification, testing and release of materials being used for manufacturing of excipients?
68.	Specification for all incoming material is available?
69.	Is testing procedure for all incoming material available?
70.	Is there SOP for sampling of material?
71.	Is there system to approve the suppliers/manufacturers of raw material? (It is required for consistency in product quality)
72.	is there SOP available to follow controls for bulk deliveries? ■ Bulk deliveries should have additional control to assure material purity and freedom from contamination e.g., dedicated tankers, temper-evident seals, a certificate of cleaning, analytical testing and / or audit of the supplier)
73.	Is there procedure for customer communication?
74.	Is master production record available?
75.	Is batch production records includes following? ■ Date/time each step was completed or date/time log of key parameters ■ Identification of major equipment and lines used ■ Material inputs to enable traceability, for example batch number and quantities of raw material/intermediate, time it was added etc.

S.No.	Checkpoints
	■ in-process and laboratory control results ■ The quantity produced for the defined batch and a statement of the percentage of theoretical yield, unless not quantifiable ■ Inspection of the packaging and labeling area before and after use ■ Labeling control records ■ Description of excipient product containers and closures ■ Description of sampling performed ■ Failures, deviation and their investigations ■ Results of final product inspection
76.	Is the detailed cleaning procedure? Is the SOP has mention of following details? ■ Schedule ■ Cleaning agent ■ Procedure for disassembling and re-assembling ■ Cleaning verification ■ Time frame after cleaning and before usage for next product ■ Cleaning procedure for • Product change over • Batch changeover
77.	Is there SOP / Policy available for recovery of solvents, mother liquors and second crop crystallization?
78.	Is there procedure to check appropriateness of recovered solvents prior to reuse?
79.	Is the use of mother liquors or filtrates containing recoverable amounts of excipients is being documented in batch records?
80.	Is there procedure for In-process inspection at defined locations and times?
81.	Is in-process sampling carried out according to approved sampling procedure?
82.	Is in-process testing carried out according to approved specification and testing method?
83.	Is there SOP available for issuance and control of labels?
84.	Is there procedure for reconciliation of packaging and labeling materials?
85.	Is there procedure for process validation? OR product review reports? (Process consistency can be determined through process capability studies, development and scale – up reports etc.)
86.	Customer property Is there procedure for verification, storage and maintenance of customer-supplied materials intended for incorporation in to the customer's excipient?
87.	Is there procedure for handling, storage and preservation of the raw materials? ■ Appropriate storage condition ■ Outdoor storage also acceptable provided containers give suitable protection against deterioration and identifying labels remain legible and container cleaned prior to opening and use
88.	Packaging system Is there specification and testing methods available for packaging materials?
89.	Is cleaning procedure available in case of re-use of container?
90.	Is there adequate warehouse for proper segregation of material?
91.	Is there a system to record temperature and humidity at warehouse?
92.	Is there procedure to maintain distribution records? -what is the retention period for distribution records?
Measurement, Analysis and Improvement	
93.	Is specification and testing procedure available?
94.	Are all instruments qualified?
95.	Are SOPs available for calibration of instruments / equipment?
96.	Are SOPs available for operation of instruments / equipment?
97.	Is there a system for labeling of calibration status?
98.	Are reagents/volumetric solutions are labeled for identity & used before date?
99.	Is there procedure for standardization of volumetric reagents?
100.	Is there written procedure for recording analytical data? Are Laboratory control records written with sufficient details as mentioned below? ■ Description of sample, batch number, date of sampling ■ Statement referencing each test method used ■ Records of raw data including chromatograms, graphs, spectra etc. ■ Calculation record ■ Comparability with specification ■ Date of analysis ■ Analyzed by
101.	Is document of reference standard available? Following details shall be in place

S.No.	Checkpoints
	■ COA ■ Storage location and temperature record ■ Reconciliation record
102.	Is document of working standard (secondary reference standard) available? Following details shall be in place ■ COA ■ Storage location and temperature record ■ Reconciliation record ■ Labeling ■ Characterization of Working standard
103.	Is there documented procedure available for qualification of working standard?
104.	Re-evaluation period is defined for working standard?
105.	Is there procedure to carry out microbial analysis of final excipients? If yes, ■ Adequate facility available? ■ Contracted out? ■ Written contract available? ■ Contract lab audited for competency?
106.	Are scientifically sound and validated analytical methods available to carry out testing of different excipients?
107.	Are following details available on certificate of analysis? ■ Batch No. ■ Retest date ■ Address of manufacturer ■ Product name ■ Acceptance criteria and results
108.	Is any repacking / re-processing activity contacted outside? If yes, re-packers / re-processor's details mentioned in COA
109.	Is there approved procedure available for conducting stability studies? ■ Carried out in final container? ■ Procedure reflects to include re-process batch or re-work batch in stability?
110.	Is appropriate back-up data available to support the re-test / expiry date assigned to the product? If no, What is the procedure to assign re-test / expiry date?
111.	Is there defined procedure for release of material?
112.	Is there procedure for investigation of OOS?
113.	Is there procedure for retained sampling? It should include ■ Quantity to be retained ■ Retention time
114.	Is back up for impurity limit is available? OR system for impurity profiling?
115.	Is there SOP for control of nonconforming product to prevent inadvertent use?
116.	Is there procedure for reworking or reprocessing?
117.	Is there system to perform risk assessment during approval of reworking to include following ■ New impurities that may be introduced as a result of reworking ■ Additional testing to control the reworking ■ Records and traceability to the original batches ■ Suitable acceptance criteria for the reworked excipient ■ Impact on stability or the validity of the re-evaluation interval ■ Performance of the excipient
118.	Is separate space available for storage of returned products?
119.	Is there procedure for handling return goods? Are following details part of the record for returned goods? ■ Name and address of consignee ■ Batch No. ■ Quantity returned ■ Reason for return ■ Use / disposal decision

7. Conclusion

This overview highlights the importance of GMP and vendor qualification of Pharmaceutical excipient manufacturers for quality, safety and efficacy of drug product. It is anticipated that the mentioned approach will be a useful tool for quality assurance personnel who are in the process of implementation of a vendor qualification system in general and manufacturers of pharmaceutical excipient in particular.

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