The Joint IPEC-PQG Good Manufacturing Practices Audit Guideline

FOR PHARMACEUTICAL EXCIPIENTS

2008

IPEC Good Manufacturing Practices Audit Guideline for Pharmaceutical Excipients

I. Purpose and Scope

In the pharmaceutical industry it is the responsibility of the drug product manufacturer to ensure the quality of all starting materials and other components contained in or used in the manufacture of the final product dosage form. Through auditing the producer of pharmaceutical excipients, a user is able to determine whether adequate controls are in place to ensure the producer is capable to manufacture a product of suitable quality. The IPEC-PQG Audit Guideline (the Audit Guideline) is therefore designed as a tool to assist in evaluating the manufacturing practices and quality systems of excipient manufacturers. It is also a helpful reference to assist excipient manufacturers in meeting appropriate good manufacturing practice (GMP) requirements to assure consistent product quality.

The Audit Guideline is applicable whenever an excipient manufacturer or subcontractor is audited. It is intended to have international application, bearing in mind that production of pharmaceutical excipients covers a diverse range of different industries and processes which often have uses other than pharmaceutical applications. Although the audit may include other areas such as delivery logistics and order processing, the Audit Guideline is intended only to cover aspects of GMP relating to excipient manufacture. For auditing of repackagers or distributors, see the IPEC *Good Distribution Practices Audit Guideline for Pharmaceutical Excipients.*

II. Content and Usage

The Joint IPEC-PQG "*Good Manufacturing Practices Guide for Pharmaceutical Excipients*"©2006 was used as the basis to construct the questions or reminder phrases contained in the Audit Guideline, and should serve as the primary source for evaluating responses provided by the auditee. The auditors should be familiar with the introduction, definitions, and general guidance that are contained within the IPEC-PQG GMP Guide, and should refer to the guide if further details are needed.

The Audit Guideline is intended to address the foundation of the requirements, and not all of the details, necessary to manufacture excipients in compliance with applicable GMPs. It may not include all of the appropriate questions or reminder phrases for a specific audit, nor may all of the points be appropriate to every audit. As an international document, it also cannot specify all national legal requirements, nor cover in detail the particular characteristics of every excipient. However, its use is intended for individuals experienced and competent in the area of auditing who should be diligent in selecting which areas of GMP are relevant to a particular audit and in determining the appropriateness of questions (and the answers provided) based on the characteristics of the excipient manufactured, the processes employed, and specific requirements of the excipient user.

III. Format

This Audit Guideline is provided in two formats, either of which may be used by the auditor based on personal preference:

- Detailed questions arranged in the same sequence as in the GMP Guide. This format is useful as a training tool for personnel of both the auditing company and one being audited.

- Short "reminder" phrases arranged in the same sequence as in the GMP Guide, a format which generally is more useful during an audit.

IV. Acknowledgements

This Guide was prepared by a team from The International Pharmaceutical Excipients Council (IPEC) and the Charted Quality Institute (CQI) Pharmaceutical Quality Group (PQG).

IPEC

IPEC is an international industry association formed in 1991 by manufacturers and end-users of excipients. It is an association comprising three regional pharmaceutical excipient industry associations covering the United States, Europe and Japan (which are known respectively as IPEC-Americas, IPEC Europe and JPEC). IPEC's objectives are to contribute to the development and harmonization of international excipient standards, the introduction of useful new excipients to the marketplace and the development of good manufacturing practice for excipients.

IPEC first published its GMP Audit Guide for Bulk Pharmaceutical Excipients in 1995 and it was revised in 2004 to align it with the revised 2001 GMP guide.

For further information see www.ipec.org

PQG

The PQG was formed in 1977 to promote development of a consistent approach to pharmaceutical quality and good manufacturing practice. The group has since expanded and is now incorporated within the United Kingdom's Charted Quality Institute.

In 1990 the PQG published three codes of practice to cover pharmaceutical raw materials, printed and contact packaging materials. In 1995 the codes were revised and were integrated into ISO 9002:1994. The code for raw materials was revised and reissued as PS 9100:2002 Pharmaceutical Excipients, an application standard and GMP guide for pharmaceutical excipients.

For further information see www.pqg.org

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JOINT GMP AUDIT GUIDELINE

FOR

PHARMACEUTICAL EXCIPIENTS

2008

Format: Detailed Questions in Sequence of the IPEC-PQG GMP Guide

GUIDELINE	NOTES
4 QUALITY MANAGEMENT SYSTEMS - EXCIPIENT QUALITY SYSTEMS	
4.1 General Requirements	
4.2 Documentation Requirements	
4.2.1 General	
4.2.2 Quality Manual Is there a Quality Manual and if so, what is the current version of it? If not, is there a suitable alternative? Is there a Quality Policy or a similar statement of the intent to meet excipient GMP requirements? Has the manufacturer defined the point at which GMP should be applied and maintained? How is a commitment to applying the appropriate GMPs expressed? How does it explain which activities are covered by the GMPs and which are not?	
4.2.3 Control of Documents	
Is there a list of Standard Operating Procedures (SOPs) for areas of the operation affecting quality?	
Does the document control system cover the complete written manufacturing instructions such as: • the quality and identity of raw materials, • equipment, • manufacturing flow, • operating parameters, • in-process sampling and testing, • equipment cleaning, • packaging materials, • labelling, and • documentation of each significant step?	
How are current documents made readily available to employees? (Standard Operating Procedures (SOPs), manufacturing instructions and test methods)	
Is there an SOP for writing, handling and updating SOPs?	
What is the procedure for periodic review of SOPs? Does it include update and approval by responsible personnel and is training performed after updates?	
How is conformance to SOPs verified and documented?	

GUIDELINE	NOTES
What is the system to assure that unneeded or obsolete documents are removed from use? Are only current versions of the documents being used?	
Are documents that impact product quality reviewed and approved by the quality unit or other designated qualified personnel independent from production?	
How are documents controlled (electronic and paper copies)? Are obsolete versions withdrawn from use? How are they identified? How are owners indicated?	
4.2.4 Control of Quality Records	
What is the system used to track, control, and maintain all records that relate to the requirements of the Quality System?	
How are unplanned process changes including critical process excursions documented?	
Where electronic signatures are being used, are they controlled to provide equivalent assurance to written signatures?	
Is the record retention policy justified and what is the rationale? Is this described in a written records retention policy?	
Is a copy of the product label retained with the batch record?	
Are the records legible, indelible, signed, dated and kept in a suitable environment to minimize deterioration or damage?	
4.3 Change Control	
Are there adequate written procedures for a change control system for those changes that may have an impact on the quality of the excipient or their conformance to GMP? Does it include review and approval of changes to raw materials, processes, documents, and equipment?	
Does a unit independent from production (e.g. the Quality Unit or Regulatory Affairs) have the responsibility and authority for the final approval of changes?	
If the company performs qualification and validation activities, does the change control system address the requirement to evaluate the impact of a change on these records?	
Does the change control system require consideration for notifying customers or regulatory authorities?	
How does the change control system link to any DMF or CEP submissions?	
Is a log of changes maintained?	
5. MANAGEMENT RESPONSIBILITY	
5.1 Management Commitment	
How has Management demonstrated the importance of customer satisfaction and compliance? Is it documented in a formal statement such as a corporate Quality Policy?	

GUIDELINE	NOTES
5.2 Customer Focus	
What is the policy for accommodating customer audits of the facility?	
How are customer requirements determined and translated into the Quality System?	
5.3 Quality Policy	
What evidence is there that all personnel are aware of the Policy?	
Does the policy support continual improvement of the quality management system?	
5.4 Planning	
5.4.1 Quality Objectives	
What measurable objectives have been established for conformance to the Quality System and GMP requirements?	
5.4.2 Quality Management System Planning	
What process is there for identification of adequate resources needed for adherence to GMP?	
Is there any observable evidence that adequate resources have not been provided?	
5.5 Responsibility, Authority and Communication	
5.5.1 Responsibility and Authority	
What means are used to show the independent reporting relationship between the Quality Unit and Production?	
Are there organization charts?	
Are there clearly written job descriptions?	
Where are the Quality Unit's authority and responsibilities clearly defined in writing?	
What documentation supports the Quality Unit’s independent authority to approve or reject procedures, specifications, and process changes that potentially impact product quality?	
What documentation shows the Quality Unit has independent authority to reject raw materials, packaging components and finished batches?	
When the responsibilities of the Quality Unit that have been delegated to other personnel, what controls have been put in place to ensure their proper implementation?	
What role does the Quality Unit play in investigating deviations, failures and complaints?	
How does the Quality Unit document their approval or rejection of new suppliers of quality critical materials and services?	

GUIDELINE	NOTES
How does the Quality Unit exercise their responsibility for the review of appropriate manufacturing documentation and batch disposition decisions?	
5.5.2 Management Representative	
How often does the management representative report on the conformance of the Quality System to top management?	
5.5.3 Internal Communication	
How are GMP and regulatory requirements, quality policies, quality objectives and procedures communicated throughout the organization?	
How is top management informed of quality critical situations?	
5.6 Management Review	
5.6.1 General	
Does top management hold periodic reviews to confirm continued conformance to the Quality System?	
How is top management involvement in the Review demonstrated?	
How are the opportunities for improvement and the need for changes captured, reviewed, implemented and recorded?	
5.6.2 Review Input	
Does the input to the management review include, for example, audit results, customer complaints and feedback, product conformity, process performance, status of corrective and preventive actions and relevant regulatory / legislation changes?	
5.6.3 Review Output	
Does the review output address resources needed for improvement of the Quality System and define actions to be taken?	
6 RESOURCE MANAGEMENT	
6.1 Provision of Resources	
Does there appear to be adequate resources to perform and supervise the operations necessary for producing, packaging, testing, storing and releasing excipients in compliance with applicable GMP requirements?	
6.2 Human Resources	
6.2.1 General	
How are qualifications (training, experience and education) documented and related to the assigned tasks?	

GUIDELINE	NOTES
If used, who reviews the qualifications of consultants and contractors to assure they have sufficient education, training, and experience to advise on the subject for which they are retained?	
Are consultants and contractors appropriately trained before being allowed into the facility?	
6.2.2 Competence, Awareness and Training	
Is there an SOP for identifying training needs and providing the necessary training on a regular basis?	
What are the qualifications for individuals performing GMP training?	
Are job-specific training requirements clearly defined?	
How does the training programme ensure that personnel understand that deviations from procedures may have an impact on the customer's product quality?	
Is there personal hygiene training for personnel handling product so they understand the precautions necessary to prevent the contamination of the excipient? How is it documented?	
What records are kept to demonstrate that GMP training is conducted in a timely manner for new and temporary employees as well as consultants and contractors?	
What is the frequency of continuing GMP training and is it sufficient to ensure that employees remain familiar with applicable GMP requirements? How broadly is the training conducted within the site?	
How are training effectiveness and employee competency assessed?	
How are training and qualifications documented for each employee?	
How are changes in regulatory requirements monitored, interpreted, and communicated to employees?	
6.2.3 Personnel Hygiene	
How are personnel hygiene requirements and protective equipment specified and communicated to employees?	
Are personnel observed to comply with requirements for cleanliness, special clothing, protection, and hair coverings as required in the various manufacturing, packaging and testing areas? Is there appropriate signage for such requirements?	
Are personnel required to report any health conditions that may have an adverse effect on the product?	
Are personnel with illness or open skin lesions that may contaminate or otherwise adversely affect the safety or quality of the product allowed to work in any operation that could cause the product to become contaminated?	

GUIDELINE	NOTES
Is there a policy prohibiting loose and/or unsecured jewellery or other items in operations where they can fall into the product? Are personnel observed to be in compliance?	
Where can lab and operating personnel store and consume food, beverage, or tobacco products? Are these locations designated and separate from production areas?	
What measures within the facility have been taken to prevent unauthorized and unescorted access to critical processing operations and other sensitive areas?	
6.3 Infrastructure (Facilities and Equipment)	
6.3.1 Buildings and Facilities	
Are there adequate space and environmental controls to ensure product integrity and to preclude mix-ups or cross-contamination, especially in drying, milling, blending, packaging and warehousing operations?	
Where the excipient is exposed, are there adequate measures to prevent contamination including microbial?	
What other materials are produced or stored in close proximity to excipient production or where it is exposed to the environment? Does the facility use or produce highly sensitizing or toxic substances? If so, what controls are used to prevent cross-contamination of the excipient? What evidence is there that these measures are effective?	
Are facilities maintained in a good state of repair?	
Are there adequate laboratory facilities to perform required testing?	
Is there adequate space around finished excipient locations in the warehouse to facilitate cleaning?	
6.3.2 Equipment	
How is equipment commissioned prior to initial use?	
Is equipment maintained in a good state of repair?	
If processing occurs outdoors what controls are in place to minimize risk to excipient quality?	
6.3.2.1 Equipment Construction	
Is equipment constructed so that product-contact surfaces are not reactive, additive, or absorptive and will not adversely affect the product?	
Is equipment designed and used in a manner that minimizes the potential for contamination of product with lubricants, coolants, metal or seal fragments, or other extraneous materials?	

GUIDELINE	NOTES
If product exposure to, or contamination with, lubricants or coolants is possible, are these materials suitable for use in food applications?	
What provisions are made for monitoring the product for metal etc. contamination where appropriate?	
How is the equipment designed, where necessary, to minimize the possibility of contamination from operator contact in operations such as unloading of centrifuge bags, use of transfer hoses, and operation of drying equipment and pumps?	
6.3.2.2 Equipment Maintenance	
Is there a system for cleaning, inspecting and approving equipment for use in manufacturing after maintenance and repairs have been performed?	
Are there SOPs and appropriate documentation for inspection (monitoring the condition) and maintenance of equipment and for measuring and test instruments? Do the SOPs assign responsibilities; include schedules; describe methods, and equipment, and materials to be used?	
Are records kept of preventive maintenance, repairs, and use?	
6.3.2.3 Computer Systems	
If computerized systems are used in a manner that can impact excipient quality, have they been demonstrated to consistently function as expected?	
What process is used to control changes to systems and programs that can have an effect on the quality of the product (see 4.3), to assure that changes receive the proper review and approval with regard to potential effects before being instituted and that only authorized personnel can make such changes? Are personnel trained subsequent to changes?	
How is access to computerized systems limited in order to protect records from tampering, and prevent data alteration?	
If passwords are used as a security measure, are there provisions for periodic changing of passwords? Are there designees for all critical system operations and emergencies?	
What is the procedure for reviewing and updating security access when a person leaves the department or company? Is their access to the system or their access codes to the system revoked in a timely fashion?	
What backup systems are in place, such as copies of programs and files, duplicate tapes, or microfilm, and has retrievability of information from master tapes and backup tapes been verified? Are there procedures in place for disaster recovery, in the event of a power outage, loss of server and computerised systems etc?	
6.3.3 Utilities	

GUIDELINE	NOTES
Which utilities are used in the production, storage or transfer of materials that could impact excipient quality? How have these utilities been assessed and appropriate action taken to assure they do not contaminate the excipient?	
6.3.4 Water	
If water is used in the manufacture of the excipient, what is its source and is it suitable for its intended use?	
If water is used where it could contaminate the excipient, does process water at a minimum meet WHO guidelines for drinking (potable) water quality? Is there an internal written specification for process water?	
Where water can impact excipient quality: • How is process water periodically monitored for chemical and microbial quality? • Is the process water supplied under continuous positive pressure or are other means used to prevent back flow? • Where the water is purified on-site, are there chemical and microbial quality standards and action limits for such water, with an established monitoring program? • Where the water is purified, is the purification system periodically sanitized and appropriately maintained? • If chemical or microbial action limits for process or purified water are exceeded, how is the cause investigated, the problem corrected, the impact of the contamination of products manufactured with the water assessed, and the results of the investigation documented?	
6.4 Work Environment	
Are exposed materials protected from overhead contamination?	
Are production areas that present potential for contamination properly controlled and equipped with exhaust or other appropriate systems, including prevention of microbial contamination?	
6.4.1 Air Handling	
Has the effectiveness of air handling systems used to protect the excipient been demonstrated to provide such protection?	
If air is recirculated to areas where product is exposed, is it filtered and controlled to eliminate cross-contamination? Are such filters periodically checked and replaced and where is this documented?	
6.4.2 Controlled Environment	

GUIDELINE	NOTES
Is the manufacturing environment appropriately controlled for the process taking place to protect the excipient against deterioration and contamination? How is it monitored?	
If a special environment is required, is it continuously monitored?	
In the event of an interruption to the special environment, is the impact upon the quality of the excipient evaluated and documented?	
6.4.3 Cleaning and Sanitary Conditions	
Are facilities maintained in an appropriately clean, sanitary and orderly manner?	
Where excipient quality can be adversely impacted, are there adequately detailed SOPs for sanitation and cleaning? How is compliance monitored and documented? Do the SOPs assign responsibilities; include schedules; describe methods, equipment, and materials to be used; and require maintenance of records?	
How is waste segregated and storage containers identified? What is the frequency of disposal?	
Has the manufacturing environment been evaluated for the potential for contamination by physical or chemical materials or by microbes in the area?	
6.4.4 Pest Control	
Where necessary, is there a program to protect quality critical materials and product from contamination due to insects, rodents, birds, and other vermin (including domestic animals)? What evidence is there to show that it is adequate?	
Where necessary, how are windows, doors, or other openings to the outside adequately protected from entry by pests? If raw materials or intermediates are stored in silos, tanks, or other large containers, how are the vents adequately protected to prevent entry of birds and insects?	
If used, are rodenticides, herbicides and pesticides appropriately evaluated?	
If an outside party performs pest control, how is that party's performance and compliance monitored? Does the party use a site map and issue a report? Is the report reviewed by the manufacturer?	
Are pest control records kept? What corrective and preventive measures have been taken?	
If the nature of raw material (such as botanicals) results in unavoidable contamination, what are the controls to prevent the increase or spread in contamination or infestation?	
6.4.5 Lighting	
Is there adequate lighting?	

GUIDELINE	NOTES
Is the lighting protected from shattering in areas where the product may be exposed?	
6.4.6 Drainage	
Where the excipient is open to the environment, are drains of adequate size? Are they equipped with an air break or other mechanism to prevent back flow?	
Is the plumbing system free of defects that could cause contamination of the excipient?	
6.4.7 Washing and Toilet Facilities	
Are there adequate hand washing, drying and sanitizing facilities at appropriate locations in the plant? Are all in good repair? Do they provide hot and cold water, soap or detergent, and have air dryers or single service towels?	
Are there clean, readily accessible toilet facilities that are maintained in good repair?	
Are there facilities for showering and/or changing clothes?	
7 PRODUCT REALIZATION	
7.1 Planning of Product Realization	
Is a process flow diagram or other suitable description of the process steps available for the audited products?	
Is the unit operation batch or continuous or a combination of the two?	
Is the excipient produced in equipment dedicated to its manufacture or is the equipment also used for other products?	
Has the process been fully described regarding: • reactions, • purifications, • critical steps, • operating parameters, • process limitations, • impurities, • key tests needed for process control, • product specifications, • sampling plans, and • test and release procedures?	
Have process parameters critical to quality been defined, and if parameters are exceeded, is the affect on quality known?	

GUIDELINE	NOTES
Is there a system for identifying major equipment, instruments, and production lines? Is this information included in batch production and control records where appropriate?	
7.2 Customer-Related Processes	
7.2.1 Determination of Requirements Related to the Product	
Is there a system to determine customer requirements related to the product and supply of the product?	
How does the manufacturer communicate the agreed customer requirements to the appropriate personnel?	
7.2.2 Review of Requirements Related to the Product	
Is there a procedure in place to assure that the manufacturer and the customer have mutually agreed upon the specifications and other requirements? If not, what is the alternative process?	
7.2.3 Customer Communication	
Is there a system to assure that any mutually agreed customer-initiated changes are promptly incorporated?	
Is there an adequate system in place to assure that significant process changes, including the use of subcontractors and their effect on the excipient are communicated to the customer?	
7.3 Design and Development	
How are design and development activities translated into plans for manufacturing?	
7.4 Purchasing	
7.4.1 Purchasing Process	
What is the program to qualify or disqualify suppliers of raw materials, packaging components and services that might affect quality, and to verify that they have capability to consistently meet agreed-upon requirements?	
Does this program include periodic audits by qualified auditors (or other verification techniques) of suppliers when deemed necessary?	
What is the program for the evaluation and approval of subcontractors?	
Does this program include periodic audits of subcontractors?	
What system is in place to follow up on corrective actions for audit findings for suppliers and subcontractors?	
Are materials purchased against an agreed specification? How is it ensured that materials are only purchased from approved suppliers?	

GUIDELINE	NOTES
Are materials purchased that might result in the excipient being at risk with regard to Transmissible/Bovine Spongiform Encephalothaphies (BSE/TSE), allergens, Genetically Modified Organisms (GMOs) etc?	
7.4.2 Purchasing Information	
Have the specifications, which were approved by the Quality Unit or their designee, for the raw material or packaging component been provided to the supplier for review and concurrence? What system is in place to assure that revisions to the specifications are provided on a timely basis to the supplier?	
What system is in place to assure that suppliers and subcontractors notify the company of significant changes?	
How are relevant contract manufacturers and laboratories notified of the requirement to adhere to appropriate sections of the IPEC-PQG Excipients GMP Guide?	
7.4.3 Verification of Purchased Product	
Are procedures in place covering the means to quarantine quality critical materials on receipt until they have been approved?	
Is sampling for release performed according to a plan that assures that the sample is representative of the batch? Are methods of sampling designed to prevent contamination and cross-contamination?	
Do bulk deliveries have additional controls to assure material purity and freedom from contamination (e.g. dedicated tankers, tamper-evident seals, certificate of cleaning, testing, and/or audit of the supplier)?	
Are there adequate written and approved instructions and specifications for quality critical material sampling and testing, including investigation of nonconforming results?	
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?	
If quality critical materials are accepted on COA, have suppliers been appropriately certified or qualified, including verification and periodic monitoring of the results on the COA?	
7.5 Production and Service Provision	
7.5.1 Control of Production and Service Provision	
7.5.1.1 Production Instructions and Records	
How is the execution of significant processing steps verified?	

GUIDELINE	NOTES
Are records available and readily retrievable for each batch of excipients produced and do they include complete information relating to the production and control of each batch? Do records include information such as: • date/time each step was completed, • identification of persons performing and checking each significant operation, • identification of major equipment and lines, • material inputs to enable traceability, • in-process and laboratory control results, • statement of yield, unless not quantifiable (e.g. as in some continuous processes), • inspection of the packaging and labelling area before and after use, • labelling control records, • description of sampling performed, • failures, deviations, investigations and • results of final product inspection?	
7.5.1.2 Equipment Cleaning	
If equipment is not dedicated, what other types of materials are manufactured in the same equipment? What controls are used to prevent cross-contamination and how have they been justified (e.g. model product)?	
Are there written cleaning procedures and do they contain sufficient detail to allow operators to clean each type of equipment in a reproducible and effective manner?	
For continuous processing: is the frequency of cleaning specified and justified?	
Are there data to show that cleaning procedures for non-dedicated equipment are adequate to remove the previous materials?	
Have cleaning procedures been demonstrated to be effective?	
Is there an adequate system for documenting cleaning and use of the equipment (e.g., a cleaning and use log)?	
Are utensils and sampling devices cleaned and stored in a proper manner to prevent contamination?	
If product is campaigned, is there an established interval between complete cleanings of the equipment and has it been justified?	
7.5.1.3 Recovery of Solvents, Mother Liquors and Second Crop Crystallizations	
Are recovered solvents re-used in the same step of the process or can they be used in other processes?	

GUIDELINE	NOTES
If fresh and recovered solvents are commingled, are the recovered solvents sampled and assayed and found to be satisfactory prior to commingling? How is the quality of commingled solvents monitored on an established schedule?	
If secondary recovery procedures are performed on mother liquors or filtrates, how are the recovered materials shown to meet applicable specifications? Are these recovery procedures written? How is traceability maintained?	
7.5.1.4 In-Process Blending/Mixing	
Are there defined blending/mixing parameters?	
Where finished product is blended or mixed, how has the reproducibility of the blending or mixing process to ensure homogeneity been demonstrated?	
Is the blending/mixing equipment completely emptied between batches or between campaigns? If not what controls are applied?	
Are nonconforming batches blended or mixed with other lots that do conform to specifications?	
How are tailings or partial containers of excipient handled?	
7.5.1.5 In-Process Control	
How is process control assured? For example, are there approved instructions, set-points, limits, and specifications, where appropriate, for such items as at- and in-line testing, failure investigation, process controllers, etc.?	
Are in-process samples taken and test results recorded? How are in-process samples disposed of (not returned to production for incorporation into the final batch)?	
Have personnel performing in process testing been trained and is the training documented?	
Do manufacturing instructions describe how to use in-process control data to control the process? Have actions to be taken when the results are outside specified limits been defined?	
What is the fate of materials that fail to meet specifications or are produced when the process has been demonstrated to be outside specified limits?	
7.5.1.6 Packaging and Labelling	
Is there a written procedure for clearing the packaging area after each packaging operation, and cleaning before the next operation, especially if the area is used for packaging different materials?	

GUIDELINE	NOTES
Do procedures require excess labels to either be immediately returned to controlled storage or destroyed? Are excess labels with batch numbers destroyed?	
How are labels controlled?	
Is there an SOP for the receiving, reviewing, handling, storage, issuance, and accountability of pre-printed labels?	
If labels are printed as needed, what system is used to verify the accuracy of the labels?	
Is there a procedure to ensure that the printed labels contain the correct information?	
7.5.1.7 Records of Equipment Use	
How is the sequence of activities for each piece of equipment demonstrated i.e. production, maintenance and cleaning?	
7.5.2 Validation of Processes for Production and Service Provision	
How has the current process been shown to be capable, i.e., has it been demonstrated to operate consistently to produce final material that meets established specifications from batch-to-batch?	
What techniques are used to demonstrate ongoing process capability? How is it reviewed? What determines the need for revalidation?	
7.5.3 Identification and Traceability	
7.5.3.1 Traceability	
Is there a system in place to trace quality-critical materials back to their original manufacturers?	
Is an identification code associated with each lot of incoming quality-critical material to enable traceability in the manufacturing operation?	
Are batch / lot numbers assigned such that they are not duplicated and enable tracing of all processes and batch records for each batch?	
If processing is on a continuous basis, how is a batch defined? Is the timeframe during which a particular batch of quality-critical material processed through the plant documented?	
If a new lot number is assigned to a reprocessed lot, can it be traced to the original batch?	
If multiple sites produce this material, how can the manufacturing site be determined?	

GUIDELINE	NOTES
7.5.3.2 Inspection and Test Status	
Are quality-critical materials approved before being used in production? Have requirements been defined for continuously fed quality-critical materials?	
What controls are exercised to assure that quality-critical materials are not used in a batch prior to release by the Quality Unit?	
How are containers and equipment labelled to clearly identify the contents and, if appropriate, the stage of manufacture?	
What system is used to identify the status of all quality-critical materials, intermediates and finished products?	
If filled unlabelled containers are set aside for future labelling, is there sufficient identification to determine chemical identity, quantity, lot number, and other information needed for traceability?	
Is there an effective system for monitoring and retesting or re-evaluating stored quality-critical materials to assure that they are not used beyond their recommended expiration or use date?	
Are quarantine procedures established with designated areas, labels, or with a suitably controlled computer system?	
7.5.3.3 Labelling	
Does the final product label contain adequate information to identify the contents, quantity, batch number, and manufacturer?	
If special storage conditions are necessary based on the results of stability testing, are they specified on the label?	
7.5.4 Customer Property	
If a customer supplies materials for incorporation into the customer's excipient, what systems and procedures are in place for handling such materials, including verification, storage, maintenance, and accountability for loss or damage?	
How are materials supplied to the excipient producer by the customer handled?	
Is there a technical or commercial agreement in place to ensure the confidentiality of any intellectual property provided by the customer? How is this controlled by the excipient manufacturer?	
7.5.5 Preservation of Product	
7.5.5.1 Handling, Storage, and Preservation	
Is the warehouse clean and well organized, and materials easily located? Is there adequate space for pest control and housekeeping?	

GUIDELINE	NOTES
Does the excipient manufacturer have any scientific evidence (e.g. stability data) to indicate the acceptable conditions for the storage of the excipient? Is it known whether control of humidity, temperature, or protection from light etc. is necessary to protect the excipient? Are these controls in place? Are appropriate records in place to demonstrate the implementation of these controls?	
Where raw materials or intermediates are stored in silos, tanks or other large containers, how is the dispensing of such materials monitored for appropriate accuracy?	
If materials are stored outside, do the containers give acceptable protection to the contents? Are labels indelible? Are such containers cleaned before their contents are subjected to further processing?	
How is stock rotation managed (e.g. First in First out; First expired First out)?	
7.5.5.2 Packaging Systems	
What documentation supports the use of the container/closure system, demonstrating that it is adequate to protect product from deterioration and contamination and that it does not alter the excipient beyond its specifications?	
How are product containers and closures handled and stored in order to protect them from contamination and deterioration, and to prevent mix-ups?	
If returnable excipient containers are reused, are they cleaned using appropriate cleaning procedures and inspected before use? Are previous labels removed or defaced?	
If trucks or railroad cars are used to transport product, where is the cleaning of the trucks and cars documented? Is there a record of the previous product in the truck or railroad car?	
For non-dedicated trucks and railroad cars, how is it assured that there are no objectionable residues from prior materials?	
Are all trucks and railroad cars inspected before being filled with product?	
Are tamper-evident seals used where possible, including on trucks and railroad cars?	
7.5.5.3 Delivery and Distribution	
Are adequate distribution records maintained for all product shipments?	
Do shipping records allow traceability of the batch to specific consignees and vice versa in case of a retrieval?	

GUIDELINE	NOTES
Is there an SOP for conducting a product retrieval or market withdrawal? How and when was the procedure last verified?	
7.6 Control of Measuring and Monitoring Devices	
Are there procedures for calibration of quality-critical equipment and for measuring and test instruments? Do the procedures assign responsibilities; include schedules; describe methods, equipment, and materials to be used, including standards traceable to national standards; define re-calibration frequency and limits for accuracy and precision and require maintenance of records?	
If calibration operations are performed in-house, do the procedures specify handling and storage conditions for the traceable standards?	
Is there a procedure specifying that equipment and instruments cannot be used if they are beyond the calibration due date?	
What actions does the calibration procedure describe to be taken if measurements done using equipment or an instrument that is subsequently found to be beyond the due date or is out of calibration limits, and does it require documentation of such actions?	
How is the current calibration status of quality-critical instruments and equipment known to users?	
Where are records or logs maintained for calibration operations?	
What is the system for routine verification that such equipment as scales, pH meters, and HPLC perform as designed?	
8 MEASUREMENT, ANALYSIS AND IMPROVEMENT	
8.1 General	
Do monitoring and measuring activities include the Quality System as well as parameters that define excipient quality?	
8.2 Measurement and Monitoring	
8.2.1 Customer Satisfaction	
How is customer satisfaction determined? Are parameters such as customer complaints and return of excipients covered?	
Does analysis of customer satisfaction drive improvement activities?	
8.2.2 Internal Audit	
Is there an internal quality audit programme that covers all areas of the operation to verify that SOPs and other procedures and policies are being followed, and to determine effectiveness of the Quality System? Are audits performed at specified intervals? Are audits scheduled on the importance and status of the activity performed?	
Are internal audits documented?	

GUIDELINE	NOTES
Are management personnel aware of the audit findings and the corrective actions to be taken?	
Are necessary steps taken to correct any areas of non-compliance based on the findings and recommendations of the internal audits? Who is responsible for implementing the corrective actions?	
How are corrective actions documented?	
Do follow-up audit activities include verification of the effectiveness of corrective actions?	
8.2.3 Measurement and Monitoring of Processes	
Are critical process control points and product characteristics under control? Are appropriate techniques applied to verify this?	
Are there documented procedures defining the implementation and control of these techniques?	
What monitoring occurs of the management system process and process failures?	
How are out-of-trend results and deviations noted? What actions are taken when these happen?	
8.2.4 Measurement and Monitoring of Product	
Are test methods documented?	
What evidence is there that the test methods are fit for purpose?	
If the excipient is claimed to be compliant to compendial requirements, are the test methods those defined in the applicable pharmacopoeia? If not has the test method been shown to provide equivalent results?	
Is there an adequate system for reviewing and implementing compendial changes?	
Are periodic reviews of product quality and conformance measures conducted?	
8.2.4.1 Laboratory Controls	
Do laboratory records contain: • a sample description, • batch number, • date sample was taken, • test method reference(s), • raw data, • calculations, • test results and their comparison to specification, and • identity of analyst(s) and the date each test was performed,	

GUIDELINE	NOTES
Are reagents and solutions properly labelled? Are they traceable to records describing their preparation? Do they have an expiry date indicated? Is there a procedure in place for these activities? Are there records of any standardization?	
Are reference standards properly labelled and stored in a manner to protect them from deterioration? Are Certificates of Analysis from suppliers of primary reference standards available? Is there a procedure for qualification of secondary reference standards including definition of the requalification period?	
8.2.4.2 Finished Excipient Testing and Release	
Are there complete written and approved instructions for performing testing of final product that specify methods, equipment, operating parameters, and acceptance specifications?	
How does the Quality Unit perform batch release including review of appropriate manufacturing, packaging, labelling, and testing records before batches are released for sale?	
Is every batch tested to the full specification before shipment? If not, has the use of reduced testing been justified? Is it approved before shipment?	
What controls are applied to assure that the excipient conforms to the documented specifications when the excipient is manufactured using a continuous process?	
8.2.4.3 Out-of-Specification Test Results	
Is there an SOP for investigation of Out-of-Specification (OOS) results and retesting, including a target time frame for completing investigations?	
How are the results evaluated? Under what conditions may an OOS result be discounted?	
If statistical methods are used in the evaluation of an OOS are they documented in the relevant SOP?	
Are investigations completed and matters resolved before batch release?	
Has the impact of OOSs on laboratory operations, other equipment, batches, products, etc. been considered?	
8.2.4.4 Retained Samples	
Are retained samples kept for every batch for an appropriate interval? How is this interval defined? Does it relate to the expiry or retest interval assigned to the excipient? Is this documented?	

GUIDELINE	NOTES
Is the retained sample size at least twice the amount required to perform all specification testing?	
Are retained samples appropriately packaged and stored?	
8.2.4.5 Certificates of Analysis	
Does the excipient manufacturer provide certificates of analysis (CofA) for each batch? Do they comply with recognized guidance?	
Does the CofA contain sufficient information for the intended use of the excipient?	
How are the results determined for each test reported on the CofA? Is skip lot testing performed and indicated?	
8.2.4.6 Impurities	
Are impurities known and limits established? Have appropriate safety data, requirements of official compendia and/or sound GMP considerations been considered in establishing those limits?	
Are manufacturing processes adequately controlled in order to avoid exceeding such limits?	
Is testing performed on the finished material for residual solvents (especially those used in crystallization and final washes) if used in the process? Are these results included on the CofA?	
8.2.4.7 Stability	
Is stability or historical data available to support the recommended storage conditions?	
If an expiration / re-evaluation interval has been assigned how is this interval determined? Was it based on data from a stability study on this product or a similar product ("model product" approach)?	
If a "model product" approach is followed, is there a scientifically sound and documented rationale for the selected products?	
Is there a written stability program, approved by the Quality Unit that specifies sample size, storage conditions, testing intervals, and tests to be performed?	
Does the container used in stability testing simulate the market container?	
Are assay methods for stability testing stability-indicating?	
How are stability data reviewed and trends monitored, adverse trends addressed, and appropriate management notified?	

GUIDELINE	NOTES
8.2.4.8 Expiry/Retest Periods	
Is an expiration or re-evaluation date assigned to the material? If so, what is it? Where is it listed in order to inform the customer?	
8.3 Control of Nonconforming Product	
Is there a procedure for determining the fate of final product that fails to meet specifications (e.g., reprocessing, downgrading to a lesser grade, release with agreement of the customer, destruction)?	
What records are maintained of nonconforming product, related investigations and corrective actions?	
How are nonconforming products clearly identified and segregated to prevent unintentional usage or sale?	
If product is to be destroyed, is it tracked, controlled, and destroyed in a timely and appropriate fashion? Are records of such destruction maintained?	
Is there a procedure that describes how an excipient can be retrieved from distribution? Are records kept of such activities?	
8.3.1 Reprocessing	
If reprocessing (repeating steps that are already part of the normal process) is performed, where are complete written instructions found including any additional testing that may be required?	
8.3.2 Reworking	
If reworking (performing steps that are not part of the normal process) is performed, is there a documented review of risk to excipient quality and approval by the Quality Unit?	
If reworking is performed, are there sufficient investigation, evaluation and documentation to assure that the final product is at least equivalent to other acceptable product, meeting all established standards, specifications and characteristics? Is the impact on stability, impurities, etc. considered and are appropriate controls applied for these issues?	
Are individual non-conforming batches blended with others?	
8.3.3 Returned Excipients	
Is there a procedure for handling returned goods, including proper identification, segregated storage, testing, and Quality Unit involvement in the evaluation and determination of their fate?	
Where are records of returned goods maintained and do those records include the appropriate information?	
If returned goods are to be reprocessed or disposed of, is it done according to a procedure, with Quality Unit involvement? Where is it documented?	

GUIDELINE	NOTES
8.4 Analysis of Data	
Is the effectiveness of the Quality Management System evaluated?	
What measures are used and what data is considered to perform this analysis?	
Are there periodic reviews of key indicators? What are these indicators?	
8.5 Improvement	
8.5.1 Continual Improvement	
What inputs drive continual improvement activities? How are these managed?	
What procedures are established for investigation of nonconforming products, returns, complaints, etc.? How are these causes determined and how are appropriate parties, including management, notified?	
8.5.2 Corrective Action	
Are procedures for corrective actions implemented to address the root causes of nonconforming products, returns, and complaints?	
Are there procedures in place to cover how customer complaints, retrievals etc. are received and what actions are taken?	
8.5.3 Preventive Action	
Are procedures for preventive actions implemented to address problems at a level corresponding to the risk?	

The International Pharmaceutical Excipients Council
Pharmaceutical Quality Group

JOINT GMP AUDIT GUIDELINE

FOR

PHARMACEUTICAL EXCIPIENTS

2008

Format: Reminder Phrases in Sequence of ISO 9001:2000 Clause Headings

GMP SECTION	ITEM	COMMENTS
4 QUALITY MANAGEMENT SYSTEMS-EXCIPIENT QUALITY SYSTEMS		
4.1 General Requirements		
4.2 Documentation Requirements		
4.2.1 General		
4.2.2 Quality Manual	• Quality Manual • Quality Policy • GMP starting point	
4.2.3 Control of Documents	• Written manufacturing instructions • Process fully described • Verification of significant steps • SOP availability and control • Periodic review of SOPs • Electronic control	
4.2.4 Control of Records	• Record retention SOP • Good Documentation Practices	
4.3 Change Control	• Change control procedure • Control of production changes • Independent approval of changes • Impact on qualification or validation • Change control log • Notification to customers and regulatory authorities	
5. MANAGEMENT RESPONSIBILITY		
5.1 Management Commitment	• Commitment to customer satisfaction • Commitment to GMP compliance	
5.2 Customer Focus	• Customer requirements • Customer audit policy	
5.3 Quality Policy	• Policy deployment, management support • Continual improvement	
5.4 Planning	• Measurable conformance objectives	
5.4.1 Quality Objectives	• Conformance objectives	
5.4.2 Quality Measurement System Planning	• Adequate resources	

GMP SECTION	ITEM	COMMENTS
5.5 Responsibility, Authority and Communication		
5.5.1 Responsibility and Authority	• Reporting relationship of Quality Unit and Production (organisation charts) • Job descriptions • Clarity of Quality Unit authority and responsibilities, delegation • Batch release	
5.5.2 Management Representative	• Periodic conformance reports to top management	
5.5.3 Internal Communication	• Quality System communication • Top management notification of quality-critical issues	
5.6 Management Review		
5.6.1 General	• Senior management Quality System review	
5.6.2 Review Input	• Defined	
5.6.3 Review Out	• Resources and improvements identified	
6. RESOURCE MANAGEMENT		
6.1 Provision of Resources	• Adequate resources	
6.2 Human Resources		
6.2.1 General	• Education, training and experience • Consultant qualifications	
6.2.2 Competence, Awareness and Training	• Adequate training experience and qualifications • Training SOP • Training programme • Trainer qualifications • GMP training records • GMP training frequency • Measure of training effectiveness • Communicating changing regulations	
6.2.3 Personnel Hygiene	• Personal hygiene training • Clothing • Reporting of illness • Loose items like jewellery and pens • Consumption of food, beverage, and tobacco products • Access controls	

GMP SECTION	ITEM	COMMENTS
6.3 Infrastructure (Facilities and Equipment)		
6.3.1 Building and Facilities	• Space • Contamination control • Toxic products • Environmental controls, • Laboratory facilities • State of repair	
6.3.2 Equipment	• Commissioning • Maintenance • Outdoor equipment	
6.3.2.1 Equipment Construction	• Contact surfaces • Lubricants coolants etc • Design to minimise contamination	
6.3.2.2 Equipment Maintenance	• Procedures • Records • Hand over / hand back	
6.3.2.3 Computer Systems	• Access controls • Change controls • Consistent function • Back up, disaster recovery	
6.3.3 Utilities	• Risk of contamination	
6.3.4 Water	• Specification • Treatment and monitoring • Positive pressure / back flow	
6.4 Work Environment		
6.4.1 Air Handling	• Effectiveness • Recirculation	
6.4.2 Controlled Environment	• Required • Monitoring • Deviations	
6.4.3 Cleaning and Sanitary Conditions	• Appropriately clean • Procedures, schedules • Waste control	
6.4.4 Pest Control	• Free of infestation • Contractor controls • Records, review of effectiveness	
6.4.5 Lighting	• Adequate	

GMP SECTION	ITEM	COMMENTS
6.4.6 Drainage	• Adequate • Air break	
6.4.7 Washing and Toilet Facilities	• Adequate facilities • Clean	
7. PRODUCT REALIZATION		
7.1 Planning of Product Realization	• Process flow diagram • Critical parameters • Batch or continuous • Multi purpose • ID of equipment and lines	
7.2 Customer-related Processes		
7.2.1 Determination of Requirements Related to the Product	• Customer requirements • Agreed additional requirements	
7.2.2 Review of Requirements Related to the Product	• Mutually agreed specifications • Contract review	
7.2.3 Customer Communication	• Implementation of customer Requirements • Notification to customers of significant changes	
7.3 Design and Development	• Technology transfer	
7.4 Purchasing		
7.4.1 Purchasing Process	• Qualification and control of suppliers • Approved supplier list • Audit of key suppliers • Selection and control of subcontractors • Follow-up of audit corrective actions • Material specifications • BSE/TSE etc risks	
7.4.2 Purchasing Information	• Purchasing agreement • Supplier review of specifications • Supplier notification of significant change	
7.4.3 Verification of Purchased Product	• Procedures for approval and release • Quarantine • Sampling procedures and conditions • Testing / verification Bulk deliveries	

GMP SECTION	ITEM	COMMENTS
7.5 Production and Service Provision		
7.5.1 Control of Production and Service Provision		
7.5.1.1 Production Instructions and Records	• Controlled master batch instructions • Retrievable batch records • Suitable details	
7.5.1.2 Equipment Cleaning	• Dedicated or controls for cross-contamination • Cleaning effectiveness and justification • Documentation of cleaning • Storage of utensils and sampling device • Continuous processes, frequency of cleaning	
7.5.1.3 Recovery of Solvents, Mother Liquors and Second Crop Crystallizations	• Controls in place • Traceability	
7.5.1.4 In-Process Blending/Mixing	• Blending procedures • Defined blending parameters • Part containers / tails	
7.5.1.5 In-Process Control	• Program • Sampling procedures • Results recording • Control actions	
7.5.1.6 Packaging and Labelling	• Procedures • Label control • Mix up prevention	
7.5.1.7 Records of Equipment Use	• Sequence of activities	
7.5.2 Validation of Processes for Production and Service Provision	• Process consistency	
7.5.3 Identification and Traceability		
7.5.3.1 Traceability	• Material to their manufacturer • Material through production • Unique batch numbering	
	• Batch definition for continuous processing • Traceability of reprocessed material	

GMP SECTION	ITEM	COMMENTS
	• Origin of manufacturing site	
7.5.3.2 Inspection and Test Status	• Approval of materials and packaging • Controls for unapproved materials • Identification of containers and equipment • Status identification • Identity of unlabeled containers • Evaluation of raw materials beyond expiration or use date • Quarantine control	
7.5.3.3 Labelling	• Excipient labelling content • Special storage condition labelling	
7.5.4 Customer Property	• Procedures • Agreements for confidential information	
7.5.5 Preservation of Product		
7.5.5.1 Handling, Storage, and Preservation	• Appropriate conditions and records • Outside storage • Bulk storage dispensing • Stock rotation	
7.5.5.2 Packaging Systems	• Adequate protection to excipient • Storage of packaging components • Reusable packaging • Bulk container cleanliness • Bulk container seals • Tamper evident seals	
7.5.5.3 Delivery and Distribution	• Distribution records • Traceable to consignee • Retrieval or market withdrawal procedure	
7.6 Control of Measuring and Monitoring Devices	• Calibration procedures, records and status • Standards-handling and storage • Frequency and limits • Out of calibration actions	
8. MEASUREMENT, ANALYSIS AND IMPROVEMENT		
8.1 General	• Quality management processes	

GMP SECTION	ITEM	COMMENTS
8.2 Measurement and Monitoring		
8.2.1 Customer Satisfaction	• Measurements (e.g. complaints returns, feedback)	
8.2.2 Internal Audit	• Program, conducted; frequency • Audit documentation • Corrective measures • Verification of corrective actions	
8.2.3 Measurement and Monitoring of Processes	• Measurement of critical process control points • Use of appropriate techniques • Periodic review and actions	
8.2.4 Measurement and Monitoring of Product	• Documented test methods • Fit for purpose • Compendial methods used • Compendial changes • Periodic reviews of product quality	
8.2.4.1 Laboratory Controls	• Procedures and records • Reagents and standards	
8.2.4.2 Finished Excipient Testing and Release	• Quality Unit responsibility • Testing instructions • Release criteria • Continuous processes	
8.2.4.3 Out-of-Specification Test Results	• Procedure, records and actions	
8.2.4.4 Retained Samples	• Kept, size and storage • Retention period	
8.2.4.5 Certificates of Analysis	• Format and content • Alignment to specification • Skip lot testing	
8.2.4.6 Impurities	• Defined and controlled • Residual solvents	
8.2.4.7 Stability	• Data to support storage conditions • Determination of expiry/re-evaluation period • Stability programme • Container type • Stability-indicating method and parameters • Results review and actions	

GMP SECTION	ITEM	COMMENTS
8.2.4.8 Expiry/Retest Periods	• Defined and communicated	
8.3 Control of Nonconforming Product	• Procedure and records • Process for retrieval • Quarantine • Destruction records	
8.3.1 Reprocessing	• Reprocessing instructions	
8.3.2 Reworking	• Rework instructions • Excipient quality impact assessment	
8.3.3 Returned Excipients	• Procedure and records • Identified and quarantined	
8.4 Analysis of Data	• Measures of Quality Management System effectiveness • Types of data • Periodic reviews	
8.5 Improvement		
8.5.1 Continual Improvement	• Inputs that identify continual improvement opportunities	
8.5.2 Corrective Action	• Root cause analysis • Complaints	
8.5.3 Preventive Action	• Risk assessment	