PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

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AIDE-MEMOIRE

INSPECTION OF PHARMACEUTICAL QUALITY CONTROL LABORATORIES

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1. DOCUMENT HISTORY

Adoption by the PIC/S committee	13 September 2005
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2. INTRODUCTION

Inspections of sites involved in testing of medicinal products should be more and more specific, thorough and conducted under normal working environment. These inspections may include a complete assessment of laboratory's conformance with the code of GMP or they may be limited to specific methodology or aspects of the laboratory. Inspection process of a laboratory involves the assessment of laboratory functions in full operation. Consequently, PIC/S has developed the Aide Memoires, which can be considered a good tool for enhancing the understanding and performance of inspectors.

3. PURPOSE

3.1. The purpose of this document is to provide guidance for GMP inspectors to assist in training and preparing for inspections.

3.2. The Aide-Memoire was drafted with the aim of facilitating effective planning and conducting of GMP inspections of laboratories. The Aide-Memoire should enhance the efficiency of the GMP inspection and evaluation process.

4. SCOPE

4.1. This document applies to laboratories for testing of the finished medicinal products, intermediates, starting materials for the production of medicinal products and in-process controls.

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

5. AIDE-MEMOIRE

The AIDE MEMOIRE in Annex consists of 9 tables containing general subjects and items to be investigated during the GMP inspection of laboratories. Some important questions and relevant references to the PIC/S documentation are included as well.

Some more and specific aspects to be investigated by inspectors, respecting the special type of laboratory and nature of testing, are included in two supplements of Annex.

6. REVISION HISTORY

Date	Version Number	Reasons for revision
25 September 2007	PI 023-2	Change in the Editor's co-ordinates

AIDE-MEMOIRE

FOR INSPECTIONS OF PHARMACEUTICAL QUALITY CONTROL LABORATORIES

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Explanation to all tables below:
PIC/S G. = PIC/S Guide to GMP; It.= item ; SMF = Site Master File; IPCs= in process controls; EuPharm= 4th ed. 2002; VMP = Validation Master Plan;

1.	GENERAL			
	Area of operation / items	**Notes**	**Crucial questions** *« show me..»*	**Supporting documents**
1.	**General information**	• Name of the establishment • Physical address, phone No., FAX No. Email • Postal address	• Who is the contact person (name, phone No, e-mail)	
1.1.	**Test activities**	• QC laboratory status and activities on site	• Licensed by a competent national authority • Regularly inspected by a competent national authority	PIC/S G. 1;
1.2.	**Activities contracted out (Contract testing)**	• Name(s)/ address/addresses) of the company / companies • Type of activities, written contract	• Licensed by a competent national authority • Evaluation / Re-evaluation of the contract laboratory by the customer (contract giver)	PIC/S G. 7.1; 7.15; 7.13
2.	**QUALITY ASSURANCE SYSTEM**			
2.1.	**General**	• QA system description; definition of the quality policy and legal conditions • Organisation chart /QA staff • Functionality of QA	• Document available? • Key personnel; reporting lines, responsibilities and release criteria clearly defined? • Review period (procedures, processes)	PIC/S G. 1.2.; 1.4. PIC/S G.1; 2.6; 2.7; 6.1 and Annex 16
2.2.	**Suppliers quality ensuring**	• Suppliers approvals, contracting • Purchasing control/vendors evaluation	• Policy for supplier's quality assessment defined? • Audits, qualification/ evaluation made?	PIC/S G. 1.2.; 4.14; 5.25 and Annex 2; It. 25; Annex 8 It.3
2.3.	**Self inspection**	• Self inspection / audit system and performance	• How and by whom performed? How reported? • How are corrective measures implemented? • Schedule available and is adhered to?	PIC/S G . 1.2.; 9.1 9.2.; 9.3.
2.4.	**Trending**	• Results/OOS-results	• Do you assess trends? How and by whom are trends evaluated? SOP exists?	PIC/S G . 6.9.
2.5.	**Change control**	• System, responsibilities, follow up actions	• How are changes documented, managed, controlled?	PIC/S G. 1.3. ; Annex 15. It.43.
2.6.	**Risk management**	• Risk management method/approach	• Are all critical parameters included? • How is this related to validation process?	PIC/S G.Annex 15. It..44

3.	DOCUMENTATION			
	Area of operation / items	**Notes**	**Crucial questions** *« show me..»*	**Supporting documents**
3.1.	**General information**	• System description (preparation, revision. distribution, archiving) of documentation (change control) • Handling of copies from controlled documents • Syntax of documents (electronic or paper)	• Defined in writing (format, numbering system, approval criteria, distribution, return, interval for revision etc.). • How is the process of archiving managed (location, protection)? • SOP comprises the authorisation for copying, identification of copies from official and controlled documents?	PIC/S G. 4.1.-4.11 Annex 18 It.6.7. - 6.10.
3.2.	**Laboratory documentation**	• Specifications (SPECs)	• Specifications are consistent with the information currently held in the dossier?	PIC/S G. 1; 4.1.-4.3
		• SOPs	• Exists for, sampling, testing, equipment handling and other laboratory processes? Are they complete? Where are previous versions archived? • Standard form introduced?	PIC/S G . 4.4. 4.19.-4.29
		• Test instructions, analytical procedures, methods	• Specifying equipment, methods? Working details described? • Comply with licence dossier	PIC/S G . 4.15.-4.18.
		• Test records/test batch protocols	• Data comply with SPECs/instructions, complete, signed, alterations commented?	PIC/S G . 4.1.;-4.8.
		• Log books	• What is the form and content of the personnel analytical notebooks, worksheets, general lab notebooks? • Exists for equipment, calibration, maintenance, standards, sample receipt etc.? • Standard form includes complete data (lab staff identity, dedication, data to be recorded etc)? Paginated?	PIC/S G . 4.28.-4.29
		• Raw data /e.g. chromatograms, spectra, results), out prints	• What is your definition of raw data? • Recorded/attached directly into relevant laboratory notebooks data (no scrap or loose paper)	
3.3.	**Data traceability**	• Procedure, record on receipt and usage of materials, standards • Sample tracking • Analytical raw data traceability Note: For questions see It 9.1. below	• How is traceability ensured? How is the system of identification defined (e.g. how is traceability of working standards to primary standards ensured)? • How is the (identified) "history" of sample recorded (receipt log, storage conditions, handling, security, safety data etc.)	PIC/S G . 4.8.; 6.17-
3.4.	**Electronic documentation/ computerised systems**	No difference in requirements on documentation whether in paper form or electronic form. Aide Memoire related control of computerised systems (e.g. access control, audit trail, back up) is covered by PIC/S document PI 011-1		

4.	PERSONNEL			
	Area of operation / items	**Notes**	**Crucial questions** *« show me..»*	**Supporting documents**
4.1.	**General**	• Number of employees (total); specified to positions and different testing • QC Manager and deputy (other key personnel)	• The number is adequate? What is the annual average staff turnover? • Is there a document specifying qualifications, experiences, duties, responsibilities and staff presence on site?	PIC/S G 2.8; 2.9; 6.6.;
4.2.	**Training**	• Training system, programme/plan • Training on special reasons • Documentation on training • Evaluation of training effectiveness (evaluation and re-evaluation)	• System is described? Who is responsible? Who trains (trainer's qualification)? • Is a competent list available and updated regularly? • What specific training is given e.g. maintenance, cleaning staff etc.)? • SOP/records on training exist? Was programme fulfilled? • What is the interval for training re-evaluation?	PIC/S.G. 2.6 viii; 2.8; 2.9. 2.10.; 2.20 PI 012-1, 7.1.-7.3.
5.	**PREMISES AND EQUIPMENT**			
5.1.	**Premises**	• Location of the QC laboratories • Facility design, rooms separation (e.g. clean and dirty, different testing activities). • Temperature, humidity, ventilation and recording systems/alarms. • Storage areas (e.g. for documents, for samples etc.) • Labelling	• Are QC labs separated from production areas? • Where type of testing is carried out e.g. chemical, biological (microbiological) testing? Is the laboratory equipment located in appropriate area (e.g. clean equipment in clean room)? • How is the system of ventilation/humidification/temperature designed? Is it monitored continuously? Is this system separated for QC area from other areas? System of alarms for critical equipment exists? • How are the documents/sensitive instruments protected? Are storage conditions monitored? Where is defective equipment stored? • Is there clearly indicated dedication of rooms, areas (directions), status? • Are dedicated rooms/laboratories clearly identified?	PIC/S G 3. 26.- 3.29.; 6.5.; 6.6 PIC/S G. 3.1. PIC/S G. 3.3. PIC/S G. 4.8.; 4.9.; 3.44.
5.2.	**Equipment**	• Instrumentation • Assembly (DQ,IQ,OQ,PQ) • Calibration • Labelling • Log books • Cleaning Note see also item 5.4. below	• Brief description of major equipment available? • Relevant validation documents, SOP(s) for line with qualified assembly and documentation of all possible configurations available? Appropriate environmental conditions clearly stated? • Calibration procedures defined in writing? Documentation (e.g. records) available? Intervals for calibration defined? Calibration status indicated? • Equipment status indicated? • Exist for every major equipment? Are data complete (see also item 3.2. above)? • SOP(s) exists? Records available (require for critical equipment (as applicable)?	PIC/S G. 3.34 - 3.44 2.6.vii 2.6.vi

	PREMISES AND EQUIPMENT - continued			
	Area of operation / items	**Notes**	**Crucial questions** *« show me..»*	**Supporting documents**
5.3.	**Equipment validation**	• Qualification • Design qualification (DQ) • Installation qualifications(IQ) • Operational qualifications (OQ) • Performance qualifications (PQ) Note: For more details on PQ of different laboratory apparatuses see Supplements 1 and 2 to this Aide.	• IQ, OQ, PQ was carried out prior to first use? • Who approves? Fully documented (including possible involvement of suppliers and/or third party)? • Included intervals for revalidation? Requirements and specification for delivered equipment (URS) exists? Relevant checks were made? • Details on specifications and acceptance criteria are provided? Operators have been trained? • Sufficient details of procedures, materials and certified reference materials are available? Results are recorded in a manner amenable to establishing trends? Results are checked and evaluated by supervisor or delegate? Raw data are consistent with data in summary report? Results are within acceptance criteria applied?	PIC/S G. 2.6.vii; and Annex 15
5.4.	**Cleaning sanitation**	• Cleaning/sanitation system	• Validation was carried out? Relevant documents available? What are the limits for equipment cleaning? • Which equipment, glassware and other containers are used for cleaning/sanitation? • Who cleans? What are the intervals for cleaning areas specified? *SOP?*	PIC/S G. 3; 3.37
5.5.	**Maintenance**	• System • Preventive maintenance • Documentation	• How is maintenance programmed, performed and documented? Are the critical systems, areas, equipment included? Which work is contracted? • Are the regular/extraordinary maintenance programs available? Who "releases" equipment after maintenance/repair for laboratory performance? • Is there a schedule including time frames available? Is there inventory of items to be included into the maintenance system? Is there system for the formal acceptance of equipment back into service (and vice versa)?	PIC/S G. 3.2.
6.	**MATERIALS AND SUPPLIES**			
6.1.	**Materials**	• Laboratory reagents, standards • Reference substances)RM • Handling of highly toxic, hazardous and sensitising materials, poisons	• List(s) of materials available? The suppliers are listed, assessed? (see also item 2.2. above) What are requirements of identification tests? How is labelling (e.g. date of receipt)? Testing kits used? How new lots are traced back to the previous lots? • How are RM handled, labelled, stored (expiration)? Primary standards are available? Which? Are the secondary RM are acceptable? Traceability to official standards assessed? Working standards prepared? How used? Is there an SOP for the in-house calibration of reference materials. How expiry date and potency value are assigned to each reference material characterised in –house? • How are these materials handled (stored)? Are there relevant instructions available? Which measures are introduced to avoid cross-contamination? SOP for waste disposal available?	PIC/S G. 6.19.-6.21.

	MATERIALS AND SUPPLIES- continued			
	Area of operation / items	**Notes**	**Crucial questions** *« show me..»*	**Supporting documents**
6.2.	**Water and water systems**	• Water system/quality • Water sampling • Water testing	• Is the laboratory water system described? How is the laboratory water prepared? Water quality is defined (SPECS)? What is the quality of water used for microbiological testing? • Where, when and how is your laboratory water sampled (SOP)? • What kind of quality testing is done for your water used for different types of analyses?	Annex 1 to PIC/S G. It.35;44
7.	**SAMPLING AND SAMPLES**			
7.1.	**Sampling**	• General policy • Sampling • Place of sampling for raw materials • Starting/packaging materials sampling • IPC's sampling /Intermediates sampling • System of air sampling • System of water sampling • Procedures/records • Retained samples • Re-sampling Note: for re-sampling see item 9.3.below	• Show me the description of sampling system (authorisation, statistics application, sampling tools/areas)! What is the number of samples taken and justification for reduced sampling? • Sampling performed how? By whom? SOP(s) for sampling available? Includes the details on containers, labelling, equipment cleaning etc.?) • Is there separate sampling area or area in stores? How is the risk of cross contamination/bacterial contamination prevented? • What is the representative amount of sample as defined in the SOP? • System of IPC's/intermediates sampling described (SOP)? • What type of air sampler is used and why? What is the sample volume/testing time, media used, transfer time (SOPs)? Is equipment calibrated (protocol)? What disinfection procedure is used? • See item 6.2. above • What sampling techniques including equipment used? • Show me the store for retained samples of raw materials and final products! SOP (time period, number specified?) exists?	PIC/S G. 1.4; 6.11-6,14 and Annex 8 It.1.9. PI 012-1; 11.1 Annex 8 to PIC/S G.1. It.2- 5 PIC/S G. 6.7.-6.11
7.2.	**Samples**	• Handling of samples • Retained samples • Samples tracking Note: For samples tracking see Item 3.2. above	• How are the composite samples blended? How are (labelled, transferred, registered, distributed) samples for testing and contract testing handled (if applicable)? SOP(s) available? Proper accountability of samples assessed? Are there used some contract facilities? Responsibilities defined? • The amount, time period, storage conditions defined? How long are samples stored prior testing? Show me the documentation!	PIC/S G. It. 6.4.; and Annex 8 It. 6 - 9 PIC/S G. 64; 6.14.

	SAMPLING AND SAMPLES - continued			
	Area of operation / items	**Notes**	**Crucial questions** *« show me..»*	**Supporting documents**
7.3.	**Personnel for sampling**	• Staff	• Specifically trained?	Annex 8 to PIC/S G. It. 2; PI 007 1, 8.1.-8.9.
8.	**TESTING**			
8.1.	**Testing general**	• QC system • Flow sheets • Methods (see also item 8.2. below) • Contract testing • Re-testing Note: for re-testing see Item 9.3.below	• Written document available? Which types of testing performed (e.g. microbiological, immunological, chemical etc.)? • Specifying important steps? • Which methods are used for testing: standardised (e.g. Pharmacopoeial), modified or developed "in house? • Which analyses are performed on contract? (see also item 1.2. above)	PIC/S G.6.15-6.21 PI 012-1, 11.2.
8.2.	**Testing of raw materials**	• System • Methods	• Procedure(s) available? SPECs exists? Comply with marketing authorisation? Which is extend of (all raw material tested, full testing made)? Identity testing made? Which materials are released on base of supplier's certificate? • Approved/validated? Acceptance limits specified?	PIC/S G. 4.10; 5.31 and Annex 8, It.3-4
8.3.	**Testing in process, controls (IPC)**	• Testing methods/equipment • Testing in the processing areas (laboratory)	• Procedures available? Approved, validated? By whom? Parameters/limits comply with SPECs (or to values specified in processing documents)? • Who prepares and controls quality of reagents and standards used? Who controls the equipment and quality of testing? Personnel (operators) trained? Where is documented?	
8.4.	**Testing of intermediates**	• System • Sampling	• What is the testing strategy (extend, methods, parameters and limits used)? Which results are transferred into the final product protocol? • Who takes samples for this testing?	
8.5.	**Testing of final products**	• System • Sampling • Samples handling	• In which stages of processing are taken samples for final product testing? What kind of control is performed on final packages? • What is the sampling plan (which norm is used). How do you ensure the representativity of samples per batch? • How you handle the rests of final product samples (e.g. large volume containers)?	PIC/S G.1. It.1.4. vi; 1.4 vii; 6.14; 6.17;

	TESTING – continued			
	Area of operation / items	**Notes**	**Crucial questions** *« show me..»*	**Supporting documents**
8.6.	**Stability testing**	• System • On going • Premises/equipment	• Approach/policy described? Matrixing/bracketing applied? Performed in place or contracted? Full testing made? Critical parameters defined? • What is the program (intervals, number of batches/products defined)? Analytical methods are suitable? What is the extend of testing in case of changes? Which measures are taken in case if OOS results were tested? • Appropriate storage stations available? Dedicated, validated, labelled? • Thermometers and humidity meters calibrated? Is there continual monitoring of temperature and humidity? How are stored light sensitive materials? • Alarms system exists/described (log book)?	CPMP/ICH 2736/99; CPMP/ICH 4104/00; CPMP/ICH 420/02;
8.7.	**Validation of test methods**	• Policy • Validation process • Validation data • Method transfer	• Method validation is part of VMP? General SOP on method validation available? Validation report formally approved? Who approves? • Validation purposes specifies? Validation completed and documented in each protocol for parameters defined in ICH: - precision (System and method) - intermediate precision - Accuracy, - Specificity - Reproduceability - linearity (range), - limit of detection, - limit of quantitation, - robustness (including solution stability and filter compatibility) • Documented in each SOP or protocol: - Acceptance criterion for each parameter defined and met, - System suitability test procedure has been developed, - Acceptance criterion for each system suitability parameter defined and met. • Raw data stored • Is there a SOP on method transfer?	PIC/S G. 4.10; ICH Guide

9.	RESULTS AND RELEASE OF TEST RESULTS			
	Area of operation / items	**Notes**	**Crucial questions** *« show me..»*	**Supporting documents**
9.1.	**Handling of test results**	• Transfer of raw data • Laboratory Management System (LIMS) • Summary of raw data • Evaluation of test results • Trending Note: For questions see item 2.4. above.	• How are testing results (raw data) transferred into the summary protocol? Are analytical data reviewed by responsible person? How? • Is the system validated? Training of operating personnel was carried out? Is the access authorise and controlled? How? Security of results ensured? What is your change control system? • Who writes the final protocol? How and where are the raw data archived (see also item 3.1. above)? • Who is responsible for comments and evaluation of the results (QC manager)?	Annex 11 to PIC/S G.
9.2.	**Failures - Out of Specification (OOS) test results**	• System/OOS • Laboratory errors (operator, equipment) • Process/Procedure related errors • Evaluation of OOS results • Test results invalidation • *Corrective action*	• Is there a SOP for OOS result investigation? • How is laboratory investigation and formal investigation beyond the lab performed? • What is your reporting procedure? QA is involved? • What is the procedure on decision related to OOS? Reasons defined? • How are invalidated test results? Who can invalidate the testing results? • *How a corrective action implemented?*	
9.3.	**Failures- Re-testing and Re-sampling**	• Company's procedure (re-testing programme, criteria for re-sampling")	• How often can a retest be performed? How many times could be testing repeated (testing into compliance)? • What are criteria for re-sampling (e.g. if the sample was not representative)?	PI 012-1 It.13
9.4.	**Release of test results/ analytical reports/ certification**	• Process release of test results • Feedback to batch release • Preparation of Analytical (summary) Report • Preparation and release of Certificate of analysis	• SOP available? • Who's responsible for review, decisions, conclusions and formal release of batch? How much is taken into the consideration the validity of analytical results? • Who prepares and approves Summary Report (QC manager)? • Who approves Certificate of analyses? QA involved?	PIC/S G. 1.2.Vii; 1,4,; 2.6.i; 5.59-5.60

Note:
Some more details and specific items related to testing in chemical, physical-chemical and microbiological laboratories to be investigated in addition to above described subjects, are involved in Supplements 1 and 2

AIDE-MEMOIRE FOR INSPECTIONS OF PHARMACEUTICAL QUALITY CONTROL LABORATORIES

GMP inspection in chemical and physical-chemical laboratories

	Area of operation / items	Notes	Crucial questions *« show me..»*	Supporting documents
1.1.	**Chemical testing**	• Procedures in place	• Up dated? Valid? (see also AIDE Item 3.2.)	PIC/S G.6.15.-6.21
		• Reagents preparation	• Date of preparation and factors indicated on label comply with relevant method?	Eupharm. 4.2.1.; 4.2.2.
		• Volumetric glassware	• What is the level of volumetric glassware (e.g. pipettes calibration)?	PIC/S G. 3.41. 6.5; 6.19;
		• Volumetric solutions	• How are solutions labelled (indicated date of preparation)? What is the accuracy, stability, storage conditions defined (SOP)?	Eupharm.
		• Indicators for titration	• Show me your system for housekeeping of indicators!	Eupharm. 2.2.4.
			• What is the interval for titration indicators change?	
		• Water bath	• Scale of thermometer/calibration level correspond to the parameters specified in relevant methods?	
1.2.	**Physical and physical-chemical testing**	• Titrations	• Performed visual or using instruments? If visual how is personnel trained and tested?	Eupharm. 2.2.3.
		• Conductometric and pH measurements	• Under which conditions is sample solution measured? Temperature adjusted? If not how is result calculated?	Eupharm. 2.2.38.
			• Temperature controlled/adjusted?	Eupharm. 2.2.6.
		• Refractometry	• Temperature controlled adjusted?	EuPharm. 2.2.7.
		• Relative density testing	• Temperature controlled/adjusted?	EuPharm. 2.2.8.;2.2.9.
		• Polarimetry	• RM used? What is traceability to official standards. How many readings made?	
		• Viscosity testing		

	Area of operation / items	Notes	Crucial questions *« show me..»*	Supporting documents
1.3.	**Qualification for some laboratory apparatuses**	• Balances	• Are balances calibrated prior to use by suitable masses • Are masses certified? Is certificate available? How often is certification performed? • Show me your in-house calibration programme? Is there a SOP? What are the acceptance criteria and how is it linked to the external calibration results? • How often balances are calibrated? Are calibration certificates available?	PIC/S G. It.3.41
		• pH meters	• How and when is calibration performed? (daily, before use)? • Calibration buffers are relevant for pH range measured in laboratory?	Eupharm. 2.2.3.
		• Conductometer	• Which calibration material is used for determination of cell constant?	Eupharm. 2.2.38.
		• Titrator (KF determination only)	• Which material is used for the calibration of the titrator?	
		• Reference thermometers	• Are the working thermometers compared with a certified thermometer within relevant range? • How often the certified thermometer is sent for calibration? Are records available?	
		• Melting point apparatus • Refractometer • Polarimeter	• How is each instrument calibrated (SOP)? Which certified materials/device is used?	EuPharm 2.2.14-16; 2.2.6.; 2.2.7.
		• Disintegration	• Is instrument calibrated? • Is thermometer for water bath suitable and calibrated?	EuPharm
		• Dissolution	• Show me the documentation on physical calibration (shaft wobble, level, spindle speed, vibration, vessel temperature)! • Which materials are used for chemical calibration of the system (USP calibrator)?	EuPharm
		• UV VIS spectrophotometers	• Absorbance accuracy, λ accuracy, resolution, limit of stray light controlled for UV equipment?	Eupharm. 2.2..25.
		• IR spectrophotometers	• Verification of wave number scale has been carried out? λ accuracy, resolution, base line flatness controlled for the instrument?	Eupharm. 2.2..24.
		• Atomic absorption (AA)	• Performance monitored? Linearity and trends assessed? How (by choosing frequently analysed elements or another element such as cooper)?	Eupharm. 2.2.23.
		• HPLC/GC	• Is there well defined system suitability tests? Acceptance criteria have been defined?	EuPharm. 2.2.28.
		• Water testing TOC equipment	• Which material is used for calibration (RM)?	

AIDE-MEMOIRE FOR INSPECTIONS OF PHARMACEUTICAL QUALITY CONTROL LABORATORIES

GMP inspection in microbiological laboratories

	Area of operation / items	Notes	Crucial questions *« show me..»*	Supporting documents
1.	**PREMISES AND EQUIPMENT**			
1.1	**Premises**	• Areas / Sterility testing area	• How is the design and fittings of the area? Where are sterility tests carried out? In isolator? How is assessed protection against microbiological contamination during aseptic operations? Appropriate instructions for access into the critical areas exist?	PI 012-1 It.8.1.; 8.3.
		• Areas for positive control tests and fertility testing	• Fertility testing performed? Where? • Is there area for positive tests/fertility testing separate from areas where product is tested?	PI 012-1 It.11.6
		• Air supply and ventilation system in microbiological laboratory	• Is the system properly designed? Show me the schematic drawing. Is the ventilation system separated from other areas? What are the pressure differentials (e.g. airlock-test room)? Are there visual alarms?	PI 012-1 It.8.1.2.
		• Area of preparation	• Where are prepared materials for aseptic operations? Where are prepared culture media for testing? Is there any segregated area/room for manipulation with culture media?	
		• Washing room	• How and where are decontaminated materials from microbiological testing? Is there some segregation of washing area to the clean and non clean part?	
1.2.	**Equipment**	• Isolators used for the sterility testing	• IQ, OQ, PQ made? Show me the results (report)! Show me the results of leak test in general (same as LAF)!	Annex to PIC/S G. It. 7-9; PI 014-1
		• Incubators	• Show me the document involving the temperature mapping! Calibration of instrument for measurements of humidity was made? How is tested CO_2 (calibration)?	
		• Autoclave	• Show us the results of validation (cold points, cycles number, stacking)! How do you maintain autoclave. What is the quality of steam (quality SPECS)? What kinds of control test are performed in the steam?	Annex 1 to PIC/S G. It.36;
		• Sterilisation by autoclave	• What equipment is sterilised? How is equipment sterilised? Raw data available (cycle/ temperature records)? How are goods handled, which have been run a failed cycle (SOP)?	Annex 1 to PIC/S G. It.55-68;
		• HEPA Filters (validation/maintenance)	• What ways do you have to ensure the integrity of filters (HEPA)? What is the frequency of their replacement? How do you ensure there is no leakage after replacement	Annex 1 to PIC/S G. It.29; PI 012-1 It.8.1.2.

	Area of operation / items	Notes	Crucial questions *« show me..»*	Supporting documents
	PREMISES AND EQUIPMENT - continued			
1.2.	**Equipment continued**	• Colony counter unit • Particle counter • Microscope	• Calibration made? How? • Show me the document on qualification! • Which type used? Was qualified?	
2.	**MATERIALS**			
2.1	**Testing materials**	• Settle plates	• What media type is used (Bacteria &yeasts moulds suitable)? Have the plates been irradiated (zero results!)? What is exposure time and how is it calculated (dryness!)?	EuPharm 2.6.
		• Culture media(kind, purpose)	• Is there tested each batch (growth promotion, selectivity, sterility)? Is there an agreement available on shipment (plates) of prepared media? How is shipment validation performed? How do you guarantee that shipment conditions are kept constant	PI 012-1 It.11.3.
		• Culture collection/ Reference. standards	• How do you store the reagents and strains used for the identification? Show me the inventory! Are identifications of strains carried out on arrival? Expiration indicated on labels?	
2.2.	**Protective garments**	• Preparation • Use in performance	• How are gowns washed / sterilised? • Which protective garments are used by operators at sterility testing? Are they suitable for intended use? Are the laboratory coats located in appropriate manner? Instructions for use exist? Training of operators was made? What standard for micro assays is used?	
3.	**TESTING**			
3.1.	**Microbiological testing (product)**	• Incubation	• Show us the limits of incubation! What is the incubation time and temperature? What is the frequency of observation of sample during incubation?	EuPharm.2. 6.1. and Suppl.4.7. It.2.6.1.13.
		• Growth promotion	• Do you have records (registration/incubation)? Which micro-organisms used?	PI 012-1, 11.3.-11.6. PI 007-1, 5.2.-5.5.; 9.9.1.-9.9.2
		• Positive controls	• The procedure for sub-cultures available? Which controls do you have? How often do you perform positive controls and why?	PI 012-1, It.11.5.
		• Negative controls	• Do you perform negative product controls? Show me SOP (number of containers/samples)!	
		• Bioburden	• Limits defined/used in production/in process controls? Does bioburden IPC´S show the worst case conditions?	
		• Micro-organism – identification	• Which system do you use to identify? If certain system is chosen VITEC- how is validated?	

	Area of operation / items	Notes	Crucial questions « show me..»	Supporting documents
3.2.	**Microbiological testing Environmental**	• System of performance	• How is monitoring performed at rest/in operation? What is the frequency? How is testing verification performed? Is the monitoring involved in validation plan? Are there available documents on pre-qualification/re-qualification?	PIC/S G. 1.3. ; Annex 15. It.43.
		• Sampling location	• Location/sampling sites selected? How is worst case determined? Water system/area included? Which mode/method is used (SOP)? How are deviations handled? Validation made?	PI 012-1, It.10.3
		• Swabs • Settle plates	• Which types of swabs/solutions are used? Which swabbing techniques are used? • Which media used? What is the method, time exposure, surface area/limits and recovery rate? The recovery plate for the surfaces validated: How?	PI 012-1, It.10.4-10.5.
		• Contact plates	• Vendor verification was made? Preparation/expiry date specified? Sterility test of contact plates performed? Incubation and frequency described (SOP)? Identification of organisms made? What is the time lapse from fumigation to taking sample?	
		• Limits for microbiological testing	• Limits defined for raw materials/finished products, water, air quality, equipment within processing and testing areas, for personnel, storage areas, detergents (cleaning validation)? Limits justified? How? • What are your action/alert limits? What is the procedure if the limits overshoot? Note: The particulate matter (with respect to situation "in site") should be controlled in addition.	