GUIDANCE FOR THE APPROVAL OF SUPPLIERS OF RAW MATERIALS USED IN THE MANUFACTURE OF UNLICENSED MEDICINAL PRODUCTS

3rd Edition

November 2011

ACKNOWLEDGEMENT

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DISCLAIMER

This guidance has been produced by the above working group on behalf of the NHS Pharmaceutical QA Committee. This does not represent an NHS policy on supplier approval but rather aims to provide a consistent framework for individual NHS Trusts that hold a Manufacturers Specials License to base their local supplier approval procedures upon.

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CONTENTS

GUIDANCE FOR EVALUTING AND APPROVING SUPPLIERS OF STARTING MATERIALS USED FOR THE MANUFACTURE OF UNLICENSED MEDICINAL PRODUCTS

PURPOSE AND SCOPE

This document is intended to provide a guidance framework for NHS Specials' manufacturing activity for a consistent and risk-based approach to evaluate and approve suppliers of starting materials. The harmonised approach will allow sharing of information, within the NHS, and the development of the national database of supplier information.

Units accessing information on the database will need to recognise that the onus remains on them to establish that the level of approval is appropriate for their particular dosage form and taking into account any specific clinical need.

INTRODUCTION

Traditionally, the sourcing of raw materials, by NHS Specials' manufacturers, has been to procure material from a supplier who is able to supply an appropriate pack size, at an acceptable cost and with the availability of TSE certification to ensure regulatory compliance. The regulators now increasingly require manufacturers to have a greater understanding of the supply chain 'pedigree' and the associated risks.
This guidance document provides a risk-based strategy for the evaluation and selection of raw material suppliers. This strategy requires identification of potential supply chain risks without an undue increase in regulatory burden.
Combined with the harmonization of procurement strategy between NHS manufacturers, this approach will allow sharing of information and development of a 'national' approved strategy for raw material sourcing.

The supplier approval process must be supported by evidence of effective GMP compliance of the API manufacturing site(s). The regulatory expectation is often that this will be confirmed via audit of the API manufacturing site by or on behalf of the manufacturing unit. Audits should be conducted at intervals not exceeding three years, by persons with appropriate training and experience, to confirm the current GMP status of the site.
The conundrum faced by the Specials' manufacturer is the need to source materials of suitable quality, on-time delivery and in quantities suitable for small-scale manufacturing. It is recognized that majority of APIs are manufactured outside the EU and therefore there are financial constraints to audit manufacturers for each of the APIs, notwithstanding the manufacturer of API may not host an audit with a small scale manufacturer.
It must also be considered that Specials' manufacturers often source materials from distributors, brokers or repackers.

PROPOSED SUPPLIER EVALUATION AND SELECTION CRITERIA

In order to comply with regulatory requirements NHS Specials' manufacturing unit should have increased emphasis on purchasing controls for active pharmaceutical ingredients (APIs) and critical excipients. This will require implementation of appropriate levels of controls on suppliers, based on product risk and criticality.

The best suppliers should accept the new reality of increased transparency of the supply chain. Repackers, brokers and distributors who can establish and guarantee the level of quality assurance through rigorous auditing and supply chain verification will be invaluable for NHS manufacturers to meet the regulatory requirements.

The overall selection process for starting materials can be broken down into three stages – risk assessment, risk control and risk review. Information available and decisions made at each stage should be fully documented and justified. The factors to be considered and evaluated are outlined below.

Quality Risk Assessment

Supplier risk

- Experience of supplier
- Previous quality performance
- Security of supply (i.e Supply chain pedigree) – Transparency to at least first tier supplier e.g knowledge of repacker's supplier.
- Satisfactory PQQ or audit (see appendix 3 and 4)

Product Risk

- Starting material pedigree and intended use (see appendix 1)
- Service – delivery on time and in suitable pack sizes to meet clinical need

Quality Risk Control

- Material specification agreed with supplier
- Sampling and testing plan
- Quality and technical agreements
- Quality information – original manufacturers C of A, TSE certification, residual solvents etc

Quality Risk Review

Periodic Review of

- Supplier performance
- Effectiveness of quality system

Surveillance

- NHS National Database Information
- EDQM and FDA databases
- TSE status

INSPECTION, SAMPLING AND TESTING

The extent of sampling and testing should be determined by local QA . This will take into account qualification status of the supplier at local and 'national' level and dosage form to be manufactured.

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All ingredients for use in licensed manufacture must be approved before use by quality control. The level of testing will depend on a number of factors and will be defined locally. However tests can generally be placed within the following categories.

a. Visual inspection – On receipt, each container must be inspected for seal integrity, authencity of originator's labelling details and appearance (i.e damage)..

b. Sampling – there should be procedure that defines the number of samples to be taken in relationship to the size of the delivery and whether individual or composite samples

c. Identity (reduced testing)– With the exception of licensed medicinal products, CE marked 'devices' and unlicensed medicinal products from approved suppliers; representative sample(s) from each container or each batch should be tested for identity for each delivery..

The results of all other tests in the certificate of analysis will be evaluated .

d. Periodic (or skip-lot) testing – the extent of, analysis of individual and/or pooled samples would vary from partial monograph testing to full analysis. The level of testing will be influenced by probability of identifying adulteration by analytical means and /or whether these tests are performed by supplier.

e. TSE Status – The TSE status for all starting materials must be ascertained before they can be used in pharmaceutical preparation. There also needs to be a continuing robust documented system in place to provide sufficient assurance that each batch of starting material used is compliant with the regulations. For high risk products, reference to EDQM certificates should be required for each batch received. For other products, there should be reconfirmation process at least every two years for materials. A suitable template letter for establishing TSE status is included as Appendix 4.

RISK EVALUTION METHODOLOGY

RISK PRIORITY NUMBER (RPN) = SUPPLIER RISK NUMBER X MATERIAL COMPLIANCE RISK X MATERIAL /DOSAGE FORM RISK

SUPPLIER RISK NUMBER

1	Direct from manufacturer, large well respected western supplier
2	Ethical 3rd party supplier with well established change process, manufacturing qualification and audit program in place. GMP/ISO compliant manufacturer.
3	Supply through 3rd party, quality and technical agreement in place including change control over manufacturer. GMP/ISO compliant manufacturer
4	Ethical 3rd party supplier with well established change process, manufacturing qualification and audit program in place. Far eastern manufacturer
5	Direct from manufacturer, non EU/MRA source, limited reputation
6	
7	Supply through 3rd party, quality and technical agreement in place, including change control over manufacturer. Far eastern supplier
8	
9	Supply through 3rd party with no change process or qualification program, western manufacturer with limited quality history
10	Supply through 3rd party with no change process or qualification program, far eastern supplier

COMPLIANCE RISK NUMBER

1	MHRA approved site / FDA approved product and site
2	CEP with EDQM inspection / NHS audit with no major findings or satisfactory response concluding that the site meets the requirements of EU GMP
3	Approval from recognised regulatory authority i.e. Health Canada, Australian TGA, Japan, Swiss Medic *or* a detailed audit report performed by or on behalf of the supplying agent concluding that the site is compliant with EU GMP
4	DMF available, ISO registered, GMP certified by country of manufacture
5	3rd party audit report with no significant issues or satisfactory response
6	PQQ completed. No significant issues or satisfactory response
7	No regulatory data, some historical compliance data showing satisfactory performance
8	Audit or PQQ completed with outstanding issues
9	No regulatory data, ISO registration
10	No regulatory data, no inspection history

The supply history from the manufacturing / supply company can also be factored into this category and assignment of risk factor shaded depending on the history i.e. supplier complaints, delivery performance, quality issues, etc.

MATERIAL / DOSAGE FORM RISK

1	Raw material for “non-medical use” e.g. product used in diagnostics kit
2	Excipient for non sterile topical product
3	Excipient for non sterile oral liquid product
4	API for non-sterile topical product
5	API for non sterile oral liquid
6	API for sterile topical product / Excipient for sterile ophthalmic product
7	Excipient for other sterile product
8	API for sterile ophthalmic API for sterile i/v product, excipient for Aseptic product
9	API for Sterile Aseptic product
10	Intrathecal products

RISK PRIORITY NUMBER

CATEGORY	RPN	ACTION
1	<50	No further work, keep risk assessment on file
2	>50<125	Ensure regular quality risk review programme in place. If quality issues occur subsequently move to category 3
3	>125<200	Obtain further supplier information. Consider viability of access to audit report. Increased testing programme
4	>200	Consider alternative supplier and professional assessment of clinical risk

NHS Contact details: **NHS Address**
Direct Line
Direct Fax
Email

Date

Starting Material Supplier
Address

Dear Sir

TSE Status of Raw Materials used in the manufacture of Unlicensed Medicinal Products
(EU Commission Directive 1999/82EC)

As you are no doubt aware, legislation on the above came into force in the UK on 30 July 2003 (SI2003 No. 1680). The Regulations have been implemented within the NHS to protect our patients from TSE contamination.

I am therefore writing to you to ask if you could complete the attached document regarding TSE status and return it together with any related documentation.

The form has been devised by the NHS Pharmaceutical Quality Assurance Committee. It is intended that a summary of all replies will be placed on a central database and therefore this should prevent future duplication of effort for both the NHS and suppliers.

Many thanks

Yours faithfully

Name
Designation

Name of Starting Material: _____

Grade: _____

Supplier: _____

Supplier Reference Code: _____

1) Is this material manufactured by the supplier? Yes/No

- If NO, please state the manufacturer _____
- If NO, is the material repackaged by the supplier? Yes/No

(if not manufactured by the supplier please also forward questionnaire to manufacturer for completion)

2) Is the above material of animal origin? Yes/No

- If NO, please state whether the material is *vegetable / *synthetic (*delete as applicable)
- If YES, please provide information on the category of potential tissue infectivity, animal source, geographical BSE risk classification and ability of production process to remove or inactivate TSE agents* to enable a risk assessment to be undertaken. (* SI 2003 No.1680)

_____

_____

3) Has any animal material been used in the same processing plant? Yes/No

If YES, please provide details of validated segregation and/or clean down procedures in place?

_____

_____

_____

4) Does the above material have valid EDQM (European Directorate on the Quality of Medicines) Certification? Yes/No

- If YES, please forward certificate and/or provide certificate reference number:

_____

I certify that the above information is correct and that there will be no change to this status without our prior written notification.

Name: _____ Designation: _____

(Please print)

Signature: _____ Date: _____

On behalf of: _____ (Name of supplier/manufacturer)

NHS PHARMACEUTICAL QUALITY ASSURANCE COMMITTEE

SUPPLIER APPROVAL PRE QUALIFICATION QUESTIONNAIRE

All Yes / No answers to questions should be supplemented as follows:
If Yes, please give further details and if No, please give details of the alternatives in place

GENERAL INFORMATION (COMPANY CONTACT DETAILS)	
1.	**NAME - HEAD OFFICE (ADDRESS & CONTACT DETAILS)**
	OTHER SITES (ADDRESS & CONTACT DETAILS)
2.	**SIZE OF COMPANY & STRUCTURE OF COMPANY** **No. of personnel employed**

SUPPLIER PRE QUALIFICATION QUESTIONAIRE

COMPANY ACTIVITY		
1.	**Are all the materials which you sell approved for pharmaceutical use?**	
2.	**Does the company supply any materials manufactured elsewhere and supplied without further processing, packaging, etc?** **If so, give details**	
3.	**Are you a subsidiary of an organisation in which the majority of manufacture is from sites other than those listed on P1.**	
4.	**Does the company supply any materials bought in bulk and repackaged before distribution?** **If so, give details.**	
5.	**Does the company manufacture any of the materials supplied?** **Please list.**	

SUPPLIER PRE QUALIFICATION QUESTIONAIRE

SECTION 1
TO BE COMPLETED BY ALL SUPPLIERS

REGISTRATION		
1.	**Are you licensed by the MHRA or equivalent.**	
2.	**Give details of other company quality systems (e.g. ISO 9000).**	
3.	**Please give details of staff training programme.**	

CERTIFICATE OF ANALYSIS		
1.	**Will you supply an original Certificate of Analysis (or photocopies of the original) for each batch of material supplied?**	

COMPLAINTS/CUSTOMER RELATIONS		
1.	**What formal policy do you have for dealing with customers and for dealing with complaints.**	

SUPPLIER PRE QUALIFICATION QUESTIONAIRE

SECTION 1
TO BE COMPLETED BY ALL SUPPLIERS

SOURCES		
1.	**Please give details of the suppliers you have audited, if necessary on a supplementary page. What percentage of the total does this represent.**	

RECEIPT AND WAREHOUSING		
1.	**What checks are made on materials before they are received into stock.**	
2.	**What steps are taken to ensure that materials are adequately segregated, e.g. materials received, bonded, rejected or returned.**	
3.	**Is the environment in the warehouse controlled and monitored for temperature and humidity?** **Please give details.**	
4.	**Do you have a separate store for materials received and returned goods**	
5.	**Are systems in place to ensure correct goods are supplied?** **Please give details.**	

SUPPLIER PRE QUALIFICATION QUESTIONAIRE

SECTION 1
TO BE COMPLETED BY ALL SUPPLIERS

LABELLING AND TRANSPORT		
1.	**How do you transport your materials to your customers?**	
2.	**Are procedures in place to ensure product is labelled correctly and complies with e.g. COSHH Regulations?** **Please give details.**	
3.	**What is your standard delivery time from receipt of order.**	
4.	**Do you have a batch numbering system in place?**	

Completed by: **…….**

Position: **…….**

Date: **…….**

SUPPLIER PRE QUALIFICATION QUESTIONAIRE

SECTION 2
TO BE COMPLETED BY COMPANIES REPACKING MATERIALS SOURCED ELSEWHERE

PACKAGING		
1.	**Into what type of container do you pack your materials?**	
2.	**Are materials packed/produced in a controlled environment?** **Please give details.**	
3.	**Do you have a detailed line clearance procedure. If no, please give details of how this is controlled.**	

SUPPLIER PRE QUALIFICATION QUESTIONAIRE

SECTION 2 (cont'd)

QUALITY ASSURANCE/QUALITY CONTROL		
1.	**Are all products supplied tested to a documented specification. Does this include chemical tests.** **If so, give details.**	
2.	**Are copies of specifications available?**	
3.	**Do you keep reference samples of materials where appropriate?**	
4.	**Do you have laboratory facilities**	
5.	**If no do you have access to laboratory facilities.**	
6.	**Please give details of laboratory facilities.**	

SUPPLIER PRE QUALIFICATION QUESTIONAIRE ASSESSMENT

ASSESSMENT OF THE QUESTIONNAIRE	
Is the response acceptable: If no, state the reason why. If no, what follow up is required?	YES/NO

FOLLOW UP REPORT	
Was the follow up satisfactory? Provide details	

FINAL DECISION	
Supplier Risk Number Assigned Compliance Risk Number Assigned	

COMMENTS

COMPLETION DETAILS	
COMPLETED BY (NAME)	SIGNED:
(POSITION)	DATE COMPLETED:

ASSESSMENT
RECORD APPROVED BY: POSITION

SUPPLIER AUDIT CHECKLIST

	Y	N	COMMENTS
GENERAL			
Brief company history			
How long has company been manufacturing the material being audited?			
What other materials are manufactured at this site?			
Are any toxic, hazardous, or sensitizing materials manufactured in the same building or the same equipment?			
About what percentage of sales of this material is to pharmaceutical manufacturers?			
Is the facility or material ISO certified? If so, when?			
When was the last FDA or other regulatory inspection, and what were the results of the inspection?			
Have the inspectional issues been resolved?			
Are all operations performed by this company at this site?			
If not, what other sites / companies are used and for what functions?			
Have the other companies been audited and are reports available?			
If a subcontractor is used to manufacture the material, is there a system in place to notify the customer before such material is shipped to the customer?			
Is this same material manufactured at other sites?			
If multiple sites manufacture this material, what provisions are in place to provide ongoing assurance that the same processes are used and that the materials have the same quality and characteristics?			
If multiple sites produce this material, can the site be determined from the batch number?			
For active ingredients marketed in the US, is there a Drug Master File and is it up to date?			
Is there an SOP for performing recalls? Are mock recalls periodically performed?			
Have there been any recalls in the last 5 years? If yes, give details.			
If the company is now selling raw materials to NHS PMUs, does it have current NHS PMUs Specifications for them?			
If the material is of animal origin, does the company certify that it is BSE free?			
Is there a procedure in place to assure that the company and its client have agreed upon specifications and other requirements? If not, is there a system to assure that the client's requirements and specifications are understood and can be satisfied?			
ORGANISATION AND PERSONNEL			
What is the reporting relationship of QA and production?			
Approximately how many employees are in the company? At this site?			
Are there written job descriptions describing the required qualifications and training needed for each job?			
Is there an SOP for training, addressing both permanent and temporary employees?			
Are training and qualifications documented for each employee, including temporary employees?			
Are there initial and ongoing CGMP and/or ISO training and job-specific training for operators and analysts?			
Is training performed and documented when SOPs are created or updated?			
Do employees have adequate training, experience, and qualifications for their responsibilities?			
Are changes in FDA and other regulatory requirements tracked and communicated to employees?			
Is there personal hygiene training for personnel handling product so they understand the precautions necessary to prevent contamination of the excipient?			
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?			

If there are parts of an operation where loose and/or unsecured jewelry or other items could fall into the product, is there a policy prohibiting such items?			
Are personnel required to wear clean, intact, and sanitary protective apparel (e.g., outer garments, hair coverings, gloves) where necessary to protect the product from contamination by perspiration, hair, cosmetics, and other foreign substances?			
Are personnel observed to be in compliance with requirements for cleanliness, hair coverings, special clothing or protection in the various manufacturing, packaging, and testing areas?			
Is there a policy limiting the storage and consumption of foods, beverages, and tobacco, and the storage of clothing and personal belongings, to designated non-production areas?			
FACILITIES			
BUILDINGS AND HOUSEKEEPING			
How old are the facilities?			
Is there adequate security to assure there is no entry by unauthorized persons?			
Are facilities of suitable size, design, and construction for the operations being performed?			
Are facilities maintained in a clean and orderly manner and in a good state of repair?			
Are the surrounding grounds maintained in a clean and orderly manner so as not to attract pests or constitute a potential source of contamination?			
Are there provisions for power backup sources for critical systems if main power should fail, and/or an SOP for recovery from power failure?			
Is there adequate lighting and, where appropriate to protect exposed product or machinery, is it equipped with protection against shattering?			
Are transfer lines, pipes, and valves labeled (contents, direction of flow, etc.) where appropriate?			
Are there adequate space and environmental controls to ensure product integrity and to preclude mix-ups or cross-contamination, especially in drying, milling, blending and packaging operations?			
Are openings to reactors, centrifuges, etc. protected from overhead contamination where needed?			
In areas where product is exposed, are the overhead fixtures and pipes free of accumulated dirt and other material?			
Are production areas that present a potential for contamination appropriately controlled and equipped with exhaust or other appropriate systems?			
If air is recirculated to areas where product is exposed, is it filtered and controlled to eliminate dust cross-contamination? Are filters periodically checked and replaced and is this documented?			
If compressed air and gases are used in cleaning or in processing, are they filtered to prevent contamination of product? Is there an established program for checking and replacing such filters?			
Are there clean, readily accessible toilet facilities that are maintained in good repair, are equipped with self-closing doors, and do not open directly into the production area where product is exposed to airborne contamination (unless they are equipped with double doors or positive air-flow systems? Are signs posted requiring personnel to wash their hands before returning to work?			
Pest Control			
Is there an SOP for Pest Control?			
Are facilities properly maintained against rodents, birds, insects, and other vermin and are records kept? Are only approved rodenticides and pesticides used?			
If pest control is performed by a licensed pest control contractor, is that company's performance and compliance adequately monitored? Does the company provide a detailed written report of its activities and any rodenticides or pesticides used?			
If there are open windows, are they adequately screened?			
If raw materials or intermediates are stored in silos, tanks, or other large containers, are the vents adequately protected to prevent entry of water, birds, and insects?			
WAREHOUSE / RECEIVING / SHIPPING			
Is the warehouse clean and well-organized, and can materials be easily located?			
Are shipping docks protected from weather where necessary?			
Are temperature and humidity controlled appropriately for materials stored in the warehouse, to protect against deterioration and physical, chemical, or microbial contamination? Are they monitored?			
Are materials requiring special storage conditions (e.g., refrigeration, freezing, low humidity) stored accordingly?			

Is there an SOP for receiving materials, including verification of material received vs. material ordered, quantity received, lot numbers, etc?			
Is an identification code assigned to each lot of incoming raw materials to enable traceability?			
Are containers of incoming raw materials inspected upon receipt to ensure that their condition has not contaminated the material or caused deterioration?			
Are there written pumping procedures for bulk tank materials? Is each tanker compartment sampled and released prior to transfer?			
Is the amount of raw material reconciled where possible when materials are dispensed or returned to stock?			
Is there an adequate system for designating and controlling quarantined and rejected materials?			
Are nonconforming materials clearly identified and segregated to prevent unintentional usage or sale?			
Are appropriate controls exercised to assure that unapproved product is not shipped to customers?			
Is there an SOP for handling returned goods, including proper identification, segregated storage, and QA involvement in evaluation and disposition?			
If materials are to be destroyed, are they tracked and controlled and destroyed in a timely fashion? Are records of such destruction maintained?			
EQUIPMENT			
CONSTRUCTION, INSTALLATION, QUALIFICATION			
Is there an SOP for qualifying new or significantly changed equipment?			
Is equipment dedicated to the process?			
If equipment is not dedicated, what other materials are manufactured in the same equipment?			
Is equipment of suitable type and size for intended use? Is it constructed so that product-contact surfaces are not reactive, additive, or absorptive and will not adversely affect the product?			
Is equipment designed to preclude adulteration of product with lubricants, coolants, fuel, metal fragments, or other extraneous materials?			
Are holding, conveying and manufacturing systems designed and constructed so as to allow them to be maintained in a sanitary condition?			
Is equipment installed with sufficient clearance to allow access to both the equipment and the surrounding area for cleaning and maintenance operations?			
Are freezers and cold rooms equipped with thermometers or other temperature sensing devices / recorders, and with automatic temperature controls and automatic alarms?			
Is equipment operated in a manner that will prevent contamination and cross-contamination and will ensure product integrity?			
MAINTENANCE AND CALIBRATION			
Is there a master list of all equipment that specifies those requiring maintenance and/or calibration?			
Are there SOPs for inspection (monitoring the condition) and maintenance of equipment and of measuring and testing instruments? Do SOPs assign responsibilities; include schedules; describe methods, equipment, and materials to be used; and require maintenance of records?			
If equipment and instruments malfunction or are determined to be defective, are they immediately taken out of use?			
If water is purified for use in the process, is the purification system periodically sanitized and appropriately maintained?			
Are there SOPs for calibration of critical equipment, and measuring and testing instruments? Do SOPs assign responsibilities; include schedules; describe methods, equipment, and materials to be used, including calibration over actual range of use and standards traceable to national standards; and include specifications and tolerances?			
If calibration operations are performed in-house, do SOPs specify proper handling and storage conditions for the traceable standards?			
Does an SOP specify that equipment cannot be used if it is beyond the calibration due date, and describe actions to be taken if equipment is used that is found to have been beyond the due date or is found to be out of calibration limits?			
Is calibrated equipment labeled with date of calibration and date next calibration is due?			
Is equipment in use observed to be within calibration dating?			
Are periodic verifications performed on critical production scales (e.g., for raw material dispensing or portable scales) to assure that they remain within calibration in the time between full calibrations?			
Are records maintained for maintenance and calibration operations?			

EQUIPMENT CLEANING			
Are there written procedures for cleaning, specifying cleaning agents and methods?			
Are there data to show that cleaning procedures for non-dedicated equipment are adequate to remove the previous materials? For active ingredients, have these procedures been validated?			
Are there data to show that the residues left by the cleaning and/or sanitizing agent are within acceptable limits when cleaning is performed in accordance with the approved method?			
Are seams on product-contact surfaces smooth and properly maintained to minimize accumulation of product, dirt, and organic matter and to avoid growth of microorganisms?			
Is there an adequate system to assure that unclean equipment and utensils are not used (e.g., labelling with clean status)?			
Is there proper storage of cleaned equipment so as to prevent contamination?			
Are utensils and sampling devices cleaned and stored in a proper manner to prevent contamination?			
If returnable product containers are reused, are they cleaned using appropriate methods, previous labels are removed or defaced, and are they inspected before use?			

COMPUTERISED SYSTEMS

VERIFICATION / VALIDATION OF GMP-RELATED APPLICATIONS			
Is there a list of all computerised systems and computer applications, defines their uses, and identifies which ones perform CGMP-related functions?			
Are there established procedures and policies covering the validation of GMP-related computerised systems, equipment and instrumentation? Do these procedures define required validation / verification documentation?			
Are any computerised systems used in the manufacturing process and testing laboratories to perform GMP-related functions?			
Have such computerised systems been validated / verified (demonstrated to consistently function as expected)? Are reports available?			
In computer-controlled manufacturing operations, if the sequence of steps or events is important, is it enforced by the system? Has this function been challenged and verified?			
Have any spreadsheets used for performing calculations been verified as being accurate and functioning as expected? Are formula cells secure, with access limited to authorized personnel?			
Are routine accuracy checks performed for the various computer-controlled operations to verify that input to and output from the computer or related system are reliable and accurate? Are the degree and frequency of these verifications appropriate in relation to the complexity and reliability of the computerized system?			
BACKUPS			
Are suitable backup systems in place, such as copies of programs and files, duplicate tapes, or microfilm?			
Has retrievability of information from master tapes and backup tapes been verified?			
CHANGE CONTROL			
Is there a system to control changes to systems and programs that can have an effect on the quality of the product?			
Does the system 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?			
Is a log of system and program changes maintained?			
SECURITY			
Is there appropriate security to limit access to computerized systems, protect records from tampering, and prevent data alteration?			
If passwords are used as a security measure, are there provisions for periodic changing of passwords? Does a responsible person (e.g., system administrator) have a list of all passwords in case of emergency?			
If anyone leaves the department or company or otherwise loses authority to access the systems, are there procedures to immediately remove that person's access codes from the system?			

FDA: 21 CFR PART 11 (FOR FACILITIES SUBJECT TO FDA JURISDICTION)			
Is there an SOP or written policy that describes the electronic records retention system that is in use?			
Is the system capable of producing accurate and complete copies of records in both paper and electronic formats?			
Is there a secure, computer-generated audit trail that records the date and time of operator entries and actions that create, modify and delete electronic records?			
Is an audit trail retrievable throughout the records retention period?			
If a change is made, is the previous information still available?			
Is there an SOP concerning electronic signatures?			
Does it include a system to ensure that individuals are fully accountable and responsible for actions that are initiated under their electronic signatures?			
Does it prohibit electronic signatures from being used by, or re-issued to, anyone else?			
Is the identity of an individual verified before an electronic signature is issued?			
Are electronic signatures unique to an individual?			
Are non-biometric electronic signatures made up of at least 2 components, such as an identification code and password, or an ID card and password?			
Are there controls in place to ensure the uniqueness of each combination of ID code and password, so that no two individuals can have the same combination?			
If the signature is biometric, has it been shown to work only for one individual?			
OPERATIONS			
For excipients, at what point in the process is it determined that the material is intended for sale to a pharmaceutical manufacturer?			
Is processing on a continuous or batched basis, in an open or closed system? Continuous / Batched			Open / Closed
If processing is on a continuous basis, how is a batch defined?			
If any processing occurs out-of-doors, is it conducted in closed systems (if appropriate) or otherwise protected from contamination and pests?			
Is there a potential for contamination or cross-contamination from any source? If so, how it is controlled / prevented?			
Are there complete written master manufacturing instructions that specify formula, names and codes of raw materials, equipment, manufacturing flow, operating parameters, in-process sampling, packaging materials, labeling, and documentation of each significant step?			
Have process parameters critical to quality been defined and have consequences been described regarding the effect on quality if critical parameters are exceeded?			
Are critical process parameters monitored and recorded?			
For an active ingredient, has the current process been validated and is validation documented, i.e., - Has it has fully described regarding reactions, purifications, critical steps, operating parameters, process limitations, impurities, and key tests needed for process control? - Has it been demonstrated to operate consistently to produce final material that meets established specifications and is uniform from batch to batch?			
If reprocessing / recovery is performed, are there complete written instructions including any additional testing that may be required to assure that the final product is at least equivalent to other acceptable product, meeting all established standards, specifications, and characteristics?			
If reprocessing / recovery is performed on an active ingredient, has it been validated to assure final product meets all specifications and the quality is not diminished?			
Is the identity of major equipment and lines recorded in the batch manufacturing record?			
Are any unplanned process changes (process excursions) documented in the batch record?			
Are there written instructions describing how to use in-process data to control the process?			
If appropriate, is finished product blended to ensure a homogeneous batch?			
If the product is blended, are there blending parameters and/or homogeneity specifications?			
If the product is campaigned, is there a policy or SOP defining how many lots are permitted, or how long a period of time is allowed, between complete cleanings of the equipment?			
Are materials and equipment clearly labeled as to identity and, if appropriate, stage of manufacture?			
PACKAGING AND LABELLING			

Is there documentation to support the use of the container/closure system, demonstrating that it is adequate to protect product from deterioration and contamination?			
Is there an SOP for receiving, handling, storing, and accountability of pre-printed labels?			
Is there a written procedure for clearing the packaging area after one packaging operation, and cleaning before the next operation, especially if the area is used for packaging different materials?			
If filled unlabeled containers are set aside for future labelling, is there sufficient identification to determine name, strength, quantity, lot number, and other information needed for traceability?			
If metal detectors or magnets are used to protect against metal contamination, are they periodically challenged to assure continuous proper operation and is this documented?			
Packaging in Trucks and Railroad Cars			
If product is packaged in 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?			
Is the cleaning of the trucks and cars documented?			
Is there adequate protection around the filling openings or filling operation to prevent contamination from the environment?			
Are tamper-evident seals used where possible, including on trucks and railroad cars?			
QUALITY SYSTEMS			
RESPONSIBILITIES AND AUTHORITY			
Are the QA/QC organization's authority and responsibilities clearly defined in writing?			
Does QA have authority to review and approve or reject:			
procedures and specifications?			
process changes impacting on the identity, quality and purity of the material?			
raw materials, packaging materials, in-process materials, and product batches?			
new suppliers or subcontractors?			
Does QA assure that manufacturing and testing records are reviewed before batches are released for sale?			
Is there an adequate system for reviewing and implementing compendial (e.g., USP) changes?			
Is there an adequate program for handling complaints, including investigation to determine the causes, corrective actions, verification of the effectiveness of corrective actions, a target time frame for responding; trend analyses, and notification of appropriate parties including management?			
CHANGE CONTROL			
Is there an adequate system, described in an SOP, for controlling changes within the production process, including review and approval of changes to processes, documents, and equipment?			
Is QA involved in the change control process?			
Is a log maintained for changes to processes, materials, and methods?			
Has “significant process change” been defined for the product?			
Is there a system in place to assure that significant process changes and their effect on the product are communicated to the customer?			
AUDIT PROGRAMS			
Is there an internal quality audit program 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 systems?			
Based on the audit findings and recommendations, are steps taken to correct any areas of noncompliance? Are corrective actions documented? Is their effectiveness verified in subsequent audits?			
If any contractors (e.g., laboratories, packagers) are used, are they periodically audited and is their performance monitored?			
INVESTIGATION OF NONCONFORMANCES			
Is there an SOP for investigation of manufacturing deviations and batch failures to determine the cause and institute corrective actions to prevent the situation from recurring?			

Is there an SOP for determining the disposition of in-process and final material that fails to meet specifications (e.g., reprocessing, downgrading to a lesser grade, destruction)?			
Are records maintained of nonconforming materials, related investigations and corrective actions?			
How are nonconforming batches handled?			
How many batches have been rejected in the past year due to failure to meet specifications?			
For active ingredients, is there an SOP for investigation of out-of-specification (OOS) test results to assure that a uniform procedure is followed to determine why the OOS result occurred and that corrective actions are implemented?			
RAW MATERIAL CONTROL			
Is a list of acceptable suppliers maintained and are incoming raw materials checked against it?			
Are statistical sampling plans used to assure that the samples are representative of the lot?			
Are sampled containers labeled with sampler's name and date of sampling?			
Are there complete written instructions for testing and approving raw materials, including methods, equipment, operating parameters, acceptance specifications?			
Are raw materials approved before being used in production? Are appropriate controls exercised to assure that they are not used in a batch prior to release by Quality Control?			
If raw materials are accepted on certificates of analysis, have suppliers been appropriately certified or qualified, have results on the COA been verified by in-house testing, and is periodic monitoring performed?			
If raw materials are accepted on certificates of analysis, is at least an identification test performed (where safe) on every batch and receipt?			
Is there an effective system for monitoring and retesting or re-evaluating stored raw materials to assure that they are not used beyond their recommended use date?			
If secondary recovery procedures are performed on mother liquors, filtrates, or solvents, are the recovered materials shown to meet applicable specifications?			
If fresh and recovered solvents are commingled, are the recovered solvents sampled and assayed and found to be satisfactory prior to commingling, and is the quality of commingled solvents monitored on an established schedule?			
Are there chemical and microbial quality standards for process water, with an established monitoring program? If water is used in the process, is it at least potable water?			
Is feed water coming into the plant periodically monitored, either through in-house testing or reports from municipality testing?			
IN-PROCESS TESTING			
Are there complete written instructions for testing and approving in-process materials, including methods, equipment, operating parameters, acceptance specifications?			
If operators perform in-process testing, have they been trained and was the training documented? Does QC periodically verify their results?			
FINAL PRODUCT CONTROL			
Is every batch sampled according to a plan that assures that the sample is representative of the batch?			
When and where is the finished product sampled for release?			
Is every product batch tested and approved before shipment?			
Are there complete written instructions for testing and releasing final product, including methods, equipment, operating parameters, and acceptance specifications?			
If the final product is compendial (e.g., USP / EP / JP), are the tests and specifications compendial or are additional tests performed? List additional tests.			
If additional tests are performed, are they included on the certificate of analysis (COA)?			
If skip lot testing is done, does the COA clearly indicate which tests are performed on every lot and which are created via skip lot testing?			
Have non-compendial methods been validated, including accuracy, linearity, specificity, ruggedness, and comparison with compendial methods, OR have compendial methods been verified to function properly in the company's laboratory?			
Are specifications for non-compendial methods the same as those of NHS PMUs?			
Have specifications for particle size and bulk density been established where appropriate?			
Have impurity profiles been developed and limits been established?			

For active ingredients, have forced degradation studies been conducted, degradation pathways described, degradation products identified, and limits established?			
Are specific identity tests used to distinguish between the end product and related compounds, intermediates, by-products, process contaminants, degradation products, solvents, and other impurities?			
Is testing carried out on the finished material for residual solvents (especially those used in crystallization and final washes) and any organic volatile impurities (OVI) (benzene, chloroform, 1,4-dioxane, methylene chloride, trichloroethylene) used in the process? Are the results included in the COA?			
Stability Program			
What is known about the stability of this material?			
Is an expiration date assigned to the material? If so, what is it?			
For excipients, if an expiration dating period has been assigned, are stability data available to support the intended period of use of the material?			
For active ingredients, is there a written stability program, approved by QC, that specifies sample size, storage conditions, testing intervals? Are data available to support the expiration dating period?			
For active ingredients, are ICH stability guidelines followed?			
Are assay methods for stability testing stability-indicating? Have they been validated?			
If stability testing is performed, is it done on time according to intervals and tests specified in a stability protocol?			
Are stability failures investigated and reported to management?			
Are retention samples kept for every batch for at least one year past expiration date or, if no expiration date is assigned, according to a written policy?			
Are analytical and stability data reviewed and trends monitored? Are adverse trends addressed, and is appropriate management notified?			
LABORATORIES			
Do laboratories have adequate space and are they clean and orderly, with appropriate equipment for required tests?			
Are cellular phones prohibited from the laboratory?			
Are calibrated instruments labeled with date calibrated and date next calibration is due?			
Are daily or weekly calibration verifications performed on analytical balances using a range of weights (high, middle, low) based on the operating range of the balance?			
Are appropriate reference standards used and are they stored in a proper manner to ensure stability? Are their expiration dates adequately monitored so they are not used beyond the expiration dates?			
Are reagents and microbiological media adequately controlled and monitored to assure that they are periodically replaced and that old reagents are not used?			
Are all containers of materials or solutions adequately labeled to determine identity, preparer, and dates of preparation and expiration (if applicable)?			
Are data recorded in notebooks or on pre-numbered sheets, including appropriate cross-reference to the location of relevant spectra and chromatograms? Are equipment ID numbers recorded for each analysis?			
Are data and calculations checked by a second person and countersigned?			
Microbiology Laboratories			
Are positive and negative controls used for testing? Are their results recorded?			
Is growth support testing with low levels of organisms performed on all incoming media lots and is it documented?			
Is an expiration date assigned to prepared media and are prepared media stored at manufacturers' recommended storage temperatures?			
Are isolates from microbiological testing identified if appropriate?			
Is each lot of microbial ID systems checked with positive and negative controls?			
PRODUCT QUALITY REVIEWS			
Are periodic quality reviews conducted? Are they provided to, and reviewed by, quality and production management?			

Do the periodic reviews of product quality include information such as: - a list of batches manufactured (approved and rejected) during that period, - discussion of manufacturing deviations, their causes, the corrective actions, - changes made during the year, - critical in-process data for all lots manufactured, - final product test data for all lots manufactured, - stability data, - adverse trends in any area, - summary of complaints and corrective actions, - recalls.			
Is the information in the periodic quality reviews evaluated with conclusions regarding need for revalidation? Are the evaluation and conclusion documented?			

DOCUMENT CONTROL

STANDARD OPERATING PROCEDURES (SOPs)			
Are there written SOPs for all areas of the operation? [NOTE: This refers to SOPs other than manufacturing instructions or test methods.]			
Is there an SOP for writing, handling, and updating SOPs? Are SOPs periodically reviewed and updated?			
Is a history of SOP revisions maintained?			
Are current SOPs readily available to employees?			
Is there an adequate system to assure that unneeded or obsolete documents are removed from use?			
MANUFACTURING, PACKAGING, AND TESTING RECORDS			
Are batch / lot numbers assigned in such a manner that they are not duplicated and they enable tracing of all processes and batch records for each batch?			
If a new lot number is assigned to a reprocessed lot, can it be traced to the original batch?			
Do shipping records allow traceability of specific lots to specific consignees and vice versa?			
Are there overwrites, white-outs, or pencil entries in official records?			
Are records legible? Are they appropriately signed and dated where required?			
Are batch and control records reviewed for completeness before filing?			
Is there an adequate system to track, control and maintain all records related to a batch?			
Are records retained for at least one year past the expiration date of the batch or, if no expiration date has been assigned, as specified in a records retention policy?			

ITEM	YES	NO	COMMENT
SPECIAL CONSIDERATIONS FOR CERTAIN ACTIVE PHARMACEUTICAL INGREDIENTS			
NON-STERILE ACTIVE PHARMACEUTICAL INGREDIENTS FOR PARENTERAL OR INHALATION PRODUCTS			
Are there microbiological test results for every batch?			
Are there environmental microbiological test results from areas where the material is isolated, dried, and packaged?			
If water is used in processing the final material, does it meet the requirements for Purified Water USP?			
Is endotoxin testing performed on process water?			
STERILE ACTIVE PHARMACEUTICAL INGREDIENTS			
Has personnel monitoring (microbial) been performed and have personnel been properly qualified to work in the sterile suite?			
Are there environmental microbiological test results from areas where the material is isolated, dried, and packaged?			
If water is used in processing the final material, does it meet the requirements for Water for Injection USP?			
Is endotoxin testing performed on process water?			