PHARMACEUTICAL INSPECTION CONVENTION

PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

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AIDE-MEMOIRES

INSPECTION OF BIOTECHNOLOGY MANUFACTURES

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1. DOCUMENT HISTORY

Adoption by Committee	13 September 2005
Entry into force	1 January 2006

2. INTRODUCTION

2.1 General GMP aspects and specific aspects for sterile biological medicinal products (Annex 1) and blood or plasma derived products (Annex 14) are not included in the aide memoires.

2.2 GMP aspects covering more stages in biotechnology manufacture, e.g. from cell banks to drug product, are presented in a general aide memoire in the "Specific biotech issues" section ahead of the more specific parts for the individual stages.

3. PURPOSE

3.1 The aide memoires were drafted with the aim of facilitating the effective planning and conduct of GMP inspections and the purpose is to provide a tool to harmonise GMP inspections (biotechnology and biological) to assure the quality of such inspections.

3.2 The aide memoires should enable the inspector to make both an optimal use of the inspection time and an optimal evaluation of GMP compliance.

4. SCOPE

4.1 The aide memoires applies to biotech products and classical biological products for human use, but could also be used for gene-therapy and cell-therapy products. It includes also products for use in clinical trials.
The aide memoires should be considered as a non-exhaustive list of areas to be looked at during an inspection.

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 innovation or the pursuit of excellence.

5. SPECIFIC BIOTECH ISSUES

5.1 In general, the wording "cell bank" and not "seed lot" will be used.
The aide memoire covers working cell banks and master cell banks including traceability to original cells for the master cell bank (pre-master cell bank)

5. 2 GENERAL AIDE-MEMOIRE

1.	Area of operations/item **General Biotech GMP**	Notes	Crucial questions	Supporting documents
1.1	Personnel	Prevention of cross contamination	*Procedure to avoid the simultaneous handling of other living or infectious material by the same persons *Do workers pass to other areas during one working day *Log books	Annex 2.5
		Procedure to avoid the simultaneous handling of inactivated products and non-inactivated ones by the same persons	Do workers pass from areas with non-inactivated products to inactivated products areas	Annex 2.5
		Qualifications	*Is the personnel dedicated / qualified *Is its background / education appropriate to the activity *Is there a training (qualification/continuous) *Are medical checks / X-rays done regularly and relative to the risk of infection (BCG) *Is the immunological status controlled	Annex 2. 4 & 5 Annex 18; 3.1
		Concept of hygiene	*Is there a concept of hygiene in place, including change of clothes, masks, gloves, disinfection *Is showering indicated under particular circumstances	Annex 2.5 Annex 18; 3.2
1.2	Rooms & environment	Questions to be asked (no requirements)	*Is the room classification appropriate to the activities *Is the design of the rooms and equipments appropriate to the activities *How are the pressure cascades (positive, negative, sink, containment) defined *Are negative pressure areas or safety cabinets used for aseptic processing of pathogens surrounded by a positive pressure sterile zone *Are the rooms product dedicated *Is the HVAC system adequate *Is there a concept of areas and rooms for the whole company *Is there a concept of hygiene for areas and rooms *Is there a concept of environmental monitoring *Are the pressures monitored *Is fumigation possible *Are procedures and a management in place in case of lost of integrity and damage *Are open or closed systems used *Are equipment and environmental particulate and microbial contamination controlled	

		Environmental control	Are animals used	Annex 2.6 Annex 18; 18.15
			Are rooms/premises accesses restricted to authorized persons only	Annex 2.21 & 22
			*How do you prevent cross contamination by air	
		Cross contamination		Annex 2.7
1.3	Equipment	Prevention of cross contamination	*Are equipment dedicated or multiproduct	Annex 2.7
			*Will equipment leave the room for cleaning. If so is it disinfected on beforehand and is disinfection validated	Annex 2. 6-20 Annex 18.4 & 5
			*Is production on campaign bases or continuous	
			* Are the same equipments used both for decontamination and sterilisation	
		Prevention of contamination of inactivated products by non-inactivated ones	* Are flows of contaminated materials and equipments separated from those of sterilized ones	
			* Are inter-campaign and effluents decontaminations validated and periodically revalidated	
1.4	Processes	Batch definition of the active ingredient	*Is a batch definition present and does it comply with the marketing authorisation	
		Storage conditions	*Are storage conditions for all intermediates and drug substance and drug product defined	5.36 Annex 18; 7.4
		Pooling strategy	*Does a pooling strategy exist (intermediates and drug substance) and is it in compliance with the registered details	Annex 18; 8.4
			*Are specifications set for yields	
		Yield	*Are all process parameters covered (e.g. pH, temperature, time, flow rate)	4.14; Annex 18; 8.14 & 18.41
		Process parameters		Annex 2.41, Annex 18; 8.3
			*Are protocols available for buffer preparations	
		Buffer preparations	*Are expiry dates and storage conditions specified	4.15
			*Is status and identity labelling adequate	
			*Are buffers QC-tested and released before use	
			*Is bioburden measured	
			*Are endotoxins measured	
			*Where are the buffers produced	
			*Are they produced in place	
			*Are they sterilized in place	
			*Is bioburden measured	
			*Are endotoxins measured	
		Water	*Is the water used sterile	Note for Guidance on water for pharmaceutical use
			*Is the quality of the water monitored regularly	
			*What are the specifications/quality	

		Gases Disposal of waste material	*Procedure, documentation *Is waste material disinfected with a validated method	
1.5	Performance	Routine trending	*Are critical parameters trended *Is a statistical method used *Does a formal review period exist	2.43

OPERATION-SPECIFIC AIDE MEMOIRES

1.	Area of operations/item **Cell banks and cell banking**	Notes	Crucial questions	Supporting documents
1.1	Manufacturing of master and/or working cell banks	Inter-campaign activities	*Are cleaning and decontamination procedures validated *Are they monitored	Annex 2.29 & 30
		Area and line clearance	*Procedure and documentation	ICH Q5 D 2.2.2
		Container, vessels	*Cleaning, sterilisation and testing procedure	Annex 2.16
		Culture media	*Preparation, labelling, sterilisation, sampling and testing procedure *Certificate if material of animal origin	
		Pre-master cell bank	*Specifications, analysis, certificate, testing, origin	
		Monitoring	*HVAC, including LAF *Incubation (T°, RPM…)•	
		In process controls	*Inoculation• *Viability• *Parameter indicating step of going into suspension• *Growth control• *Microbiological control•	
		Uniform composition of each container: aliquoting conditions.	*Pooling of cells for banking if more than one vessel used *Uniform suspension *Closure verification validation• *Labelling (validated to avoid loss of information on the container) *Sampling *Reconciliation *Lot number control if pooling	ICH Q5D 2.2.2 GMP Annex 2.31
		Freezing and storage•	*Time limit between aliquoting and freezing, documentation *Conditions (T°, time limits….)	

		Qualification before and after freezing (characterisation•, testing•) Quarantine	*Identity minimum before freezing *Purity minimum before freezing *Viability minimum after freezing *Dedicated, procedure after release	Annex 2.29 CPMP/BWP/ 41450/98 3.3
1.2	Maintenance of master and working cell banks	Access for authorized personnel Storage and storage conditions Protection from catastrophic events Records of use of vials Periodical monitoring•	*Procedure, names *Freezer or Nitrogen tank (liquid or gas phase) *Records (limits, corrective action procedure) *Alarm system (records, 24h link) *Risk of contamination (control related to the Nitrogen level, validation *Risk of confusion (dedicated tanks for commercial production, map and identification of the stored containers) *Identical treatment of all containers during storage (procedure) *Redundancy, remote sites (procedure, description) *Back up power *Automatic liquid Nitrogen fill systems (alarm system, contract with the supplier) *Once removed no return of containers (procedure) *Inventory *Suitability for use•	Annex 2.32 Annex 18; 18.20 Annex 2.31, 32 &33; Annex 18; 18.20 & 21 ICH Q5D Annex 2.31 & 33 Annex 18; 18.22 Annex 18; 18.23

• Input to be given by the assessors

1	Area of operations/item **Fermentation process**	Notes	Crucial questions	Supporting documents
1.1	Premises and equipment	Specification of the product/s produced	*Are dedicated facilities used for Bacillus anthracis, Clostridium botulinum, and Clostridium tetani until inactivation process is accomplished and for BCG vaccines and live organisms used for the production of	Annex 2. 6-20 Annex 2.8

			tuberculin	
		System	*Are there single harvest or continuous harvest (simultaneous fermentation and harvesting) *Are the construction, the material and the material finish (surface, roughness, polish, weld seam processing, etc.) of the following components and fittings adequate and confirm cGMP-rules: - fermenter (open, closed or a contained system?) - pipe work (dead legs…) - valves, vent filters - manometers - pH-/ oxometers - thermocouples, temperature sensors - pipes and valves for charge and discharge	
		Cleaning and sanitizing procedures	*Is cleaning and sanitizing necessary after each run (for which products)	
		Controlling	*How is the addition of the following objects registered and documented? - water - media - buffers, acids, lye's - cell substrates - induction agent - gases - anti foam	
1.2	Process	General	*Campaign fermentation or continuous fermentation? *Does the process follow an automated procedure *Is the addition of all necessary components proceeded automatically *Is the aseptic addition of the following objects guaranteed: - cell substrates - water - media - buffers - gases *Are all filters validated (incl. integrity testing) for - media - buffers - gases - anti foam - is a shift transfer log available	Annex 2. 34-40, 41-44) Annex 18. 6,7,8 &12

		Process start	CIP *is there a validation documentation *are monitoring data available, e.g. on conductivity, pH, Non-CIP cleaning *is there a validation documentation *are there data proving cleanliness, e.g. TOC, swabbing etc. SIP *is there a validation documentation *are monitoring data available, e.g. on temperature logging Non-SIP *is there a validation documentation of the sterilisation equipment / method being used *is there proof of sterility, e.g. media hold test	
		Inoculation	*Is information on seed culture/cell bank management available? *where is the cell substrate produced *Is there an expansion of culture (in pre culture / intermediate fermenter or main fermenter) *Is an inoculation procedure in place *Is there an assess on the risk of contamination during inoculation and does the company has addressed this risk *Is bioburden of seed material measured *Are endotoxins of seed material measured *Is the virus content of seed material controlled	
		Media	*Is a growth promotion test from batch to batch established *Are protocols available proving that all components are provided in the correct quantity and quality (components of animal origin: assessed for their TSE risk) *Are media produced directly	

			in the fermenter or produced in a media formulation tank *Are media filled from an external source, e.g. media bag, supplier container *Are data available proving that the media transfer does not affect media sterility *Are media sterilized in place *Are data available proving the sterility of the medium, e.g. media hold test (if conducted), filter integrity test in case of filtration, temperature curves in case of heat sterilisation *Is bioburden measured *Are endotoxins measured *Where are the agents produced *Are they produced in place *Are they sterilized in place *What type of anti foam is used *Is bioburden measured *Are endotoxins measured *What are the specifications/quality	
		Induction agents Anti foam Fermentation	*Is there a correspondence between process specifications (e.g. number of cell doublings, yield etc.) and the data of the inspected batch *Is there a proof that sampling does not pose a risk of contamination *Is there an inactivation process? *Are intermediate products stored? *Is there a proof that harvesting does not pose a risk of contamination *Do all critical operation parameters are monitored during process as: - process time - temperature - pH - pO2 - pCO2 - pressure	

		Harvesting Monitoring	- agitation rates - addition of gases - addition of buffers, acids, lye's - bioburden - viral content - endotoxins - viscosity *Are the further parameters of the fermentation process monitored: - contamination - cell identification - cell growth - cell productivity - cell viability - cell ratio (co-cultivation of two different cells) - cell aggregate formation	

1.	Area of operations/item **Extraction and isolation**	Notes	Crucial questions	Supporting documents
1.1	Equipment	Centrifugation Filtration Precipitation	Aerosol formation *What is the filter life time and how is it assessed *Adsorption to the filter	Annex 2.36 Annex 18; 18.40
1.2	Process	Storage and expiration time of intermediates	*Is storage temperature defined *Is the expiration time documented	
1.3	Qualification	Cleaning	*How is the equipment cleaned and how is it validated *Are product specific assays performed Are these assays validated * Is the holding time of dirty and clean equipment defined and covered by cleaning validation studies.	Annex 15
2	**Viral removal steps**			
2.1	Process and environment	Process parameters Precautions to prevent viral contamination	*Are critical process steps performed within their validated parameters *Are pre and post viral removal steps performed in separated area's with separate air handling units? *Is the equipment dedicated to pre and post virus removal steps * Do workers pass from pre viral to post viral areas	Annex 18; 18.51 Annex 18; 18.52 & 18.53 Annex 2.5 Annex 18; 18.38

3	**Purification**			
3.1	Column resins	Incoming acceptance criteria	*Are resins tested regarding: -Chemical/biological aspects -Physical aspects -Functional aspects	Annex 2.40
		Performance	*Is life time of resins/ maximum number of runs defined and what is the basis *Are HETP and asymmetric measurements performed *Are leachables tested *Is consistency of purification profiles a performance criteria *Are resins dedicated to one manufacturing step of one product	Annex 2.40 Annex 2.25 Annex 2.40 5.38 Annex 18; 18.53
3.2	Chromatography systems	Column packing	*Is the size of the column resin volume defined or is it calculated? *Are the flow and pressure during packing defined?	Annex 2.41
		Regular maintenance	*Inspection and preventive replacements of parts *Visual inspection of resin or other check of the column pre-use.	3.41
		Cleaning and storage	*Are cleaning procedure and used cleaning agents described *What are the storage conditions, e.g. temperature, time, storage solutions	3.36
		Operation instruction	*Preparation, use and dismantling of the system *Specifications for critical parameters e.g. linear liquid flow, column bed height, gradient slope, temperature) *Are product collection criteria strictly defined?	4.15

	Area of operations/item	Notes	Crucial questions	Supporting Documents
1.	**Drug substance**	Traceability	*Is traceability to cell banks in place	
		Characterization and Specifications•	*Is drug substance characterized by chemical and biological methods *Are specifications defined (Identity, Purity, Potency, Yield etc.)	Note for Guidance: Production and quality control of medicinal products derived by recombinant DNA Technology Annex 2.24
		Stability	*Is an on-going stability program established	Annex 18; 11.5
		Consistency	*Is consistency of the first produced batches of bulk final drug substance documented (Characterization tests, In-process controls, Specifications)	Annex 18; 12.50 Note for Guidance
		Reference material	*Is a procedure in place how to select the reference material *Is a fully characterized batch of drug substance retained as reference material	Note for Guidance Annex 2.42 Annex 18; 11.18
2.	**Drug product**	Specifications•	*Quality (e.g. appearance, particulates, pH, moisture ...) Identity Protein concentration/ Content Purity/Contamination (viral, pyrogens, microbial, chemical) Activity (potency) Sterility	Note for Guidance Annex 18; 6.17
		Stability	*Is an on-going stability program established	6.23 to 6.33
		Consistency	*Batch to batch consistency of first produced batches	Note for Guidance
3.	**Distribution**	Shipping validation	*Is temperature monitored or is transportation validated *Is there a system in place for traceability of distribution	Annex 18; 10.2 & 17.2

• Input to be given by the assessors

7. REVISION HISTORY

Date	Version Number	Reasons for revision