PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PI 030-1
13 January 2009

AIDE-MEMOIRE

INSPECTION OF ACTIVE PHARMACEUTICAL INGREDIENTS

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1. DOCUMENT HISTORY

Adoption by Committee	12.11.2009
Entry into force of PI 030-1	01.03.2009

2. INTRODUCTION

2.1 The adoption of ICH Q7 as the first truly harmonised GMP guideline for active pharmaceutical ingredients (APIs) and the associated development of regulatory frameworks to implement the guideline as a regulatory standard mark the beginning of a new era of regulation for medicines.

2.2 The adoption of ICH Q7 by PIC/S occurred in May 2001 with the current version of the guideline having been available since 1 September 2007 as GMP PE 009 (Part II).

2.3 The primary objective for implementing ICH Q7 is the reduction of the risks associated with the manufacturing quality of APIs and this cannot be achieved without an effective inspection system which addresses the specific aspects of the global API industry.

3. PURPOSE

3.1 It is recognised that due to their background and experience the majority of GMP inspectors are more familiar with the inspection of finished products. Therefore, to assist inspectors not specialised in the inspection of API manufacturers this document has been developed to provide training and guidance for the preparation and performance of such inspections.

3.2 This Aide-Memoire should also contribute to a harmonised approach for inspections of API manufacturers between the different PIC/S Members.

4. SCOPE

4.1 At the time of issue, this document reflected the current state of the art. It is not intended to be a barrier to technical innovation or the pursuit of excellence.

4.2 This Aide-Memoire focuses on the preparation for inspections and chapters and/or sections of GMP PE 009 (Part II) which are specific to the inspection of API manufacturers or critical for the quality of APIs. For sections which include requirements similar to those in GMP Guide Part I devoted to Finished Products such as personnel, documentation, etc., please refer directly to GMP PE 009 (Part II).

5. AIDE MEMOIRE

1. Preparation of API inspection		
Inspection Element	**Workflow**	**Supporting documents**
Inspection history	Review the reports of any recent inspections carried out and the outcome	Inspection reports
	If appropriate, contact the inspectorate that conducted the last inspection to verify the information	
Basic information related to the APIs	Determine the number of different APIs produced at the site	Products Quality Review(s) (PQR)
	Determine the classification of the APIs (antibiotics, hormones, cytostatics etc.)	
	Determine the intended use of the APIs (topic, oral, injectable, inhalation, etc.)	
	For each API, establish; - grade (freeze dried, micronised, sterile, etc.); - batch size; and - number of batches produced per year	
Basic information related to the site	Determine if the facilities are multipurpose or dedicated	Site Master File
	If APIs are potent or highly toxic determine the containment measures	
	Review a list of manufacturing equipment	
	Review a list of SOPs	
	Review the flow of personnel and materials through finishing areas	
	If manufacturing operations, products or services, are outsourced establish the name and address of the subcontractors	SMF
Basic information related to processes	Review: - API specifications and test methods; - Process flow charts; - Detailed description of the process; - Stability studies results; - Impurity profile; - API starting materials definition etc.	Pharmacopoeia; CEP; ASMF (previously DMF), CTD part 3.2; Batch Manufacturing Record if appropriate
	If appropriate, contact assessors of the dossiers	
	Review validation status	Validation Master Plan; list of activities scheduled
Changes	Review recent major changes (new product, equipment, building renovation or extension etc.)	
	Review scheduled major changes	

2. Quality Management System			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
Internal audits (Self inspections)	Approved and documented schedule, which covers all GMP activities available	Are internal audits being performed as scheduled? Can they be substituted by third party audits? How is the frequency of internal audits determined?	2.40
	Composition of the team appropriate	Is the composition of the audit team determined according to an SOP? Has consideration been given to: - Conflict of interest - Code of conduct - Qualifications - Independence from the area being audited (e.g. Who inspects the QA function)	
	Qualification of any external auditors	How is the suitability of external auditors assessed?	2.40, 3.30
	Effectiveness of the system to plan the corrective and preventive actions Verification of the completion of an action	How does the company ensure that corrective actions are effective and are completed in a timely manner? How do they check the effectiveness of preventive actions?	2.41
	The flow of information is effective	How is the responsible management informed about the results of the audits?	2.41, 2.18
Product Quality Review (PQR)	Regular PQRs performed in a timely manner (e.g. within three months from the end of the period being evaluated). Data from in-process controls, batch release analysis and other key quality indicators e included	Is the data evaluated for the presence of trends, and are these acted upon? Are complaint, out-of-specification (OOS) and deviation investigations, reported, considered and evaluated in the PQRs? Are the PQR results used to re-evaluate the expected monitoring ranges in Batch Manufacturing Records?	2.50, 2.51

2. Quality Management System			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
	A review of OOS, critical IPC and API test results, deviations, complaints, returns and recalls, non conformances and related investigations, including the effectiveness of the corrective and preventive actions conducted A review of changes conducted Stability program data verified	Are required changes highlighted in the PQRs implemented through the change control system?	2.5, 6.61, 6.72, 8.36, 11.15
	Based upon the review, the validation status of a manufacturing process is evaluated and recorded		2.5, 12.60
Complaints	All quality related complaints recorded and investigated according to a written procedure	How are complaints reported, including orally, recorded and investigated?	15.10
	Complaint records include all relevant details (date and source of the complaint, nature of the complaint, references to batch number and production date)	Is the nature of the complaint correctly reported – i.e. is it possible to establish if there is a recurring problem?	15.11
	The complaint investigation report identifies corrective actions and follow up/preventive actions	Has the impact of this complaint on other batches been considered?	15.11
	The final report specifies the kind of response provided to the originator of the complaint and the decision on the status of the product	Does the corrective action correctly address the problem, or it is focused on “customer satisfaction”? (i.e. the company looked for the root cause of the problem, or simply “reimbursed” the originator of the complaint?) Was source of the complaint removed in an effective manner through preventive actions?	15.11

2. Quality Management System			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
	Complaint records and reports are evaluated in the PQRs in order to identify trends, product related frequencies, and severity	Are complaints correctly evaluated in PQRs? (i.e. is there any evaluation of reoccurrence and trends?) Are corrective/preventive actions managed through the change control system?	13.12-13, 15.12
Recalls	The “recalls SOP” specifies the threshold (by way of example cases, or other means) for which a recall shall be considered The “recalls SOP” specifies who can initiate a recall, and how the recall process shall be managed. (i.e. who is to be informed, and how recalled goods are to be treated and stored)	Is the recall process clearly documented and easy to follow?	15.13, 15.14
	The recall procedure clearly defines how to inform the regulatory authorities in the case of recall related to a serious problem	Is there a requirement to inform the authorities, and request cooperation (in terms of advices and/or actions), in cases where the recall is related to a potentially life-threatening situation?	15.15

3. Personnel			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
	Cf. Scope 4.2		3.

4. Building and facilities			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
General	Product protection increases from early through to final manufacturing steps	Have procedures been implemented to protect the API from contamination during the final stages of manufacture? (e.g. sieving, milling and packaging)	4.10
	The level of product protection is dependent upon the product type and the expected time of exposure to the environment	Have procedures been implemented to protect the API when exposed to each stage of the manufacturing environment (sampling, loading, unloading, etc.)?	4.10

4. Building and facilities			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
	APIs with microbiological specifications require additional controls	What are the additional controls?	4.10
		Have controls been implemented to ensure that the activities in surrounding areas/neighbourhood are not an actual source of contamination?	SMF
		Have controls been implemented to ensure that highly toxic non pharmaceutical materials (herbicides, pesticides, etc.) are not manufactured in the same building/equipment as used for APIs.	4.43
APIs specific areas / activities	Tank farms	Are the general condition of tanks and ancillary equipment (pumps, pipes, vents, etc.) appropriate for their intended use? Are all tanks and associated pipes appropriately labelled and secure?	7.21, 7.22
	Solvent recovery plant	See recovery chapter	
	Washing rooms	Are washing areas appropriately managed and controlled?(equipment flow, storage of dirty and clean equipment, labelling)	4.10, 4.11
	Control rooms	Have computerised systems been validated? Have the backup systems been verified? Are procedures in place for the analysis of data?	5.4
	Compressed air / nitrogen / other utilities		PIC/S Aide-Memoire on Utilities (PI 009)
	Sewage and refuse	Is waste effectively removed from production areas (e.g. using closed systems like containers or plastic bags to prevent contamination of other areas)?	4.60
		Are all waste disposal systems correctly identified?	4.60
	HVAC	Does the HVAC system provide an appropriate environment for finishing areas where APIs are exposed?	4.21, 4.22

4. Building and facilities			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
Water	Drinking (potable) water acceptable if suitable for intended use	Are records of CoA available? Has testing at an appropriate frequency been conducted? Does potable water meet at the minimum WHO guidelines (e.g. free from chemicals such as carcinogens, toxic substances, metals, organochlorine pesticides, lindane, DDT, organic compounds, etc; radiologicals and micro-organisms)	4.30, 4.31, PIC/S Aide-Memoire on Utilities (PI 009) WHO Guidelines for drinking-water quality
		If water sourced from river, wells, etc. and treated by the manufacturer, has the treatment process been validated? Have the affects of seasonal variation and human activity on the water quality been addressed? Is the process monitored?	4.33
	Non-sterile API intended to be used in a sterile drug	Is the water used in the final isolation and purification steps monitored and controlled for microbial counts, objectionable organisms and endotoxins?	4.34
Design	Defined areas or other control system for different activities (storage, sampling, quarantine, production, etc.)		4.14, SMF
	Potential contamination and cross-contamination has been prevented by the location and placement of equipment		4.11
Flow of materials and personnel		Are the flow of materials and personnel appropriate for the processes? Are appropriate indications displayed in critical areas (gowning instructions, labelling for clean/unclean areas, incoming/outcoming materials, etc.)	4.13
Containment	Design of the multipurpose use containment area	Has the containment area been qualified for multipurpose use?	
		If HVAC is not dedicated, what controls are in place to prevent cross-contamination?	4.22

4. Building and facilities			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
	Penicillins and cephalosporins	Are they produced in dedicated areas?	4.40
	Other highly sensitizing, toxic, potent materials	Are sensitizing, toxic and potent materials either produced in dedicated areas or are validated inactivation and/or cleaning procedures established and maintained.	4.41
	Controls to prevent cross-contamination	Have procedures to prevent cross-contamination been established? Is the performance of these procedures being monitored? Are staffs exhibiting appropriate behaviour and personal gowning techniques to prevent cross contamination?	4.42
		Are measures in place to ensure that cross-contamination from equipment, materials and personnel moving from one dedicated area to another area is avoided?	4.42

5. Process equipment			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
	This section is to be developed at the next revision of the Aide-Memoire		5.

6. Documentation and records			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
	Cf. Scope 4.2		6.

7. Materials management			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
Suppliers qualification	Critical materials and their suppliers	Have supplier control procedures been defined and implemented?	7.11

7. Materials management			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
	Supplier evaluation	Have the following been considered in supplier control procedures? - a review of the history of supplier - completion of a questionnaire by the supplier including information about quality system, quality certifications, third party audits, site master file etc… - a supplier audit including QC labs (considered for critical materials) - evaluation of samples (for new suppliers)	7.31
	Approved suppliers list	Does the list include the name and address of the manufacturer (not only trader)? Is it an updated and controlled document? Is it available for people in charge of receiving goods?	7.12, 7.13 7.20
Starting material from animal origin with TSE risk	Additional records	- Origin of raw materials: country, supply chain, veterinary inspection / certificates, age of animals - Type of tissue used, collection method, risk of cross contamination during the collection - Manufacturing process: overview of the process, reduction of the TSE risk (validation), risk of cross contamination, cleaning validation - Traceability: supply chain, availability of the information back to the slaughterhouses / animals	National or international guidance documents (e.g. EP general monograph 5.2.8)
Change control	Changes are effectively managed through the change control system	Is the Change Control system used to manage changes to materials and suppliers?	7.14, 13.
Storage	Transportation and storage for raw materials, and intermediates requiring special handling	What systems are in place to ensure appropriate transport and storage conditions have been maintained?	7.20
	Validated electronic systems for material status control are acceptable. In such cases, physical segregation may not be required	Where status control of material is by physical location are the locations well marked? Is access to these locations restricted to designated personnel? Where status control of material is by electronic means, is access to the electronic system restricted to designated personnel?	10.11, 5.40, 7.20

7. Materials management			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
Bulk materials	Non dedicated tankers	Does the cleaning procedure, and certificate of cleaning, for non-dedicated tankers cover accessory parts, including transfer hoses?	7.22
	Note: Section 7.22 is applicable to reusable containers	If non dedicated reusable containers are used, is there evidence that they are properly cleaned?	7.22, 8.51
Sampling	Sampling plan	Are sampling plans appropriate for each type of raw material being selected for testing? Does each sampling plan include a rationale for the selected method?	7.33
	Sampling environments appropriate for the materials being sampled	Has consideration been given to the sampling environment for each material being sampled? Does the plan take into account the material type, its susceptibility to microbial contamination, its use in a particular manufacturing step and the final dosage form?	7.34
Analysis	Identity testing	Is each batch identity tested?	7.30
	Extent and frequency of testing	If reduced testing performed, how was the supplier approved? At what intervals is full testing conducted?	7.31

8. Production and in process controls			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
General considerations on the production operations and on facilities	All the production operations verified for compliance with the production documents specified in 6.2, 6.3, 6.4, 6.5 of the GMP Guide, and the process described in the ASMF or module 3, part 3.2.1 of CTD or as described by ICH M4Q	Are production operations actually performed in dedicated or multipurpose facilities? Are the critical parameters recorded and controlled? Do formal procedures describing the production process exist? Do production operations correspond with the defined process? Is the facility monitored to ensure appropriate conditions are maintained? Has the method of monitoring been verified? Is an appropriate level of protection given to centrifuges, filters, ovens, etc? Does the monitoring of the quality of water demonstrate that the specification has been met Are the critical parameters trended?	8. PIC/S Aide-Memoire on the Inspection of Biotechnology manufactures (1.4)
Compliance to registered file and general consistency		Do the parameters stated in the registered file relate to the operations documented in the Batch Record? - Process parameters, - IPC, - Specifications for intermediates and finished product Does the facility have the capability to manufacture the batch size of the APIs produced? Is the inspected site's address consistent with the registered file? Are all production areas declared in the registered file?	1.1 § 4 Registered file
Production Operations	Raw materials: Dispensing area surfaces, equipment and environment	Are dispensing areas and equipment fit for purpose?	8.10, 6.52
		Are containers suitable and appropriately labelled? Is material status controlled?	8.11
	Critical weighing activities independently confirmed and verified	Are all critical activities witnessed or subject to equivalent controls? Do production personnel verify that materials are correct prior to use?	8.12, 8.13

8. Production and in process controls			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
	Yield within expected range	Have appropriate yield ranges been set? Is the batch yield within range? For critical process steps, are deviations in yield investigated?	8.14
	Deviations documented and investigated	Are deviations documented and explained? Has an investigation been performed for critical deviations and, if necessary, corrective actions implemented?	8.15
	Process status indicated	For each major unit of equipment is the processing status identified?	8.16
	Reprocessing and Reworking appropriately controlled	What systems are in place to track materials for rework, or reprocessing, and to prevent unauthorised use?	8.17, 14.2; 14.3
Time Limits	Time limits for process operations, and for the storage of intermediates	Where time limits have been set, are these being met? Are deviations documented and evaluated?	8.20, 8.21
In-process Sampling and Controls	Written Procedures available for the monitoring and control of production process	Do written procedures exist to monitor and control the production process? Are the procedures based upon development / historical information?	8.30
	Acceptance Criteria appropriate to process step / stage	Do the in-process controls and acceptance criteria become more stringent for the later processing steps?	8.31
	Critical in-process controls are documented and approved by the Quality Unit	Has the Quality Unit given approval for in-process controls?	8.32
	In-process controls performed and documented by qualified staff	Are qualified staffs performing in-process controls? Are adjustments made to processes in accordance with pre-established and validated limits? Are IPC results documented in the batch record?	8.33
	Sampling Procedures documented and scientifically sound	Are there written sampling procedures which are scientifically sound?	8.34

8. Production and in process controls			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
	In process sampling : Prevention of contamination and assurance of the integrity of the sample	Are sampling procedures designed to prevent contamination and ensure the integrity of the sample?	8.35
Blending Batches of Intermediates or APIs	Blending of batches defined and controlled	Does the company blend batches and is this process defined and controlled?	8.40
	Only batches meeting approved specifications may be blended	Have all input batches been manufactured by the same process, been individually tested and meet specification?	8.40
		Is the blended batch tested for conformance with specification?	8.43
	Traceability of material used in a blended batch	Is it possible to identify all the input batches that make up the blended batch?	8.44
	Validation of the homogeneity of the blended batch	Is the blending operation validated to show homogeneity of the combined batch where physical attributes of API's are critical in the dosage form?	8.45
	Impact of blending process on product stability	Does the blending operation adversely affect product stability? If so have further stability tests been performed.	8.46
	Expiry / Retest date determination	Is the expiry/retest date of the blended batch based upon the expiry/retest date of the oldest batch in the blend?	8.47
Contamination Control	Prevention of contamination of batches by carry over from a previous batch	Is the carryover of degradants and microbial contamination, that could impact upon the established API impurity profile, prevented? Consider: - Frequency of inter batch cleaning. - Environmental controls - Open processing operations	8.45, 8.50, 8.51, 8.52

9. Packaging and identification labelling of APIs and Intermediates			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
Packaging and labelling	Impact of packaging materials on product quality	Do Packaging materials alter the quality of the API or intermediate?	9.21

9. Packaging and identification labelling of APIs and Intermediates			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
	Representative label	Does the BMR include a representative label?	9.36
	Prevention of cross contamination if containers reused	Are there appropriate procedures to avoid mix-up and cross contamination? Consider: - cleaning - removal of labels	9.22
	The issue of labels must be controlled	Is there an effective system for the issuing of labels?	9.3
	The labelling of an API must ensure traceability and provided instruction on any special transport or storage requirements	If and API is transferred outside the control of the manufacturer is the name and address of the manufacturer incorporated into the label. If required, are special storage conditions incorporated into the label.	9.43, 10.22
	Effectiveness of the sealing system	Has the sealing system been validated?	9.46

10. Storage and distribution			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
Storage and distribution	Appropriate storage areas	Is there adequate space including specific areas for returned, rejected, quarantined materials?	4.11, 10.10
		Have the specified storage conditions been fulfilled?	10.10
		Are FEFO / FIFO rules met?	7.42
	Controls of transfers under quarantine	If quarantined material is to be transferred, are there effective controls and documentation in place to prevent use before formal release by the manufacturer?	10.20
	Transport methods and conditions	Has the responsibility for the transport been assigned? Is the assignment appropriate?	
		How are the specified storage conditions maintained during transport?	10.21

10. Storage and distribution			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
		Is the level of control over the contractor for transportation adequate? Consider: - audits by the API manufacturer - agreements - questionnaire, etc.	10.23
	The traceability of materials and products extends to the point of first supply	Is there a system in place for product recall?	10.24

11. Laboratory controls			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
	See PIC/S Aide Memoire PI-023		11.

12. Validation			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
Validation Policy		Is the company's validation policy documented?	12.10, 12.11
		Are all critical manufacturing steps validated?	12.12
Validation Documentation	Validation protocol established and approved by the Quality Unit	Is the validation protocol compliant with the company's validation policy?	12.20
	Critical steps that require validation and acceptance criteria specified	Has the rationale for identifying certain manufacturing steps and operating parameters as critical, been documented?	12.21
	The validation approach adopted defined and documented	What is the validation approach adopted? Consider : - prospective, concurrent, or retrospective - the number of process runs	12.10, 12.4
	The results of validation must be documented Any identified deficiencies evaluated and documented	Are variations from the protocol documented and justified?	12.22, 12.23

12. Validation			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
	Any corrective actions implemented and documented		
Qualification	Qualification (DQ, IQ, OQ, PQ) conducted for critical equipment and ancillary systems (both new and existing), for intended process, as appropriate	Have all qualification activities been completed before process validation begins?	12.30
Approach to Process Validation	All operations determined critical to the quality and purity of the API are to be validated		12.12, 12.40
		If prospective validation has not been performed, has the validation approach taken been justified?	12.41
Prospective Validation	Prospective validation consisting of at least three consecutive successful batches must have been completed before commercial distribution of the API		12.42, 12.50
Concurrent Validation	Where only a limited number of API batches are manufactured, or where manufacture is infrequent, concurrent validation of at least three consecutive successful batches is acceptable	Are batches released for commercial distribution, before completion of concurrent validation, subjected to a thorough monitoring and testing programme?	12.43, 12.50
Retrospective Validation	The number of process runs selected for retrospective validation should be sufficient to demonstrate process consistency. In general, data from ten to thirty consecutive batches should be examined Test results from retained samples can be tested to obtain data for retrospective validation	Are batches selected for retrospective validation representative of all batches made during the review period?	12.45, 12.50
Impurity Profile	Process validation should confirm that the impurity profile of each		12.52

12. Validation			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
	API is within the limits specified		
Periodic Review	There should be a periodic review of systems and processes with respect to validation status	Are Product Quality Reviews used to confirm that the process under review remains validated?	12.60, 2.5
Cleaning validation	Focus: multi purpose facilities and final manufacturing steps	Are cleaning procedure validated? If not, is there any justification? Is cleaning validation directed to situations that poses the greatest risk?	
	Rational behind the use of either validated or non validated cleaning methods for equipment used at different stages of production	Are documents available regarding risk assessment which consider: -characteristics of contaminants (e.g. toxicity, solubility, potency and stability) -equipment (product contact material and relative surface area, places difficult to clean) -process flow (purification steps, bulk size, product change over) -at the minimum, selection of product(s) which represent(s) the worst case scenario (product change-over, maximum acceptable residue limit, etc.)	
	Cleaning procedures are to be validated	Are the cleaning procedures routinely used in production the same as those used in the validation studies? Are the cleaning methods applied in production the same methods as those used in the validation studies? Is cleaning routinely performed after the manufacture of the same number of batches?	12.71
	Sampling methods involving rinse/swab, with an acceptable recovery, validated (including sampling for microbiological assessment)	Are personnel performing sampling properly trained and assessed? Is the sampling method used to monitor cleaning procedures the same method used in the validation studies?	12.73 12.76
	Analytical test methods appropriately validated	Is the analytical test method sufficiently sensitive related to the established residue limits?	12.74
	Microbiological aspects	Has inhibition of microbial growth by residue been considered during test method validation?	
	When processes and equipment including	Has the effectiveness of cleaning/sanitization procedures been	12.75, 5.21, 5.23

12. Validation			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
	water system have to be controlled for microbiological contamination, there shall be appropriately validated cleaning/sanitization procedures	validated? Are “clean/dirty status” hold times and sanitizer residue limits correctly considered? Is the water used for cleaning/rinsing appropriate for the next manufacturing step?	

13. Change Control			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
	Cf. Scope 4.2		13.

14. Rejection and re-use of materials			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
Solvent and material Recovery	Specifications appropriate for the intended use	Has a rationale for solvent / material specification been documented?	14.41, 14.42
		If it is to be used for multiple processes, does the specification account for the presence of contaminants introduced from other processes?	14.41
	Outsourced services are to be controlled	Is the level of control over the supplier of outsourced services appropriate? (see section 7.3);	7.3, 16.
	Documents and records must be maintained	Are relevant SOPs, batch records and CoA available? Are recovered solvents formally approved and released for use?	14.40, 14.43
	Identification and controls of equipment used for recovery, transportation and storage of solvents	Is the identification of the equipment used recorded or cross referenced in the batch record? Are appropriate procedures in place to avoid mix-up and cross contamination?	14.41, 14.43, 5.21
Rejection	Rejected APIs and intermediate materials shall be quarantined and recorded The disposition of material shall be recorded	Do procedures exist and are they adequate? How are materials identified and stored? Is a list of rejected materials maintained? Do the Certificates of Destruction for disposed materials correspond with the list of rejected materials?	14.1

14. Rejection and re-use of materials			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
Reworking		Is an investigation performed before a decision to rework is carried out?	14.30
		Have reworked batches been subjected to: - appropriate evaluation - stability testing - a review to show equivalency to original process? Is validation performed if more than one batch is affected? Is a report issued if only one batch is affected?	14.31
	The impurity profile of a reworked batch shall be comparable to routine production batches	Are the impurity profiles of reworked batches similar to routine production batches?	14.32
	Additional testing and test methods if routine test methods are found to be inadequate	Are routine analytical methods adequate for the analysis of reworked batches? Will the methods detect additional degradants or other impurities?	14.32
Returns	Policy on returns documented	If the company accepts returns, are the returned APIs and intermediates identified as returns and subsequently quarantined?	14.50
	Records of returns maintained	Does the procedure for handling returned product require the reason for returning the product to be identified? Do the company's records allow identification of the transportation and storage history of the product, whilst the product was outside the company's control? Are the details recorded in the documentation associated with the returned product adequate and appropriate? Is returned product appropriately dispositioned for reprocessing, reworking, or destruction?	14.51, 14.52

15. Complaints and Recalls			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
	Cf. Scope 4.2		15.

16. Contract manufacturers (including Laboratories)			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
	Cf. Scope 4.2		16.

17. Agents, Brokers, Traders, Distributors, Repackers and Relabellers			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
General	Relevant sections of Part II are applicable to Agents, Brokers, Traders and Distributors (e.g. chapters 2, 3, 4, 6, 7.4, 9, 10, 11.4, 14.52, 15).		17.10, 17.11
	Repackers and relabellers are considered as manufacturers (full compliance with Part II required)		17.11, 17.40
Traceability of APIs and intermediates	Effectiveness of the system	For some APIs, consider the availability and completeness of required documentation back to the original manufacturer Are these records readily available?	17.20
Transfer of information		Is the customer informed of any additional manufacturing operation carried out on behalf of Agents, Brokers, Traders, Distributors, Repackers and Relabellers (e.g. micronisation, Gamma irradiation, freeze-drying)?	17.60
		Are the original API manufacturer's name, address and the batch number(s) supplied provided to the customer?	9.43, 17.61
		Is the original API manufacturer's name and address included on the CoA and displayed on labels?	11.44
		Is quality or regulatory related information exchanged between partners in a timely manner?	17.60
		In case of quality related problems, are Agents, Brokers, Traders, Distributors, Repackers and Relabellers involved? Are they informed of any investigation and actions undertaken?	17.71, 17.72

17. Agents, Brokers, Traders, Distributors, Repackers and Relabellers			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
Repackaging relabelling		Do procedures, records, and environmental monitoring indicate that controls are in place to avoid mix-up, contamination and cross-contamination?	17.4
		Are samples retained?	11.7
Stability		Is retest or expiry date available? When an API is repacked in a different type of container are the mandatory stability studies conducted?	17.20 17.50
		If micronisation, Gamma irradiation, freeze-drying is performed on behalf of the Agents, Brokers, Traders, Distributors, Repackers and Relabellers are the mandatory stability studies conducted according to section 11.5?	17.50 11.5

18. APIs manufactured by Cell Culture / Fermentation			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
	See PIC/S Aide Memoire PI-024		PIC/S Aide-Memoire on QC Laboratories

19. APIs for use in Clinical Trials			
Area of operations / items	**Notes**	**Crucial questions/Show me**	**Supporting documents**
	This section is to be developed at the next revision of the Aide-Memoire		19.

6. REVISION HISTORY

Date	Version number	Reasons for revision

Acronyms:

ABTDRR:	Agents, Brokers, Traders, Distributors, Repackers and Relabellers
APIs:	Active Pharmaceutical Ingredients
ASMF:	Active Substance Master File
BMR:	Batch Manufacturing Record
CEP:	Certificate of the European Pharmacopoeia
CoA:	Certificate of Analysis
CTD:	Common Technical Document
DMF:	Drug Master File
OOS:	Out of Specification
PQR:	Product Quality Review
SMF:	Site Master File
SOP:	Standard Operating Procedures

Bibliography:

1) EMEA Note for Guidance on quality of water for pharmaceutical use (http://www.emea.europa.eu/pdfs/human/qwp/015801en.pdf)

2) WHO Guidelines for drinking-water quality (http://www.who.int/water_sanitation_health/dwq/guidelines/en/index.html)

3) Related PIC/S Aide Memoires and guidance documents:

- Quality Controls Laboratories (PI 023)
- Biotech (PI 024)
- Utilities (PI 009)
- Explanatory notes for industry on the preparation of a Site Master File (PE 008)

These documents are available on the PIC/S website: (http://www.picscheme.org)

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