

Guide for inspection of manufacturers of biological products

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GLOBAL PROGRAMME FOR VACCINES AND IMMUNIZATION
Vaccine Supply and Quality
Global Training Network



World Health Organization, Geneva, 1997

The **Global Training Network** is designed for staff of National Control Authorities and selected vaccine manufacturers meeting specific entrance criteria. This document is designed for use by participants in the Global Training Network, specifically for those participating in curricula related to Good Manufacturing Practices.

Curricula and curricula material for the Global Training Network have been overseen by Expert Review Panels convened at the request of WHO and comprised of experts internationally known for their proficiency in the particular field. The Vaccine Supply and Quality Unit would like to particularly thank the experts who reviewed this document and served on the Expert Review Panel: Dr Ian Sykes, Pharmaceutical Consultancy Service, Haastrecht, Netherlands, Dr Chung K Lee, Salk Institute, Swiftwater, Pennsylvania, USA, and Ms Carolyn Woodruff, Therapeutic Goods Administration, Melbourne, Victoria, Australia. The Global Training Network is financed in part through funds donated by the World Bank.

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¹ The checklists included in this document correspond to the guidance presented in the WHO publications: *Good manufacturing practices for pharmaceutical products*, WHO TRA 823, 1992, and *Good manufacturing practices for biological products*, WHO TRA 822, 1992.

Introduction

WHO has prepared several documents offering guidance for good manufacturing practices (GMP). GMP requirements describe the compendial recommendations and other internationally adopted recommendations with reference to the manufacture and quality control of pharmaceuticals including biological products.

This Guide for Inspections presents these requirements in a form which can be used for determining whether a manufacturer complies with the GMP recommendations, as well as serving as an aid in interpreting and clarifying the GMP documents. It is also intended to support harmonization of inspection and internal audit procedures.

The audit items in each section are presented first as a list of topics with reference to the relevant WHO GMP clause(s), followed by questions formatted in checklists. The questions are concerned with the various aspects of the facility's compliance with GMP. The checklists can be used in the planning of or preparation for an inspection and are designed to be duplicated and used during the inspection process, both as an aide memoire and as a record of the observations on which to base the inspection report.

Although comprehensive, this series of questions is not exhaustive of all aspects related to GMP inspections of a biological manufacturer. There might be additional aspects which should be addressed for a specific vaccine or biological production process. Space is provided on each checklist for comments. Overall, responses to groups of questions rather than any single one may, in fact, better reflect actual compliance with good manufacturing practices.

The document is not intended to set a minimum level of compliance or an acceptable standard for manufacturers. The response to any findings is left to the discretion of the national control authorities. The aim is, rather, to increase understanding and implementation of compliance with GMP by manufacturers globally. Using this guide as a tool, it is possible that areas for improvement may be more easily identified and monitored by the national control authority and the manufacturer in the joint task of improving the quality of biological products.

It is anticipated that the guide will be of value to manufacturers for internal audits and to national control authorities responsible for carrying out inspections, as well as for evaluations for WHO or other organizations. The document is intended to be equally applicable to the evaluation of facilities in developed and developing countries. This document may also aid in training in GMP and related activities.

WHO guidance documents (3, 4) provide information on the role of inspectors and national control authority (NCA) inspections. In addition to the WHO GMP guidance documents (1, 2) which form the basis of this Guide to Inspections, WHO guides (9, 10) provide detailed information on standard operating procedures (SOPs), master formulae (MF) and validations. These documents can be referenced while preparing for an inspection.

This document has been prepared for the Global Programme for Vaccines and Immunization, WHO, and is designed to focus on biological products. It has, however, a wider implication since almost all questions are equally applicable to pharmaceutical products. The WHO guidelines for products made using biotechnology have been reviewed to ensure that the questions are worded to be relevant to these biological drugs as well. There has been no attempt to incorporate specific inspections items for blood products.

INSPECTION of _____; Date _____

<p>Full Address of Company:</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>Tel: _____</p> <p>Fax: _____</p>	<p>Products manufactured:</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p>	<p>Location of production:</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p>
<p>Inspection type: mark all that apply</p> <p>external []</p> <p> routine []</p> <p> concise []</p> <p> special []</p> <p>internal []</p> <p> annual []</p> <p> semi-annual []</p> <p> announced []</p> <p> unannounced []</p> <p> follow-up, re-inspection []</p> <p> pre-licensing []</p>	<p>Names of inspectors:</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p>	<p>Affiliation of inspectors:</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p>
<p>Department(s) being inspected:</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p>	<p>Date(s) of inspection:</p> <p>from _____</p> <p>to _____</p> <p>Normal working hours:</p> <p>_____</p>	<p>Date of most recent previous routine inspection (internal or external):</p> <p>_____</p> <p>Type: _____</p> <p>_____</p> <p>QA audit report #: _____</p>
<p>Floor plans of facility available?</p> <p>Y [] N []</p>	<p>Airflow patterns, differential pressures, and classification of production areas indicated?</p> <p>Y [] N []</p>	<p>Flow patterns for personnel, supplies, raw materials, product, and waste for production areas indicated?</p> <p>Y [] N []</p>

SUMMARY OF COMPANY ORGANIZATION AND INSPECTION

Page ___ of ___

INSPECTION of _____; Date _____

SUMMARY OF SENIOR PERSONNEL, A: (use next page if these departmental divisions are not appropriate, or for other department designations)

ADMINISTRATION Position Title _____ _____ _____	Name _____ _____ _____	
PRODUCTION DEPARTMENT Position Title _____ _____ _____ _____	Name _____ _____ _____ _____	Qualifications _____ _____ _____ _____
ANIMAL FACILITIES Position Title _____ _____	Name _____ _____	Qualifications _____ _____
ENGINEERING/MAINTENANCE Position Title _____ _____	Name _____ _____	Qualifications _____ _____
QUALITY CONTROL DEPT Position Title _____ _____	Name _____ _____	Qualifications _____ _____
QUALITY ASSURANCE DEPT Position Title _____ _____	Name _____ _____	Qualifications _____ _____

SUMMARY OF COMPANY ORGANIZATION AND INSPECTION

Page ___ of ___

INSPECTION of _____; Date _____

SUMMARY OF SENIOR PERSONNEL, B: (use for additional departments or different organizational divisions)

_____ DEPARTMENT Position Title _____ _____ _____	Name _____ _____ _____	Qualifications _____ _____ _____
_____ DEPARTMENT Position Title _____ _____ _____	Name _____ _____ _____	Qualifications _____ _____ _____
_____ DEPARTMENT Position Title _____ _____ _____	Name _____ _____ _____	Qualifications _____ _____ _____
_____ DEPARTMENT Position Title _____ _____ _____	Name _____ _____ _____	Qualifications _____ _____ _____
_____ DEPARTMENT Position Title _____ _____ _____	Name _____ _____ _____	Qualifications _____ _____ _____
_____ DEPARTMENT Position Title _____ _____ _____	Name _____ _____ _____	Qualifications _____ _____ _____

INSPECTION of _____; Date _____

1.0 PERSONNEL (TRS 822 3; 823 10, 17.6-17.15)

The manufacturing establishment and its personnel shall be under the authority of persons who have been trained in management and in the techniques used in manufacturing biological substances, and who possess the scientific knowledge upon which the manufacture of these products is based. The personnel shall include specialists with training appropriate to the products made in the establishment.

A GENERAL

GMP Item	Reference	
	TRS 822 Annex 1	TRS 823 Annex 1
1	Organizational chart.	10.3
2	Job descriptions.	10.3
3	Qualifications and numbers of personnel.	10.2
4	Independence of production from QC.	3.5
5	Suitable control of personnel movement between areas.	3.4
6	Registration of those responsible for lot release with NCA.	3.6

B KEY PERSONNEL

GMP Item	TRS 822 Annex 1	TRS 823 Annex 1
1	Sufficient numbers for supervision.	10.6
2	Appropriate skills and training.	10.7

C TRAINING

GMP Item	TRS 822 Annex 1	TRS 823 Annex 1
1	On the job training for new employees.	10.12
2	Training and education records.	3.8
3	GMP training programme.	10.12; 17.7
4	Containment procedures.	10.12
		10.13

D PERSONAL HYGIENE

GMP Item	TRS 822 Annex 1	TRS 823 Annex 1
1	Requirement for protective apparel.	10.21; 10.23 17.10; 17.11; 17.13
2	Requirement for reporting health and medical conditions.	3.2
3	Medical monitoring programme.	3.9; 3.10
4	Controlled entry requirements.	10.16
		10.17; 10.22

1.0 PERSONNEL CHECKLIST

INSPECTION of _____; Date: _____

1.0 A: General

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Is there an organizational chart? What departments are identified? Production department(s) _____ _____ _____ _____ Filling [] Labeling/Packaging [] Quality Control [] Engineering/Maintenance [] Quality Assurance [] Receiving/Warehousing [] Shipping/Distribution [] Purchasing [] Animal Procurement/Care []				Attach org chart, add other departments or indicate departments if different from list.
2	Are there job descriptions for key personnel? Are they appropriate to the activities of the department?				
3	Number of engineering staff _____ Number sufficient? Qualifications adequate? Experience sufficient? Number of production staff _____ Number sufficient? Qualifications adequate? Experience sufficient? Number of quality control staff _____ Number sufficient? Qualifications adequate? Experience sufficient? Number of quality assurance staff _____ Number sufficient? Qualifications adequate? Experience sufficient? Number of animal care staff _____ Number sufficient? Qualifications adequate? Experience sufficient?				
4	Is there a clear separation of responsibility for production from QC?				
5	Is there a clear separation of personnel from different areas handling animals, microorganisms, and product? By written procedure?				
6	Are the names and qualifications of those responsible for approving the lot processing records registered with the NCA?				

1.0 PERSONNEL CHECKLIST

Page ____ of ____

INSPECTION of _____; **Date:** _____

1.0 B: Key Personnel

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Are there sufficient key personnel to supervise assigned functions? Production Filling Labeling/Packaging Quality Control Engineering Maintenance Quality Assurance Other departments: _____ _____				
2	Are they skilled/trained in fields such as biology, microbiology, chemistry, veterinary medicine, chemical or industrial engineering, etc? Engineering Production Department(s) Filling Quality Control Quality Assurance Animal Care Other: _____				

1.0 C: Training

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Are there on the job training procedures for new employees?				
2	Are training and education records available? Are they current? Are they filed with the supervisor? Engineering/Maintenance Production Department(s) Filling Quality Control Quality Assurance Animal Care Other departments _____ _____				
3	Does a GMP training programme exist? For new employees? Annual update for all staff? Are records maintained?				
4	Is there training in containment procedures? By written procedures? Are records maintained?				

1.0 PERSONNEL CHECKLIST

Page ____ of ____

INSPECTION of _____; Date: _____

1.0 D: Personal Hygiene

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Are appropriate protective apparel required? Is there a gowning SOP for production staff? For other staff entering production areas? (Engineering/Maintenance; Cleaners; QC samplers; QA auditors) For staff in the Quality Control Lab?				
2	Are staff instructed to report health or medical problems that may have an adverse effect on the product?				
3	Is there a medical monitoring programme to ensure protection of staff and product? Vaccination where applicable? For all employees? For contractors?				
4	Do controlled entry requirements exist for: Production areas? Testing areas? Animal areas? Do procedures exist for preventing unauthorized entry into: Production areas? Storage areas? Quality control areas? Animal areas? Are the procedures in writing?				

INSPECTION of _____; Date: _____

2.0 PREMISES (TRS 822: 4; 823: 11, 17.16-17.23)

Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, buildup of dust or dirt and, in general, any adverse effect on the quality of products. (For premises where pathogenic organisms are utilized, see also 10.0 Containment Practices, A Facility Design).

A GENERAL

GMP Item		Reference	
		TRS 822 Annex 1	TRS 823 Annex 1
1	Suitability of building(s).	4.1-4.4	11.1
2	Clearly defined and appropriately controlled areas.	4.11; 5.1	11.1; 11.2; 11.7-11.17; 11.29
3	Design prevents entry of pests.	4.1	11.6
4	Adequate plumbing: drains and traps.	4.2	11.25
5	Flow patterns for materials, personnel, product and waste.	4.4	11.1
6	Adequate lighting.	4.4	11.5; 11.28
7	Building specifications updates and revalidation.		
8	Suitability for campaign production.	4.5	11.20
9	Adequacy of washing facilities.		11.7; 11.8; 11.9
10	Overall cleanliness, neatness and state of repair.		

B SUPPORT SYSTEMS

GMP Item		TRS 822 Annex 1	TRS 823 Annex 1
1	Design and validation of support systems.		17.32
2	Heating, Ventilation and Air-conditioning (HVAC) systems.	4.12, 4.13	
3	Compressed air system.		
4	Clean steam system.		
5	Water for injection (WFI) system.		17.33

C ADDITIONAL CONSIDERATIONS FOR STERILE PROCESSING

GMP Item		TRS 822 Annex 1	TRS 823 Annex 1
1	Aseptic manufacturing areas and operations consistent with WHO guidelines.		17.1
2	Aseptic manufacturing area has all required facilities.		12.4; 17.3; 17.4; 17.5; 17.17; 17.20; 17.22; 17.24; 17.37
3	Exclusions from aseptic manufacturing area.		17.21; 17.30
4	Isolation of vaccine processing.		17.39
5	Appropriate containment level.		17.1-17.5
6	Sanitation of aseptic areas.		17.34-17.37

2.0 PREMISES CHECKLIST

Page ____ of ____

INSPECTION of _____; Date: _____

Area inspected: Building: _____; Room(s) _____; Product: _____

Staff escort: _____

2.0 A: General

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Is the building used for manufacturing of product suitably located and constructed, and of adequate size to facilitate cleaning, maintenance and proper operation?				
2	Are areas clearly defined and appropriately controlled:				
a	for quarantine and storage of starting materials?				
b	for storage of in-process material?				
c	for manufacturing and processing operations?				
d	for control and laboratory operations?				
e	for quarantine and storage of finished products?				
f	for holding of rejected material?				
g	for ancillary usage, e.g. rest rooms, maintenance workshops?				
h	for animal housing?				
3	Does the building design prevent the entry of insects, vermin and other animals?				
4	Plumbing				
a	Do adequate drains exist? Are they designed with an atmospheric break to prevent back-siphonage from sewer?				
b	Are traps being maintained to ensure adequate performance?				
5	Does the design of the facility achieve a unidirectional flow of materials, personnel, product and waste so as to avoid cross-over of clean and dirty (infectious) material?				
6	Is the lighting provided adequate for the conditions necessary for the work being conducted in the area?				
7	Are facility layout drawings including mechanical, electrical and architectural kept up-to-date following changes? Is revalidation of facilities performed following refurbishment?				

2.0 PREMISES CHECKLIST

Page ____ of ____

INSPECTION of _____; Date: _____

Area inspected: Building: _____; Room(s) _____; Product: _____

2.0A General, continued

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
8	Campaign production				
a	Is the facility designed and constructed to permit production in campaigns?				
b	Has campaign changeover been validated (effectiveness of changeover)?				
c	Is there a documented procedure for changeover that described decontamination, removal of equipment, etc? Is the procedure followed?				
d	Is there a campaigning schedule available?				
9	Do washing facilities include:				
a	hot and cold water?				
b	soap or detergent?				
c	clean toilet facilities that are easily accessible to working area?				
d	clean hand drying facilities?				
10	Are the premises satisfactory with respect to:				
a	neatness and cleanliness?				
b	state of repair, e.g. paint work, cracks in floors, ceilings or walls, door seals, etc?				
c	exposed piping or electrical wiring?				
d	blocking of air ducts?				
e	equipment blocking corridors or exits?				

2.0 B: Support Systems

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Support systems, including those identified below:				
a	Are they designed and validated to assure integrity of the characteristics of in-process material and final products?				
b	Is there a planned maintenance program on each system? Is it followed?				
c	Are there specs and written procedures for the operation of the systems, sampling plan, sites monitored and alert and action levels defined?				
d	Are definitive action steps taken to resolve conditions that are out of specification?				

2.0 PREMISES CHECKLIST

INSPECTION of _____; Date: _____

Area inspected: Building: _____; Room(s) _____; Product: _____

2.0 B: Support Systems, continued

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
2	HVAC System				
a	Are prefilters present in heating, ventilation and air-conditioning (HVAC) systems and replaced on a routine basis?				
b	Are high-efficiency particulate air (HEPA) filters tested for integrity, at least annually?				
c	Are HEPA filters terminally located?				
d	Are duct work materials impervious to disinfectants that may cause corrosion?				
e	Are duct work and filters located outside the clean rooms?				
f	If fumigation procedures are used, is the facility designed to permit effective fumigation?				
g	Is the number of air changes per hour adequate for defined areas?				
h	Is the air flow adequate? (minimal pressure differential (1.21 mm H ₂ O) maintained?)				
i	Is room temperature and humidity effectively controlled?				
3	Compressed air				
a	Is the air supply free from oil?				
b	Is the air supply filtered through a sterilizing grade air filter?				
c	Is humidity controlled?				
4	Clean steam				
a	Is clean steam used for sterilization of product contact surfaces?				
b	Is the distribution system constructed of stainless steel treated to prevent corrosion and sloped for drainage?				
5	Water for injection (WFI) system				
a	Is the design of the WFI system adequate to supply sufficient water of compendial (pharmacopoeial) quality?				
b	Is there a holding tank for the WFI system, is it fitted with a sterilizing grade vent filter that is integrity tested?				
c	If WFI is stored on a continuous circulation, is it held at $\geq 80^{\circ}$ C? If not circulated, is it discarded every 24 hours or diverted for suitable use?				
d	Is WFI used as a lubricant on the recirculating pumps?				
e	Are all the dead-legs within acceptable length?				

2.0 PREMISES CHECKLIST

Page ____ of ____

INSPECTION of _____; Date: _____

Area inspected: Building: _____; Room(s) _____; Product: _____

 2.0 C: Sterile Processing

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Are the aseptic manufacturing areas and operations consistent with the WHO guidelines for sterile pharmaceutical products provided in TRS 823, Section 17, page 59ff?				
2	Does the aseptic manufacturing area include:				
a	smooth, hard non-particulate generating cleanable floors, walls and ceiling? Able to withstand cleaning, disinfecting reagents?				
b	no horizontal pipes or conduits located over exposed components, in-process material, production or product contact surfaces?				
c	environmental controls, e.g. temperature, humidity and viable and non-viable particles? Are there specifications for these controls? Has the system been validated?				
d	air supplied through HEPA filters? (Terminal filters should be employed for final formulation and filling activities).				
e	environmental monitoring system, e.g. temperature, humidity and particulates?				
f	fixtures (electrical outlets and lighting, etc.) flush mounted and sealed to prevent air leakage, water access?				
g	identification of all pipes or conduits for air, clean steam or liquids?				
h	properly equipped gowning area/air-lock?				
i	the ability to achieve appropriate air standards (Grade A, B, C, D) during operation ?				
j	appropriate air flow design including segregated air systems for different aspects of the processing, e.g. fermentation and filling?				
k	appropriate air flow design so that the area is flushed by HEPA filtered air exhausted through return ducts (not blocked by equipment).?				
l	the ability to maintain the appropriate pressure differentials between work areas with different Grades of air?				

2.0 PREMISES CHECKLIST

Page ____ of ____

INSPECTION of _____; Date: _____

Area inspected: Building: _____; Room(s) _____; Product: _____

2.0 C: Sterile Processing, continued

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
3	Does the aseptic manufacturing area exclude:				
a	access doors for servicing equipment and fixtures? (should only be from outside area)				
b	drains?				
c	sinks?				
4	Is the vaccine processing area isolated and independent of any space used for any other purpose?				
5	Are the facilities appropriately designed and validated to comply with relevant containment levels assigned to organisms involved in the manufacturing process?				
6	Is the aseptic manufacturing area cleaned according to a validated procedure? Is it followed? Is the cleaning data recorded?				

2.0 PREMISES CHECKLIST

Page ____ of ____

INSPECTION of _____; Date: _____

Area inspected: Building: _____; Room(s) _____; Product: _____

3.0 EQUIPMENT (TRS 822: 4; 823: 14, 17.24-17.33)

This section deals with all the equipment used in the preparation, processing and control of intermediate, bulk and final product. Special consideration should be given to the capacity relative to the requirements of the establishment, about the ease of operation and cleaning/disinfection, the availability of spare parts, maintenance, validation and training of staff. (See also 10.0 Containment Practices, B Equipment).

A ADEQUACY OF EQUIPMENT

GMP Item	Reference		
	TRS 822 Annex 1	TRS 823 Annex 1	
1	Appropriate design, construction and maintenance.	4.1	12.1
2	Isolation of operation lubricants and fluid from in-process or finished products.		
3	Non-interactive nature of equipment surfaces.		12.10
4	Correct sloping of pipe and/or service lines.		12.3; 12.4

B CLEANING AND MAINTENANCE

GMP Item	TRS 822 Annex 1	TRS 823 Annex 1	
1	Suitable equipment location.	4.1	12.1
2	Appropriate cleaning /maintenance/ sanitation procedures.		12.9
3	Piping systems, valves and vent filters.	4.15	
4	Valves on primary containment vessels steam sterilized.	4.15	
5	Non-fiber releasing filters for filtration.	4.13; 4.15	
6	Integrity testing of filters for sterile filtration.	4.13; 4.15	
7	Adequate performance of calibrations and validation.		17.32
8	Appropriate air filters for autoclaves and ovens.		
9	Isolation of supplies and equipment exposed to pathogens.		17.39

C STANDARD OPERATING PROCEDURES (SOPs) AND RECORDS

GMP Item	TRS 822 Annex 1	TRS 823 Annex 1	
1	Written procedures for cleaning and maintenance.		14.46
2	SOPs appropriate and comprehensive.		14.47; 14.49
3	Validation and approval of cleaning and sanitizing agents.		14.49
4	Clean equipment status identified.		
5	Recording of calibrations and qualifications.		14.47; 15.22
6	In-dated certifications.		
7	Preventative maintenance programs and records.		14.9

D AUTOMATED OR COMPUTER-CONTROLLED EQUIPMENT

GMP Item	TRS 822 Annex 1	TRS 823 Annex 1	
1	Validation of automated systems.		
2	Manual overrides.		
3	Written procedures.		
4	Computer systems controlled.		14.9
5	Back-up files regularly created and maintained.		14.9
6	Records of computerized calculations with validation data.		14.9
7	Hard copy systems to complement back-up data.		14.9

3.0 EQUIPMENT CHECKLIST

Page ____ of ____

INSPECTION of _____; Date: _____

Area inspected: Building: _____; Room(s) _____; Product: _____

Staff escort: _____

3.0 A: Adequacy

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Is the equipment appropriately designed, constructed and maintained?				
2	Are steps taken to prevent any substances required for operation, such as lubricants or coolants, from coming in contact with in-process or finished products?				
3	Are equipment surfaces that contact components or products of a non-interactive nature?				
4	Are process pipe lines or service lines whose contents come in contact with products or product contact surfaces sloped to allow proper drainage?				

3.0 B: Cleaning and Maintenance

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Is the equipment suitably located to facilitate its use, cleaning and maintenance?				
2	Are equipment and utensils cleaned, maintained and sanitized as appropriate to prevent malfunction or cross-contamination?				
3	Are piping systems, valves and vent filters properly designed to facilitate cleaning and sterilization? NOTE: Maintaining closed systems through the use of “clean in place” and “sterilize in place” is preferable.				
4	Are the valves on primary containment vessels (e.g. fermenters) steam sterilized?				
5	Are non-fiber releasing filters used for filtration?				
6	Are filters used for sterile filtration integrity tested before and after use?				
7	Are calibrations and validation being performed adequately?				
8	Are autoclaves and sterilizing ovens fitted with effective, proper air filters and are these integrity tested? Are HEPA filters used for the ovens?				
9	Are supplies and equipment which are exposed to pathogens during processing kept separate from unused items to prevent cross-contamination?				

3.0 EQUIPMENT CHECKLIST

Page ____ of ____

INSPECTION of _____; Date: _____

Area inspected: Building: _____; Room(s) _____; Product: _____

3.0 C: SOPs and Records

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Are there written procedures (SOPs) for cleaning and maintenance of equipment and utensils and are they followed?				
2	Do these SOPs include:				
a	assignment of responsibility for cleaning?				
b	defined schedules for cleaning and maintenance?				
c	descriptions of methods, equipment and materials used?				
d	instruction for protection of clean equipment from contamination?				
e	inspection of equipment for cleanliness immediately before use?				
f	assignment of identification number?				
g	documentation in record books?				
3	Are cleaning and sanitizing agents validated and approved for use by QC?				
4	Is clean equipment identified as such?				
5	Are calibrations and qualifications properly recorded?				
6	Are all certifications within date?				
7	Are there preventive maintenance programs and consistent records of work performed?				

3.0 EQUIPMENT CHECKLIST

INSPECTION of _____; Date: _____

Area inspected: Building: _____; Room(s) _____; Product: _____

3.0 D: Automated and Computerized Equipment and Systems

1	For automatic and computer-controlled systems:				
a	Is there an adequate description of the system, the components, and the operating characteristics including a logic flow diagram?				
b	Is there an individual with appropriate expertise in charge?				
c	Is there a procedure for on-going evaluation and change control?				
2	Are there manual overrides for automated production equipment or facility systems in case of failure?				
3	Are the procedures in writing?				
4	Are computer systems such as programmable scales, autoclaves, etc. controlled in order to prevent unauthorized changes?				
5	Are back-up files of computerized data created regularly and maintained?				
6	Where computerization eliminates calculations, is a written record of the program filed with the validation data?				
7	Are there alternative systems (hard copy) designed and maintained to ensure that back-up data are exact and complete and is that system secured from alteration, erasure or loss?				
8	Validation of hardware and software:				
a	Have all systems been validated?				
b	Is validation performed in-house or on contract? If on contract, are records kept of the qualifications of the contractor? If in-house, are the training and qualifications of the staff sufficient?				
c	Are records maintained?				
d	Has a risk assessment of each computer system been made? Is it appropriate?				

3.0 EQUIPMENT CHECKLIST

Page ____ of ____

INSPECTION of _____; Date: _____

Area inspected: Building: _____; Room(s) _____; Product: _____

4.0 PRODUCTION AND IN-PROCESS CONTROL (TRS 822: 6; 823: 15, 17.53-17.83)

Production and in-process controls play a specially important role in ensuring the consistent quality of biological products. Tests that are crucial for quality control but that cannot be carried out on the finished product shall be performed at an appropriate stage of production. Production steps should be effectively monitored and thoroughly documented to ensure safety, quality and efficacy of the final product.

A ADEQUACY OF STARTING MATERIALS

GMP Item	Reference		
	TRS 822 Annex 1	TRS 823 Annex 1	
1	Specifications and QC release of starting/raw materials.	6.2	13.12; 14.1; 14.15
2	Quality and stability of raw materials and components.	9.4	11.11; 11.12; 13.2 13.3; 13.5
3	Documentation for raw materials of animal origin.	6.2	13.10
4	Pre-testing or pre-screening of biological materials.		
5	Documentation for seed lots and/or cell banks.	4.6	

B PRODUCTION PROCESSES

GMP Item	TRS 822 Annex 1	TRS 823 Annex 1
1	Approved Master Formula for all products.	14.22; 14.23
2	Validated production process for each product.	5.2-5.4; 17.52
3	Validated aseptic filling procedures.	17.40
4	Time and temperature limits for production phases.	
5	Validated removal/inactivation of impurities and/or potential virus contaminants, where applicable.	
6	Testing/certification of in-process intermediates.	13.22; 16.11
7	Bioburden monitoring of raw materials.	17.44; 17.50
8	Alert and action limits for environmental monitoring.	17.37
9	Alert and action limits for water systems.	17.42

C STERILIZATION/DEPYROGENATION

GMP Item	TRS 822 Annex 1	TRS 823 Annex 1	
1	Validation of all sterilization/depyrogenation cycles.	6.5	17.54
2	Adequate supply of pure steam.		
3	Validated filter sterilization systems.		17.81; 17.82
4	Expiry date for sterilized items.		17.47
5	Filter integrity testing.		17.81
6	In-line sterilization filters.	6.4	

D IDENTIFICATION

GMP Item	TRS 822 Annex 1	TRS 823 Annex 1	
1	Correct identification of transferred materials.		
2	Supervision of dispensing/addition operation.		
3	Documentation of yields.	8.2	14.28
4	Verification of calculations.		14.28
5	Identification of containers, lines and major equipment.		14.10
6	Major equipment identified in the BPR.		14.28
7	Deviations from SOPs documented and QA/ QC approved.		14.7
8	Identification of critical system failures.		
9	Sterilization of equipment and supplies linked to product.		
10	Reference numbers for sterilized items.		17.57
11	Inspection of areas prior to use.		

12	Heat sensitive sterilization/depyrogenation indicators.		17.57
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4.0 PRODUCTION AND IN-PROCESS CONTROL CHECKLIST

Page ____ of ____

INSPECTION of _____; Date: _____

Area inspected: Building: _____; Room(s) _____; Product: _____

Staff escort: _____

4.0 A: Adequacy of starting materials

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Are there approved specifications for all starting material or raw material used in the manufacturing process and are they released by Quality Control?				
2	To ensure the quality of raw materials:				
a	is there a quarantine and release system?				
b	are the conditions of storage evaluated?				
c	do the contracts with vendors ensure quality and stability, including reporting of changes in manufacture?				
3	For raw material of animal origin:				
a	are the details of source, origin, and method of manufacture documented?				
b	are they stored in controlled environments?				
c	are expiry dates given and is there a retest policy?				
d	are rejected materials properly segregated from acceptable material?				
e	have viral removal and inactivation procedures been validated?				
4	Are biological materials that may contain infectious organisms screened or tested prior to entry into laboratories or manufacturing sites?				
5	Do Master/Working Cell Banks and Seed Stocks have detailed records of:				
a	history of cells including the number of generation doublings or passages of virus? Is there a maximum limit?				
b	characterization according to the WHO TRS relevant to the product?				
c	demonstration of purity?				
d	manufacturing procedures?				
e	appropriate storage and security with continuous monitoring of temperature, alarms and backup power supply?				
f	inventory log?				
g	adequately segregated storage to avoid mix-up or cross-contamination with other material?				
h	storage split into 2 separate locations?				
i	routine monitoring of stability (viability/purity)?				
j	demonstration of identity?				

4.0 PRODUCTION AND IN-PROCESS CONTROL CHECKLIST

INSPECTION of _____; Date: _____

Area inspected: Building: _____; Room(s) _____; Product: _____

4.0 B: Processes

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Master Formula (MF):				
a	Does the MF adequately describe the complete production process?				
b	Is the MF up-to-date and approved by QC/QA?				
c	Is the Batch Production Record form an adequate representation of the MF?				
2	Process validation:				
a	Has each phase of the production process been validated according to an approved validation protocol?				
b	Is re-validation done when required, and performed appropriately?				
3	Aseptic fill:				
a	Are suitable precautions taken to maintain aseptic conditions during the filling process?				
b	Is each filling process validated by a simulated media fill?				
c	Does the simulation use suitable medium, fill sufficient numbers of vials, and cover the full complexity of operations?				
4	Are time and temperature limits established for the completion of production phases?				
5	Are viral removal and inactivation processes validated, if applicable?				
6	Are in-process intermediate materials tested for identity, quality, strength and purity? Alternatively, are there valid certificates of quality issued from the suppliers?				
7	Is there bioburden monitoring of starting, raw, and in-process materials before sterilization?				
8	Are alert and action limits established for environmental monitoring, and are effective measures taken when limits are exceeded?				
9	Are criteria for microbial limits, physico-chemical characteristics and endotoxins established for water systems and are effective measures taken when limits are exceeded?				

4.0 PRODUCTION AND IN-PROCESS CONTROL CHECKLIST

Page ____ of ____

INSPECTION of _____; Date: _____

Area inspected: Building: _____; Room(s) _____; Product: _____

4.0 C: Sterilization/Depyrogenation

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Are all sterilization/depyrogenation processes and cycles validated and current?				
2	Is there a sufficient supply of pure steam to assure the simultaneous and proper operation of the validated number of autoclaves?				
3	Are systems for filter sterilization validated and are conditions still the same as when validation was performed?				
4	Is an expiry date given to sterilized items and is there a maximum time period established between washing and sterilization? Are storage conditions for sterilized items specified and appropriate?				
5	Are the filters tested immediately before and after use for integrity by an appropriate method such as the bubble point test?				
6	Are in-line sterilizing filters used for routine addition of gases, media, solutions, etc. to fermenters?				

4.0 D: Identification

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	If a component/material is transferred to a new container, is the new container identified with:				
a	component/material name or item code?				
b	receiving or control number?				
c	amount in container?				
2	Are dispensing/addition operations adequately supervised in that each component/material dispensed is examined by a second person to ensure:				
a	the component/material was released by QC?				
b	the amount agrees with the batch record?				
c	the container is properly identified?				
d	the components/material are added in the batch by one person and verified by a second person?				

4.0 PRODUCTION AND IN-PROCESS CONTROL CHECKLIST

Page ____ of ____

INSPECTION of _____; Date: _____

Area inspected: Building: _____; Room(s) _____; Product: _____

4.0 D: Identification, continued

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
3	Are actual yield and percentages of theoretical yield determined at the conclusion of each phase of operation with documentation of any losses?				
4	Are the yield calculations verified by a second person?				
5	Are all containers, lines and major equipment identified at all times during production for content and phase of operations?				
6	Is major equipment identified with an identification number which is recorded in the batch processing records (BPR) during production?				
7	Are all deviations from SOPs documented and subject to review by QA/QC for approval or corrective action?				
8	Are there written procedures established to specify action taken with regard to the identification and disposition of material in the environmentally controlled rooms and in the autoclave if the automatic system fails or malfunctions?				
9	Are records made of the mode, date, duration, temperature and other conditions relating to each sterilization cycle of equipment and supplies used in production. Are they maintained in a manner that permits identification of the product with the particular manufacturing and sterilization process?				
10	Are sterilized items identified by a sterilization reference number?				
11	Are inspections of areas undertaken immediately prior to use to ensure that all materials from previous operation have been removed and are these procedures adequate?				
12	Are all autoclaved and dry heat sterilized items marked with heat sensitive indicators?				

4.0 PRODUCTION AND IN-PROCESS CONTROL CHECKLIST

INSPECTION of _____; Date: _____

Area inspected: Building: _____; Room(s) _____; Product: _____

PRODUCTION SAMPLES TAKEN:

Source: _____; Date: _____;

<u>Name of product</u>	<u>Type</u>	<u>No. of Samples</u>	<u>Batch Number</u>	<u>Storage conditions</u>	<u>Test data*</u>
_____	_____	_____	_____	_____	Y/N ____
_____	_____	_____	_____	_____	Y/N ____
_____	_____	_____	_____	_____	Y/N ____
_____	_____	_____	_____	_____	Y/N ____
_____	_____	_____	_____	_____	Y/N ____

(Type: raw material, starting material, in-process, final bulk, final container)

Reason(s) for sampling:

Receipt signed by inspector and filed with company Y/N _____ (attach copy)

*: Certificate of analysis (C of A) from supplier, or QC approved test result

5.0 LABORATORY CONTROL BY QUALITY CONTROL LABORATORIES

(TRS 822: 9; 823: 3, 13.34-13.37, 16)

In process controls may be performed by production staff under supervision of an independent QC department. Finished product is the responsibility of QC. The establishment of SOPs for all laboratory procedures is essential to ensure their accuracy and reproducibility. The QC laboratory demonstrates the consistency of manufacturing by appropriate testing and review of historical records.

A ADEQUACY

	GMP Item	Reference	
		TRS 822 Annex 1	TRS 823 Annex 1
1	All specifications, standards, sampling plans, test procedures and other laboratory control mechanisms including any changes reviewed and approved by Quality Assurance.		3.2
2	Recording and justification of any deviations.		3.2
3	Laboratory controls established to ensure tested materials conform to appropriate standards of identity, strength, quality and purity.		3.3
4	These laboratory controls include all required testing and documentation.		3.4; 16.12; 16.8
5	Reagents, culture media, etc. labeled and preparation recorded in lab books with expiry dates.		
6	Appropriate testing to ensure absence of contaminating microorganisms.		16.13
7	Written sampling and testing plans for raw materials, intermediate and final products as required.		16.2-16.4

B REFERENCE REAGENTS

	GMP Item	TRS 822 Annex 1	TRS 823 Annex 1
1	Correct storage, security, identification, etc.		13.34
2	Analyzed for variation over time.		

C VALIDATION, CALIBRATION AND STABILITY PROGRAMME

	GMP Item	TRS 822 Annex 1	TRS 823 Annex 1
1	Accuracy, sensitivity, specificity and reproducibility of test methods are established, documented, validated and subject to regular review and updating.		
2	Written testing programs to assess stability characteristics to determine storage conditions and expiration dates.	9.1	16.19
3	Retention sampling system.	9.5	16.16
4	The retention sample quantity consists of at least twice the quantity needed to perform all required tests.		16.16
5	Retention samples of each lot of final product are stored under conditions consistent with product labeling.	9.5	16.16
6	Annual examination of samples for deterioration.		

5.0 LABORATORY CONTROL BY QUALITY CONTROL LABS CHECKLIST

Page ____ of ____

INSPECTION of _____; Date _____

Area inspected: Building: _____; Room(s) _____; Lab _____

Staff escort: _____

 5.0 A: Adequacy

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Are specifications, standards, sampling plans, test procedures or other laboratory control mechanisms including any revision, reviewed and approved by Quality Assurance?				
2	Are any deviations from these specs, standards, etc. recorded and justified?				
3	Do laboratory controls include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, test procedures and reference substances, designed to assure that tested materials conform to appropriate standards of identity, strength, quality and purity?				
4	Do these laboratory controls include:				
a	determination of compliance with written specifications for acceptance of each lot within each shipment of materials or holding of products?				
b	description of sampling and testing procedures for in-process materials?				
c	retest policy, identifying the rationale and criteria for retests, number of samples, and the documentation required?				
d	a comprehensive calibration program that includes calibration/certification intervals, acceptance criteria and provisions for remedial action?				
5	Are reagents, culture media, etc. properly labeled, preparation recorded in lab books and expiry dates given?				
6	Is appropriate testing done on each batch of product required to be free of objectionable microorganisms?				
7	Are there written sampling and testing plans for raw materials, intermediates, and final product that include method of sampling and the number of units per batch to be tested and are they followed?				

5.0 LABORATORY CONTROL BY QUALITY CONTROL LABS CHECKLIST

Page ____ of ____

INSPECTION of _____; Date _____

Area inspected: Building: _____; Room(s) _____; Lab _____

5.0 B: Reference Reagents

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Are all reference reagents kept secure, properly stored, identified and their integrity maintained?				
2	Are the tests results of all references and standards analyzed at appropriate intervals for statistical variation from the expected value?				

5.0 C: Validation, Calibration and Stability Programme

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Are the accuracy, sensitivity, specificity and reproducibility of test methods established, documented, validated and subject to regular review and updating?				
2	Is there a written testing programme designed to assess the stability characteristics of each product to determine the appropriate storage conditions and expiration dates?				
3	Is there a retention sampling system?				
4	Does the retention sample quantity consist of at least twice the quantity needed to perform all required tests (except for sterility and pyrogens)?				
5	Are retention samples of each lot of final product stored under conditions consistent with product labeling?				
6	Are these samples at least visually examined annually for evidence of deterioration? Is this recorded?				

5.0 LABORATORY CONTROL BY QUALITY CONTROL LABS CHECKLIST

Page ____ of ____

INSPECTION of _____; Date _____

Area inspected: Building: _____; Room(s) _____; Lab _____

QC SAMPLES TAKEN:

Source: _____; Date: _____;

Name of product	Type	No. of Samples	Batch Number	Storage conditions	Test data*
_____	_____	_____	_____	_____	Y/N ____
_____	_____	_____	_____	_____	Y/N ____
_____	_____	_____	_____	_____	Y/N ____
_____	_____	_____	_____	_____	Y/N ____

(Type: raw material, starting material, reference material, in-process, final bulk, final container)

Reason(s) for sampling:

Receipt signed by inspector and filed with company Y/N _____ (attach copy).

*: Certificate of analysis (C of A) from supplier, or approved QC test result.

6.0 DOCUMENTATION OF PROCESSING AND DISTRIBUTION (TRS 822: 8; 823: 14)

Good documentation is an essential part of quality assurance. Its aims are to define the specification for all materials and methods of manufacture and control, to ensure information necessary for batch release is recorded, and to provide an audit trail that will permit investigation of the history of any suspected defective batch.

A GENERAL

GMP Item	Reference	
	TRS 822 Annex 1	TRS 823 Annex 1
1	Maintenance of records.	6.4; 14.8; 14.26; 14.46; 14.47
2	Dating and signing of records.	8.3 14.8

B LOT/BATCH PROCESSING RECORDS (BPR)

A record of the production, processing and quality control should be prepared for each lot and/or batch, based on a master record. This document is also required for release purposes.

GMP Item	TRS 822 Annex 1	TRS 823 Annex 1
1	BPR comprehensive and complete.	8.2 14.28
2	BPR review	
3	Maintenance of BPR	

C DOCUMENTATION OF EQUIPMENT USED

Records of the maintenance, sterilization and performance of all major equipment should be kept in a way that allows their state to be linked with an identified production lot/batch.

GMP Item	TRS 822 Annex 1	TRS 823 Annex 1
1	Equipment logs kept current.	14.46
2	Dating and signing of equipment records.	
3	Required information in equipment records.	

6.0 DOCUMENTATION OF PROCESSING AND DISTRIBUTION CHECKLIST

Page ____ of ____

INSPECTION of _____; Date _____

Area inspected: Building: _____; Room(s) _____; Dept: _____

Staff escort: _____

6.0 A: General

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Are there records for:				
a	all materials used?				
b	all standard operating procedures?				
c	each lot and/or batch processing and distribution?				
d	all complaints and their investigation?				
e	all equipment, including cleaning, maintenance and validation?				
f	cleaning, maintenance and environmental control of the premises?				
2	Are all records:				
a	dated?				
b	signed by the person performing the task (and, for all critical steps, by the person checking it)?				
c	kept at the work station during the entire operation?				
d	retained and available for inspection at least 2 years after the expiry date of the lot/batch?				

6.0 B: Lot/Batch Processing Records (BPR)

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Does the BPR indicate:				
a	the name, strength and dosage of the product?				
b	the date of manufacture?				
c	the lot and batch identification no.?				
d	assurance that the copy of the master processing record is accurate?				
e	changes in the master processing record approved by QA prior to starting the operation?				
f	the complete formulation of the lot/batch?				
g	the batch number of each component or other in-process material and, when applicable, the sterilization number?				
h	the SOPs used?				
i	the yield obtained at different stages of manufacture, both actual measured values and as a percentage of the expectation?				
j	a record of each step followed?				
k	a record of all major equipment used?				

6.0 DOCUMENTATION OF PROCESSING AND DISTRIBUTION CHECKLIST

Page ____ of ____

INSPECTION of _____; Date _____

Area inspected: Building: _____; Room(s) _____; Dept: _____

6.0 B: Lot/Batch Processing Records (BPR), continued

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
l	a record of all in-process control samples taken and of the results obtained?				
m	a sample of the label on the final container?				
n	identification of packaging materials, containers, closures used?				
o	inspection of the processing area before and after use?				
p	precautions taken and special or unusual observations made throughout the manufacture of the lot?				
q	investigation of all unusual observations for the batch and, where relevant, from samples of other batches of the product?				
r	for rejected lots/batches, a record of disposal or reprocessing?				
2	Are all batch processing records reviewed and signed appropriately as indicated by:				
a	a BPR review document or checklist describing the review process?				
b	a dated signature of the person responsible for approving the manufacturing operations?				
c	an analytical report, dated and signed by the responsible person, showing whether the lot/batch complies with the specifications?				
d	decision on release or rejection of the lot/batch by the quality control department?				
3	Are the BPRs maintained on file for 2 years past the expiry date?				

6.0 C: Documentation of Equipment Used

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Are records on the use, cleaning, sterilization and maintenance of equipment kept in individual logs for each piece of equipment?				
2	Are these records dated and signed in chronological order?				
3	Do the records include information of the lot/batch including identification numbers and dates?				

7.0 ANIMALS: QUALITY, PREMISES AND CARE (TRS 822: 5)

Animals are essential in both manufacturing and quality control steps of many biological products. It is important that they are healthy and appropriate for the purpose used. National legislation in regard of animal experiments and protection of animals should be respected.

A PROCUREMENT OF ANIMALS

	GMP Item	Reference	
		TRS 822 Annex 1	TRS 823 Annex 1
1	SOPs for animal procurement.		
2	Authorization for ordering animals.		
3	Suppliers assure quality and consistency of animals.		
4	SOPs for maintenance and testing of in-house colonies.		

B RECEIPT AND EVALUATION OF ANIMALS

	GMP Item	TRS 822 Annex 1	TRS 823 Annex 1
1	SOPs for receipt of animals and required records.		
2	Quarantine of newly received animals.	5.1	
3	SOPs for evaluating health status of animals.		

C ANIMAL CARE

	GMP Item	TRS 822 Annex 1	TRS 823 Annex 1
1	SOPs for housing, feeding, handling and animal care.	5.2	
2	SOPs for identification and isolation of sick animals.		
3	Records of sickness, treatment and preventative measures.	5.2	

D ALLOCATION OF ANIMALS TO USE

	GMP Item	TRS 822 Annex 1	TRS 823 Annex 1
1	Specifications for animals are included in SOPs.		
2	Identification system for animals used or on test.		

E FACILITIES

	GMP Item	TRS 822 Annex 1	TRS 823 Annex 1
1	Sufficient appropriate animal rooms.	5.1	
2	Facilities and SOPs for waste and carcass.	5.1	
3	Facilities and SOPs for cleaning, sanitizing, sterilizing and maintaining supplies and equipment.	5.1	
4	Appropriate storage of equipment, feed and bedding.	5.1	
5	Appropriate areas for animal handling and testing.	5.1	
6	Suitably located equipment.		
7	Separate facilities for staff working in animal facilities.	5.2	
8	Appropriate functioning environmental system.		
9	Approved pest control system.	5.1	
10	Heating, ventilation, air-conditioning system.		
11	Lighting system.		
12	Noise control.		
13	Emergency power.		

7.0 ANIMALS: QUALITY, PREMISES AND CARE CHECKLIST

Page ____ of ____

INSPECTION of _____; Date _____

Area inspected: Building: _____; Room(s) _____

Staff escort: _____

7.0 A: Procurement

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Are there SOPs for animal procurement?				
2	Is a specific individual in department, authorized to order animals?				
3	Do contracts with suppliers assure the quality and consistency of the animals provided?				
4	If the animals come from the manufacturer's own breeding colony, are there SOPs for the maintenance and testing of the colony?				

7.0 B: Receipt and Evaluation

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Are there SOPs covering the receipt of animals, including identification of the responsible person and required documentation?				
2	Are the newly received animals placed in quarantine?				
3	Are there SOPs for evaluating the health status of animals prior to use?				

7.0 C: Care

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Are there SOPs covering housing, feeding, handling and care of the animals?				
2	Are there SOPs for identification and isolation of any sick animal?				
3	Are any sicknesses of animals, treatment and preventive measures recorded?				

7.0 D: Allocation of Animals to Use

Ref	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Are the specifications for animals used in production or quality control tests written in the respective SOPs?				
2	Is there a clear system of identification of animals allocated for each test or use?				

7.0 ANIMALS: QUALITY, PREMISES AND CARE CHECKLIST

Page ____ of ____

INSPECTION of _____; Date _____

Area inspected: Building: _____; Room(s) _____

7.0 E: Facilities

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Are there enough animal rooms of appropriate design to allow separate housing of:				
a	the breeding colony?				
b	different animal species?				
c	animals in quarantine?				
d	sick animals?				
e	animals on-test including tests with hazardous infectious and non-infectious materials?				
2	Are there facilities and SOPs for collection and disposal of animal waste and of dead animals, to minimize disease hazards and environmental contamination?				
3	Are there facilities and SOPs for cleaning, sanitizing, sterilizing and maintaining supplies and equipment including animal cages and racks?				
4	Are there specially designated areas for animal inoculation and sample taking, aseptic surgery, autopsy, radiography, histology and other laboratory tests?				
5	Are there separate storage areas for equipment, animal feed and bedding which are protected from infection/contamination, and with refrigeration where needed?				
6	Is equipment suitably located for operation, inspection, cleaning and maintenance?				
7	Is there separate space for locker, shower, toilet and washing facilities for staff working in the animal facilities?				
8	Is there an appropriate functioning environmental control system?				
9	Is there an implemented pest control system that is documented, validated and approved by QA showing absence of interference with the tests and maintaining animal welfare?				
10	Is the HVAC system appropriate with temperature and humidity control, and adequate air changes/hour?				
11	Is there a time-controlled lighting system?				
12	Is there an appropriate noise control system?				
13	Is emergency power available in the event of a power failure?				

8.0 QUALITY ASSURANCE (TRS 822: 9; 823: 1)

Quality assurance is a wide-ranging concept covering all matters that individually and collectively influence the quality of a product. Quality assurance procedures ensure that all products, materials, equipment, premises and personnel comply with GMP and that quality and consistency of production are maintained. The arrangements made by a company to ensure the following QA aspects are performed and suitably controlled will depend on the complexity of the operations and the organizational structure of the company.

A GENERAL

GMP Item	Reference	
	TRS 822 Annex 1	TRS 823 Annex 1
1	Records on suppliers, contractors and consultants.	8.1; 9.8
2	Records on their qualifications.	8.9; 9.9
3	Records of up-dated documents.	

B STANDARD OPERATING PROCEDURES (SOPs)

GMP Item	TRS 822 Annex 1	TRS 823 Annex 1
1	Written and approved SOPs for all manufacturing and testing activities.	1.2; 14.44; 14.46
2	Regular review of SOPs.	14.5
3	Revisions to SOPs approved by an authorized person.	14.3
4	System of distribution and control of SOPs.	14.5
5	Use of SOPs	

C EQUIPMENT

GMP Item	TRS 822 Annex 1	TRS 823 Annex 1
1	Validation and revalidation of all equipment.	1.2
2	Calibration of all instruments.	
3	Reporting, investigating and recording all deviations.	

D ENVIRONMENTAL MONITORING

GMP Item	TRS 822 Annex 1	TRS 823 Annex 1
1	Viable counts in air.	17.37
2	Non-viable particulates in air.	17.32; 17.37
3	Surfaces viable counts.	17.32; 17.37
4	Viable counts in compressed gas.	17.32
5	Non-viable particulates in compressed gas.	17.32
6	Viable counts for water.	17.32; 17.33
7	Frequency of environmental monitoring.	

E INTERMEDIATES AND FINAL PRODUCTS

GMP Item	Reference	
	TRS 822 Annex 1	TRS 823 Annex 1
1	Stability of products.	16.17
2	Quarantine and release systems.	
3	Reprocessing of unsatisfactory and returned products.	16.14
4	Evaluation and investigation of complaints.	6.1-6.4; 6.6
5	Recall of products.	8.4 7.1-7.8

F QUALITY CONTROL

GMP Item	TRS 822 Annex 1	TRS 823 Annex 1
1	Independence of QC department.	3.2
2	Validation of QC tests.	3.2
3	SOPs for all QC laboratory operations.	3.3
4	Trend analysis to monitor consistency of production.	
5	QC involved in decisions pertaining to product quality.	3.1

G INSPECTIONS

GMP Item	TRS 822 Annex 1	TRS 823 Annex 1
1	Self-inspection of each manufacturing and test area.	9.1
2	Inspection follow-up to ensure action is taken.	9.1
3	Follow-up of national control authority's inspection and recommendations.	
4	Inspection system for contractors.	8.4

8.0 QUALITY ASSURANCE CHECKLIST

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INSPECTION of _____; Date _____

Area audited: Building: _____; Room(s) _____; Department: _____

Staff escort: _____

8.0 A: General

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Are there records on suppliers, contractors and consultants?				
2	Are there records of their qualifications?				
3	Are there records on up-dating documents?				

8.0 B: SOPs

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Are there SOPs written and approved for all manufacturing and testing activities?				
2	Are the SOPs reviewed on a regular and defined schedule? at least annually?				
3	Are revisions of SOPs approved by an authorized person?				
4	Is there a system for distribution of SOPs and for revocation of outdated SOPs?				
5	Is it clear that SOPs are used and followed in both production and QC?				

8.0 C: Equipment

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Is there a system for validation and regular revalidation of all equipment, including revalidation after repairs?				
2	Is there a system for calibration of all instruments?				
3	Is there a system to report, investigate and record all deviations from specifications or malfunctioning of equipment?				

8.0 QUALITY ASSURANCE CHECKLIST

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INSPECTION of _____; Date _____

Area audited: Building: _____; Room(s) _____; Department: _____

8.0 D: Environmental Monitoring

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Is there monitoring of air for microbes?				
2	Is there monitoring of air for particulates?				
3	Is there monitoring of surfaces for microbes?				
4	Is there monitoring of compressed gas for microbes?				
5	Is there monitoring of compressed gas for particulates?				
6	Is there monitoring of water for microbes and endotoxins?				
7	Is there a defined schedule for environmental monitoring? Is it appropriate to each stage of the production process? Do the records indicate the schedule is followed?				

8.0 E: Intermediates and Final Product

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Is the stability of the final products and, if applicable, of the intermediates monitored?				
2	Is there a quarantine and release system for intermediates and final products, including clear identification of the status (quarantine, released, rejected, etc.)?				
3	Is there a system for reprocessing of unsatisfactory and returned products, subject to prior approval by quality control?				
4	Is there a system for rapid evaluation and investigation of complaints received from the field?				
5	Is there a system for rapid and effective recall of products? Is there provision for the notification of the national control authority (NCA)?				

8.0 QUALITY ASSURANCE CHECKLIST

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Area audited: Building: _____; Room(s) _____; Department: _____

8.0 F: Quality Control

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Is the QC department independent from production?				
2	Are all QC tests validated?				
3	Does the QC Laboratory have SOPs describing sampling, testing, documentation and precise criteria for release?				
4	Is QC monitoring consistency of production using trend analysis?				
5	Is the QC Laboratory involved in all decisions that may concern the quality of the product?				

8.0 G: Inspections

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Is there a system for regular self-inspection of each manufacturing and test area?				
2	Are the inspections followed up to ensure that appropriate action was taken to correct deficiencies?				
3	Following the national control authority's (NCA) inspection of the manufacturer, is there a system to follow up any recommendations received from NCA?				
4	Is there a system for inspection of contractors in respect of any manufacturing or testing activities contracted out?				

9.0 LABELLING, PACKAGING AND DISTRIBUTION

(TRS 822: 7, 8; 823: 13.16-13.20, 14.11, 14.32, 14.34, 15.24-15.34)

Special emphasis needs to be given to the control of labeling and packaging operations as the majority of product recalls are due to incorrect labeling or use of unapproved labeling components. Controls must be implemented to prevent such mix-ups.

A PACKAGING MATERIALS

GMP Item	Reference	
	TRS 822 Annex 1	TRS 823 Annex 1
1	Specifications.	13.20
2	SOPS for receipt, sampling and testing.	14.32; 14.34
3	Control and quarantine of incoming materials.	13.2
4	Control and inventory of released materials.	13.17
5	Control or reference numbers.	13.15
6	National control authority approval of label texts.	7.2

B LABELLING AND PACKAGING OPERATIONS

GMP Item	TRS 822 Annex 1	TRS 823 Annex 1
1	SOPs.	14.25
2	Segregation of operations.	13.17
3	Reconciliation of labels.	14.29
4	Specifications for reconciliation limits.	
5	Accounting of all labeled product.	
6	Line inspection.	15.25
7	Name, strength and batch number displayed.	15.26
8	On-line control of labeled or packaged product.	15.31
9	Calibration and certification of equipment used.	
10	Documented time and temperature limitations.	
11	Records of incidents and deviations and QA actions.	
12	Assignment of lot numbers and expiry dates.	
13	Sample labels and materials with records.	
14	Segregated, secure quarantine storage area.	13.23

C STORAGE AND DISTRIBUTION

GMP Item	TRS 822 Annex 1	TRS 823 Annex 1
1	Identification of all customers.	8.4
2	Records of storage: times, temperatures, etc.	
3	Records of date, quantity, mode of packaging and distribution to customer.	
4	SOPs for storage of released products.	14.44
5	SOPs for warehousing.	
6	SOPs for shipping, final transit conditions and storage.	
7	Validation and monitoring of shipping methods.	
8	Recall.	8.4 14.45
9	Maintenance of records for 2 years beyond expiry date.	8.3

9.0 LABELLING, PACKAGING AND DISTRIBUTION CHECKLIST

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INSPECTION of _____; Date _____

Area inspected: Building: _____; Room(s) _____; Dept: _____

Staff escort: _____

9.0 A: Packaging Materials

Ref	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Do primary and printed packaging materials have specifications describing qualitative and quantitative requirements?				
2	Are standard operating procedures for the receipt, sampling and testing of packaging materials available?				
3	Are incoming materials stored in controlled areas until released from quarantine?				
4	Are released materials secured in controlled areas and is inventory maintained?				
5	Are control or reference numbers assigned to each lot for traceability and control purposes?				
6	Are all label texts approved by the national control authority prior to use and is there a master file of approved labeling held by the responsible person?				

9.0 LABELLING, PACKAGING AND DISTRIBUTION CHECKLIST

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INSPECTION of _____; Date _____

Area inspected: Building: _____; Room(s) _____; Dept: _____

9.0 B: Labeling and Packaging Operations

Ref	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Are SOPs available for the labeling and packaging operations for equipment and material delivery to the floor and are these easily accessible to the operators?				
2	Are labeling and packaging operations properly physically segregated to prevent mix-up of product or packaging materials?				
3	Is reconciliation performed to ascertain the number of labels issued, used and, if applicable, returned to stock? Is the data recorded on the packaging batch records?				
4	Is there a specification for permissible reconciliation limits and action to be taken in the event of exceeding these?				
5	Is all labeled product accounted for including those destroyed during and at the completion of the operation?				
6	Is there an inspection of the line made before and after each labeling and packaging operation? Is it documented and signed by the responsible person?				
7	Is the name, strength and batch number prominently displayed at each operation?				
8	Is there adequate on-line control of the labeled or packaged product including the quality of printed text?				
9	Are the pieces of equipment used during labeling operations calibrated and certified as operating correctly before and during labeling operations?				
10	Are there documented time and temperature limitations for the labeling and packaging operations?				
11	Are incidents and deviations recorded and appropriate QA actions taken?				
12	Is there a quality control mechanism for assigning lot numbers and expiry dating prior to labeling operations?				
13	Are samples of printed labels and packaging materials used for the batch kept with the records?				
14	Is there a segregated and secure quarantine storage area for finished goods awaiting QC release?				

9.0 LABELLING, PACKAGING AND DISTRIBUTION CHECKLIST

Page ____ of ____

INSPECTION of _____; Date _____

Area inspected: Building: _____; Room(s) _____; Dept: _____

9.0 C: Storage and Distribution

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Do records allow rapid identification of all customers who have received any amount of an identified lot/batch?				
2	Are records kept on the time, temperature and other conditions of storage before distribution?				
3	Do records show the date, quantity, mode of package and dispatch of each lot/batch to the customer?				
4	Are there standard operating procedures for the storage of released finished product to the dispatch area?				
5	Are standard procedures available for warehousing?				
6	Are standard procedures available that describe the shipping, final transit conditions and instruction for storage through the distribution chain, especially the cold chain?				
7	Are the shipping methods, especially the cold chain, validated and routinely monitored?				
8	Are records detailed and retrievable so that a rapid recall of any particular lot is achievable? Is the recall process delegated to the responsible person?				
9	Are records maintained for 2 years after the expiry date?				

10.0 CONTAINMENT PRACTICES (TRS 822: 4.12-4.14; 823: 17.16-17.23)

Biological manufacturing activities may include the use of pathogens or microorganisms which pose a risk to employees, the environment or other products being manufactured. Containment standards have been developed by many countries and also by WHO (5) in relation to risk categories. These requirements should be taken into consideration during the design of facilities and equipment used and in the standard operating procedures employed. In addition to the general requirements for Premises (section 2.0), Equipment (section 3.0) and Production and In-process Control (section 4.0), the following points should be considered.

A FACILITY DESIGN

GMP Item	Reference		
	TRS 822 Annex 1	TRS 823 Annex 1	
1	Capability of air handling system.	4.13; 4.14	
2	HEPA filters for exhaust system.	4.13; 4.14	
3	Testing of HEPA filters in situ.	4.13; 4.14	
4	Air pressure vis-à-vis surrounding areas.	4.12	
5	Room design to permit cleaning and decontamination.		17.17; 17.18
6	Location of wash sinks.		17.21
7	Sealing of conduits, piping and duct work.		
8	Backflow prevention devices (liquid and gas).		
9	Maintenance of drain protection traps.		17.21

B EQUIPMENT

GMP Item	TRS 822 Annex 1	TRS 823 Annex 1	
1	Design of containment equipment.		
2	Construction and installation.		
3	Biosafety cabinets.		
4	Minimization of aerosol generation.		
5	Design of process equipment.		
6	Decontamination procedures.		

C OPERATIONAL PRACTICES AND PROCEDURES

GMP Item	TRS 822 Annex 1	TRS 823 Annex 1	
1	Decontamination SOPs, validation, and monitoring.		
2	Testing of equipment.		
3	SOPs for emergency procedures.		
4	Display of responsible person in case of emergency.		
5	Training of personnel.		
6	SOPs for dress code, controlled access and displayed list of authorized personnel.		
7	Availability of showers.		
8	Health and medical surveillance program.		
9	Biohazard signs.		
10	SOPs for transport of microorganisms.		

10.0 CONTAINMENT PRACTICES CHECKLIST

Page ____ of ____

INSPECTION of _____; Date _____

Area inspected: Building: _____; Room(s) _____; Dept: _____

Staff escort: _____

10.0 A: Facility Design

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Is the air handling system capable of maintaining the designed containment level (e.g. are supply and exhaust systems adequate for the level of containment required)?				
2	Where applicable, are HEPA filters installed in the exhaust system?				
3	Can the HEPA filters be tested in situ?				
4	Is the air pressure in the manufacturing area appropriate to the surrounding areas?				
5	Are the rooms designed to permit satisfactory cleaning and decontamination?				
6	If the procedure requires the availability of a wash sink, is it close to the exit of room?				
7	Are all conduits, piping and duct work properly sealed in the area to maintain containment?				
8	Are all liquid and gas services protected by backflow prevention devices to prevent contamination?				
9	Are all traps protecting drains maintained properly?				

10.0 B: Equipment

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Is the primary containment equipment designed to limit or prevent contact between operators and microorganisms?				
2	Is the equipment designed, constructed and installed to permit ease of decontamination and cleaning?				
3	Are the appropriate classes of Biosafety Cabinets used for the relevant microorganisms, and are they certified annually?				
4	Is the process equipment designed to minimize aerosol generation (including sampling devices)?				

10.0 CONTAINMENT PRACTICES CHECKLIST

Page ____ of ____

INSPECTION of _____; Date _____

Area inspected: Building: _____; Room(s) _____; Dept: _____

10.0 B: Equipment, continued

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
5	Is the process equipment designed to contain organisms within a closed system (e.g. fermenters or other culture vessels)? Are seals and mechanical devices associated with the equipment designed to prevent leakage and do exhaust gases pass through HEPA filtration and/or incineration?				
6	Is the process equipment capable of being decontaminated using a validated inactivation procedure?				

10.0 C: Operational Practices and Procedures

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Are there standard operating procedures for decontamination of process equipment and facilities? Have these procedures been validated and is the performance monitored?				
2	Is the equipment tested regularly for integrity of containment capability?				
3	Are standard operating procedures available and displayed outlining emergency procedures in the event of a spill or accidental release of contaminant?				
4	Is there a list displayed of responsible individuals to be contacted in the event of an emergency?				
5	Do personnel have specific training in the procedures for handling the pathogenic agents used and the method of using containment equipment?				
6	Are there SOPs for dress codes specified for containment levels applicable and is access controlled and secured? Is there a list displayed of authorized staff for entry?				
7	Are showers available where applicable?				
8	Is there a health and medical surveillance program?				
9	Are biohazard signs used and posted where applicable?				
10	Are SOPs available for the transport of microorganisms in closed systems or containers to and from the area?				

11.0 SANITATION AND CLEANING (TRS 823: 17.34-17.37)

A high level of sanitation and hygiene should be practiced in every aspect of manufacture. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product. Potential sources of contamination should be eliminated through an integrated comprehensive programme of sanitation and hygiene.

A GENERAL

GMP Item	Reference	
	TRS 822 Annex 1	TRS 823 Annex 1
1	Pest control programme.	11.6; 13.40
2	Control and disposal of sewage, refuse and trash.	13.38; 13.39
3	Location of adequately constructed waste containers.	13.38; 13.39
4	Storage of bagged/boxed items.	13.38; 13.39
5	Procedures, compliance, and validation.	14.49
6	Storage of equipment and chemicals.	17.35

11.0 SANITATION AND CLEANING CHECKLIST

Page ____ of ____

INSPECTION of _____; Date _____

Area inspected: Building: _____; Room(s) _____; Department _____

Staff escort: _____

11.0 A: General

#	Audit Item	Yes	No	NA	Observations (indicate N.O. if not observed)
1	Pest control programme:				
a	Is there a pest control programme? Is it in writing and is it followed?				
b	Are pesticides used?				
c	Is their use controlled so as to avoid product contamination?				
d	Are there records of pesticide usage?				
e	Is pesticide storage controlled?				
f	Has QA approved the pesticides and the programme?				
2	Are sewage, refuse, trash controlled and/or disposed of in a safe, timely and sanitary manner?				
3	Are adequately constructed waste containers located in appropriate areas?				
4	Are bagged/boxed items stored off the floor and spaced to allow for cleaning and proper identification?				
5	Do written procedures for cleaning and sanitation include:				
a	assignment of responsibility for sanitation?				
b	details of cleaning schedules, methods, equipment and material?				
c	routine evaluation of the effectiveness of disinfectants and cleaning agents, and chronological record of the agents used?				
d	information to be recorded?				
e	validation for effectiveness of cleaning/sanitation, and validation of removal of residual cleaning/sanitizing agents?				
f	are the procedures followed and are records maintained?				
6	Are equipment and chemicals used in cleaning appropriately maintained and stored?				

APPENDIX A

List of Abbreviations Used in this Guide

BPR Batch Processing Record

GMP Good Manufacturing Practices

Grade A, B, C, D work areas for sterile products, and Grade of clothing to be worn:

Grades describe the number of permitted non-viable and viable particles per volume of air for sterile product manufacture, and the clothing to be worn in each Air Grade work area.

(Air Grades: WHO TRS 823, Annex 1, paragraphs 17.1-17.5.3)

(Clothing Grades: WHO TRS 823, Annex 1, paragraphs 17.13-17.14)

HEPA High Efficiency Particulate Air (with filter)

HVAC Heating, Ventilation, Air-conditioning

MF Master Formula

NCA National Control Authority

QA Quality Assurance

QC Quality Control

SOP Standard Operating Procedure

TRS Technical Report Series

WFI Water for Injection

WHO World Health Organization

APPENDIX B

List of References

- 1) Good Manufacturing Practices for Pharmaceutical Products. WHO TRS 823, Annex 1, 1992.
- 2) Good Manufacturing Practices for Biological Products. WHO TRS 822, Annex 1, 1992.
- 3) Provisional Guidelines on the Inspection of Pharmaceutical Manufacturers. WHO TRS 823, Annex 2, 1992.
- 4) Guidelines for National Authorities on Quality Assurance for Biological Products. WHO TRS 822, Annex 2, 1992.
- 5) Environmental Health Criteria 141: Quality Management for Chemical Safety Testing (International Programme on Chemical Safety, WHO, Geneva, 1992).
- 6) Laboratory Biosafety Manual, 2nd ed., WHO, Geneva, 1993.
- 7) Index of Texts of Good Manufacturing Practices. Pharm/86.39.
- 8) Guide for Inspection of Manufacturers of Biological Products. WHO, CVI Task Force, 1994, Document number BLG/V9/445/6 (limited distribution).
- 9) A WHO Guide to Good Manufacturing Practice (GMP) Requirements. Part 1: Standard Operating Procedures and Master Formulae. Document number: WHO/VSQ/97.01.
- 10) A WHO Guide to Good Manufacturing Practice (GMP) Requirements. Part 2: Validation. Document number WHO/VSQ/97.02.
- 11) Guidelines for assuring the quality of pharmaceutical and biological products prepared by recombinant DNA technology. WHO TRS 823, Annex 4, 1992.
- 12) Guidelines for assuring the quality of monoclonal antibodies for use in humans. WHO TRS 822, Annex 3, 1992.