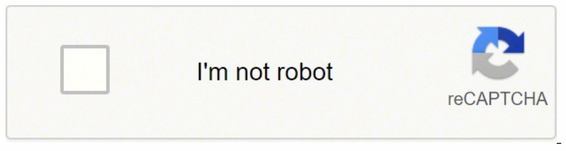
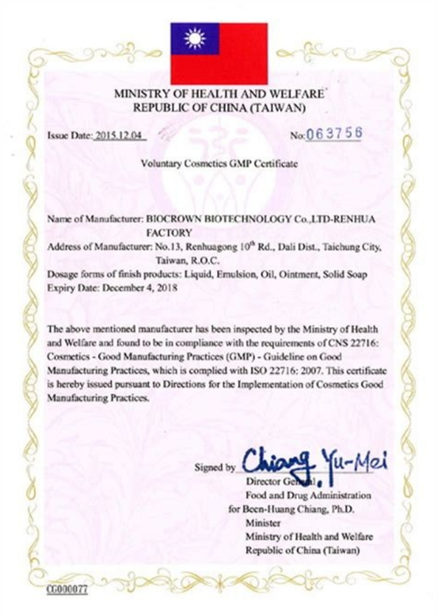


Next

Gmp certificate of analysis template



MINISTRY OF HEALTH AND WELFARE
REPUBLIC OF CHINA (TAIWAN)

Issue Date: 2015.12.04 No: 063756

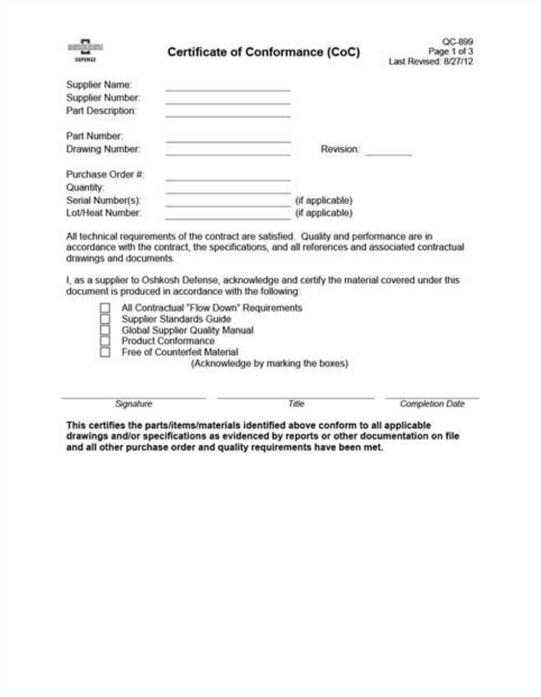
Voluntary Cosmetics GMP Certificate

Name of Manufacturer: BIOCROWN BIOTECHNOLOGY Co.,LTD-RENHUA FACTORY
Address of Manufacturer: No.13, Renhuagong 10th Rd., Dali Dist., Taichung City, Taiwan, R.O.C.
Dosage forms of finish products: Liquid, Emulsion, Oil, Ointment, Solid Soap
Expiry Date: December 4, 2018

The above mentioned manufacturer has been inspected by the Ministry of Health and Welfare and found to be in compliance with the requirements of CNS 22716: Cosmetics - Good Manufacturing Practices (GMP) - Guideline on Good Manufacturing Practices, which is complied with ISO 22716: 2007. This certificate is hereby issued pursuant to Directions for the Implementation of Cosmetics Good Manufacturing Practices.

Signed by Chiang Yu-Mei
Director General,
Food and Drug Administration
for Been-Huang Chiang, Ph.D.
Minister
Ministry of Health and Welfare
Republic of China (Taiwan)

QC030077



Certificate of Conformance (CoC)

QC-899
Page 1 of 3
Last Revised: 8/27/12

Supplier Name: _____
Supplier Number: _____
Part Description: _____

Part Number: _____
Drawing Number: _____ Revision: _____

Purchase Order #: _____
Quantity: _____
Serial Number(s): _____ (if applicable)
Lot/Heat Number: _____ (if applicable)

All technical requirements of the contract are satisfied. Quality and performance are in accordance with the contract, the specifications, and all references and associated contractual drawings and documents.

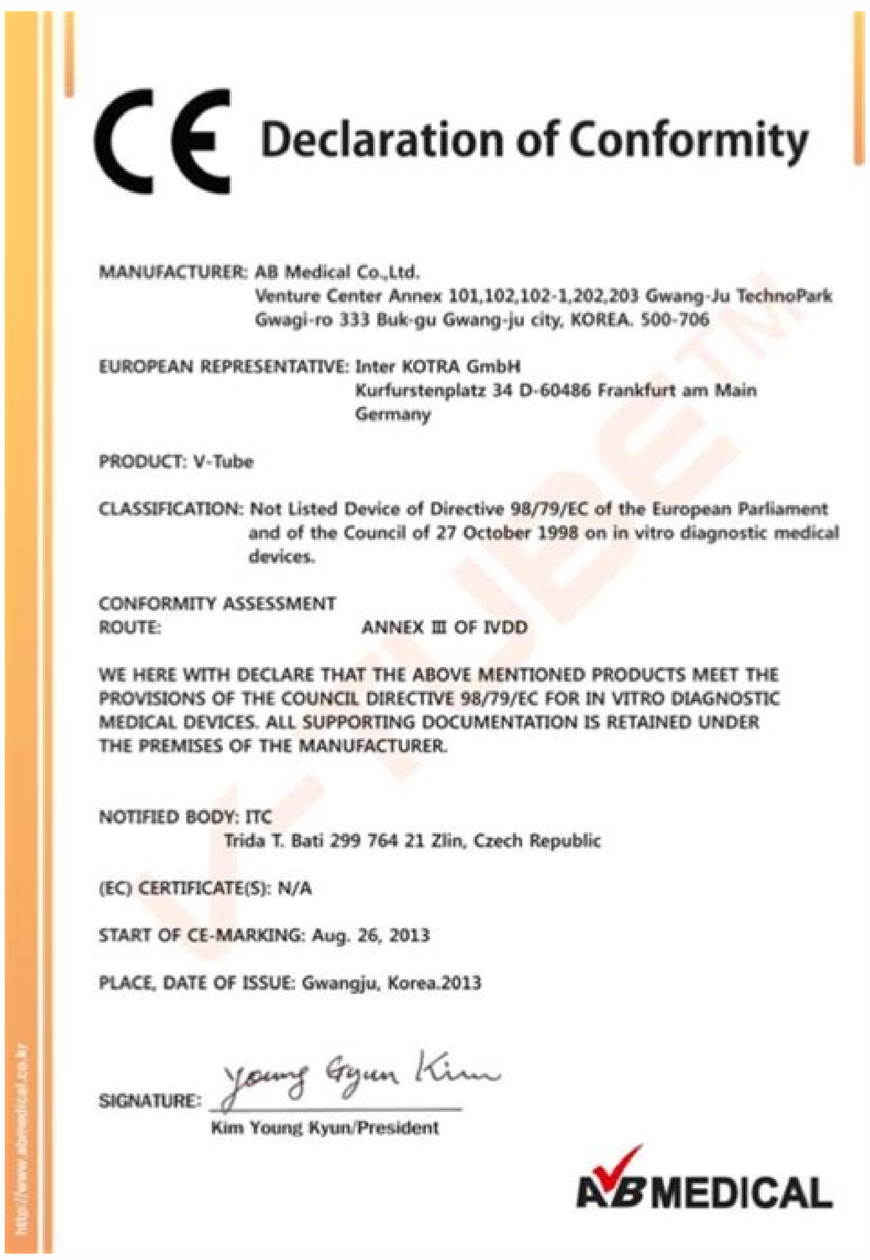
I, as a supplier to Oshkosh Defense, acknowledge and certify the material covered under this document is produced in accordance with the following:

- ☐ All Contractual "Flow Down" Requirements
- ☐ Supplier Standards Guide
- ☐ Global Supplier Quality Manual
- ☐ Product Conformance
- ☐ Free of Counterfeit Material

(Acknowledge by marking the boxes)

Signature *Title* *Completion Date*

This certifies the parts/items/materials identified above conform to all applicable drawings and/or specifications as evidenced by reports or other documentation on file and all other purchase order and quality requirements have been met.



CE Declaration of Conformity

MANUFACTURER: AB Medical Co.,Ltd.
Venture Center Annex 101,102,102-1,202,203 Gwang-Ju TechnoPark
Gwagi-ro 333 Buk-gu Gwang-ju city, KOREA. 500-706

EUROPEAN REPRESENTATIVE: Inter KOTRA GmbH
Kurfurstenplatz 34 D-60486 Frankfurt am Main
Germany

PRODUCT: V-Tube

CLASSIFICATION: Not Listed Device of Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices.

CONFORMITY ASSESSMENT ROUTE: ANNEX III OF IVDD

WE HERE WITH DECLARE THAT THE ABOVE MENTIONED PRODUCTS MEET THE PROVISIONS OF THE COUNCIL DIRECTIVE 98/79/EC FOR IN VITRO DIAGNOSTIC MEDICAL DEVICES. ALL SUPPORTING DOCUMENTATION IS RETAINED UNDER THE PREMISES OF THE MANUFACTURER.

NOTIFIED BODY: ITC
Trida T. Bati 299 764 21 Zlin, Czech Republic

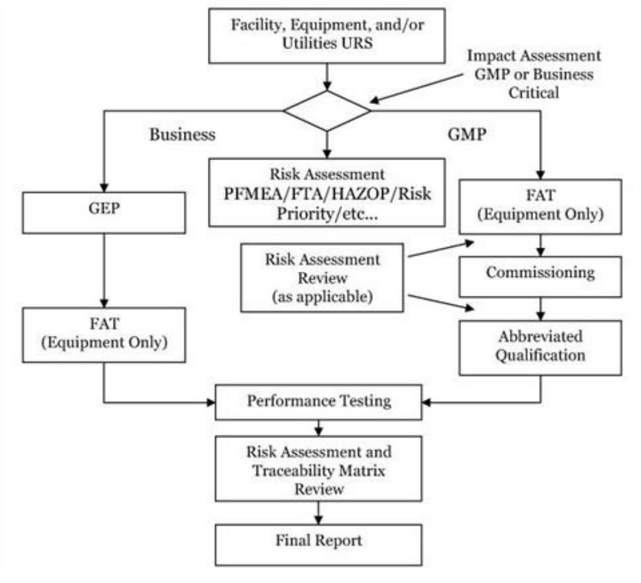
(EC) CERTIFICATE(S): N/A

START OF CE-MARKING: Aug. 26, 2013

PLACE, DATE OF ISSUE: Gwangju, Korea.2013

SIGNATURE: Young Gyun Kim
Kim Young Kyun/President

AB MEDICAL



Company Name, Inc. **Certificate of Analysis**

QAFRM-xxx Rev: 01	Implemented:	Use with QASOP-xxx	Page 1 of 2

Material:			
Lot Number:		**Date of Manufacture:**	
Attribute	*Method*	*Acceptance Criteria*	*Results*
Quality			
Color	Appearance	Colorless (≤ B_9) liquid	
pH	USP <791>	7.4 to 7.8	
Assay			
Assay – mg/mL protein	UV Absorbance	9.0 to 11.0 mg/mL	
Identity			
Peptide Map	Tryptic Map	Comparable to Reference Material	
SDS-PAGE (Silver Stain)	Reduced and Non-Reduced	Comparable to reference material. No new bands > 1 % intensity marker.	
Purity			
IE-HPLC main peak	IE-HPLC	≥ 97.0 %	
Desamido B2036		≤ 3.0 %	
SE-HPLC main peak	SE-HPLC	≥ 97.0 %	
RP-HPLC main peak (main peak plus clip B2036)	RP-HPLC	≥ 94.0 %	
N-succinyl B2036		≤ 1.0 %	
Norleucine B2036		≤ 3.0 %	
HI-HPLC main peak	HI-HPLC	≥ 94.0 %	
des-Phe B2036		≤ 2.0 %	
clip/other B2036		≤ 3.0 %	
trisulfide B2036		≤ 3.5 %	
Safety			
Bioburden	USP <61>	≤ 1 CFU/10 mL	
Endotoxins	USP <85>	≤ 1.0 EU/mg	

[PDF version of this document] Department of Human Welfare and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Centre for Biotechnological Evaluation and Research (CBER) August ICH Additional Codes are available from: Office of Training and Communications of Division Communications Management Drug Management Division Information, HFD-210 5600 Fishers Lane Rockville, MD 20857 (Tel) 301-827-4573 (Internet) Communications, Training and Assistance to Manufacturers, HFM-40 Centre for Biotechnical Evaluation and Research and Food and Drug Administration 1401 Rockville Pike, Rockville, MD 20852-1448 Internet: 1-888-CBERFAX or 301-827-3844 Mail: the 800-835-4709 or 301-827-1800 August 2001 ICH Table of Contents I. INTRODUCTION (1) Objective (1.1) Regulatory applicability (1.2) Environment (1.3) II. QUALITY MANAGEMENT (2) III. PERSONNEL (3) 8 Personnel Qualifications (3.1) Personnel Hygiene (3.2) is MENS160A; Consultants (3.3) IV. DINGS AND FACILITIES (4) V. PROCEEDING EQUIPMENT (5) VI. DOCUMENTS AND RECORDS (6) VII. MATERIAL MANAGEMENT (7) VIII. PRODUCT AND PROCESS CONTROLS (8) DISTRIBUTION AND IDENTIFICATION OF API AND INTERMEDIATE IDENTIFICATION (9) X. STORAGE AND DISTRIBUTION (10) Warehouses Procedures (10.1) Distribution of Procedures (10.2) XI. LABORATORY CONTROLS (11) XII. VALIDATION (12) XIII. CONTROL AMENDMENT (13) XIV. REQUEST AND reuse of materials (14) XV. COMPLAINS AND RECORDS (15) XVI. CONTRACT MANUFACTURES (16) XVII. Agents, breakers, tractors, DISTRIBUTORS, REPACKErs and RELABELLERS (17) XVIII. SPECIFIC GUIDE TO THE APIS MANUFACTURED BY CELL CULTURE/FERMENTS (18) 19th. APIs FOR USE IN CLINICAL TRIALS (19) GLOSSARY (20) Guidance for Industry1 Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients This represents guidance the Food and Drug Administration (FDA's) current thinking on this topic. It neither creates nor confers any rights on any person and does not operate to bind the FDA or the public. An alternative approach may be used if this approach meets the requirements of the applicable statutes and regulations. I. INTRODUCTION (1) Purpose (1.1) This document is intended to provide guidance on good manufacturing practice (GMP) for the manufacture of active pharmaceutical ingredients (API) within an appropriate quality management system. It is also intended to help ensure that the APIs meet the quality and purity characteristics they want to have or are represented. In this orientation, the term fabrication is defined to include all the operations of receiving materials, production, packaging, repackaging, labelling, receipts, quality control, release, storage and distribution of APIs and related controls. In this direction, the term must identify recommendations that, when followed, will ensure compliance with MPs. An alternative approach may be used if this approach meets the requirements of the applicable statutes. For the purposes of this orientation, the current good manufacturing practice terms and good manufacturing practices are equivalent. The overall direction does not cover the safety aspects of personnel involved in production nor the aspects related to environmental protection. These controls are the inherent responsibility of the manufacturer and are governed by national laws. This guideline is not intended to define registration and/or filing requirements or to modify pharmacokinetic requirements © Ethics. This Guideline does not affect the ability of the regulatory authority responsible for establishing specific registration/storage requirements © In the context of marketing/manufacturing authorisations or medications, the Commission would apply the APIs. All commitments in registration documents/storage must be B. Regulatory applicability (1.2) In the world community, materials may vary relative to their materials. materials. Classified as API. When a material is © classified as an API in the region or countries where © manufactured or used in a pharmaceutical product, should be manufactured according to this approach. C. The scope of application (1.3) This guideline applies to the manufacture of APIs for use in human medicines (medicines). Applies to the manufacture of APIs © kings only until © to the point immediately prior to sterilisation of APIs. Sterilization and the treatment thereof © APIs sceptic is © Kings are not covered by this approach, but should be carried out according to GMP guidelines for medicines (medicines) as defined by local authorities. This guideline covers APIs that are manufactured by chemical elements, extraction, cell culture/fermentation, recovery from natural sources, or any combination of these processes. Section XVIII (18) describes specific guidelines for APIs manufactured by cell culture/fermentation. © Whole cells, blood and plasma, blood and plasma derivatives (plasma fractionation) and gen e therapy APIs © Attica. However, it includes APIs that are produced using blood or plasma as a matchmaker. © raw laughs. Note that the dog substrates © Squids (mammals, plants, insects or dogs) © microbial squids, tissues or animal sources, including transgender animals © nicos) and the first process steps may be subject to GMP, but are not covered by this orientation. © m of this, the guidance does not apply to mother gas © di, bulk packaged medicinal products (medicines) or radiopharmaceuticals (e.g. tablets or capsules in bulk containers). The 19th (19) section © guidelines that only apply to the manufacture of APIs used in the production of medicines (medicines) specifically for classical trials (research medicines). A morning © ris-prima API © a morning © raw laughter, a morning © in between © day or an API that © used in the production of an API and that © embedded as a significant structural fragment in the API structure. An API starting material can be a parent article © a material purchased from one or more suppliers under contract or commercial contract, or produced at home. API-based materials typically define quantum properties and structure. The company should designate and document the basis of the starting point of the API production. For synthetic processes © tics, this © known as the point at which the API base materials are inserted in the process. For other processes (e.g. fermentation, extraction, purification), this foundation must be determined case by case. Table 1 gives guidance on the point at which the starting material API © normally introduced into the process. From this point on, the appropriate GMP, as defined in this Guideline, should be applied to these intermediate manufacturing steps © days and/or API. This would include validation of critical process steps determined to impact the quality of the API. However, it should be noted that the fact that a company chooses to validate a process step does not necessarily define this step as cryptic. The orientation in this document would normally apply to the steps shown in gray in Table 1. However, all the steps presented may not need to be completed. The severity of GMP in API manufacturing should increase as the process moves from the first API steps to the final steps, purification and packaging. The physical processing o f APIs, such as granulation, coating or manipulation o f the particle size (e.g. milling, micronisation) must be conducted in accordance with this orientation. This GMP orientation does not apply to previous steps in the introduction of the starting material as defined. Table 1: Application of this Guideline to the application of the type of API manufacture of this Guideline on stages (shown in grey) used in this type of manufacture of qumics products Introduction o f the starting material API in the process of production of intermediates Isolation and purification Physical, physical, physical treatment, API packaging derived from animal sources Collection o f organs, fluids or tissues Cut, mixture and/or initial processing Introduction of API input material in process isolation and purification and packaging API extracted from plant sources Collection o f starting material from cutting plants and initial extraction (s) Introduction of API to the process of isolation and purification and packaging Herbal extracts used as API Plant collection and cutting and initial extraction is Belo160; Physical treatment o f later extraction, and conditioning API, consisting of plants and/or crops and harvesting of plants and/or ground, cutting/blending of plants and/or crops, as well as harvesting, cutting/grinding of LEY160A; IT'S MY 160; Physical processing, and packaging Biotechnology: fermentation/ cell culture Planting o f the dog bank © main squids and dog bank © Work cells Maintenance of dog culture © Working cells and/or isolation o f fermentation and purification of physical processing, and packaging "Classical" Fermentation to produce an API Maintenance Planting of cell bank of cell bank Introduction of dog © Cells in fermentation isolation and purification Physical treatment, and packing II. QUALITY MANAGEMENT (2) A. Principles (2.1) Quality must be the responsibility of all persons involved in production. Each manufacturer must establish, document and apply an effective quality management system involving the active participation of management and appropriate manufacturing personnel. The quality management system should cover the organisational structure, procedures, processes and resources, as well as the activities designed to ensure that the API complies with the specified specifications for quality and purity. All quality-related activities shall be defined and documented. There must be a quality unit(s) that is independent of production and that meets both quality assurance (QA) and quality control responsibilities (QC). The quality unit can be in the form of separate QA and QC units or one individual or group unit depending on the size and structure of the organization. Persons authorised to release intermediate and APIs must be specified. All activities related to quality must be recorded at the time of its implementation. Any deviation from the established procedures must be documented and explained. Criminal deviations must be investigated and the investigation must be conducted. © rite and its conclusions be documented. NO MATTERS © ris should be released or used before satisfactory conclusion of the evaluation by the quality unit(s), unless there are adequate systems for such use (e.g. quarantine release, as described in Section X (10) or use of the material © the raw or intermediate holidays while you are and wait for the evaluation to be completed). There should be procedures to notify the responsible management in good time of regulatory inspections, serious BPF deficiencies, product defects and related (e.g. complaints related to quality, warnings and regulatory actions). B. Quality Unit(s) responsibilities (2.2) The quality unit(s) must be involved in all quality issues. The quality unit(s) shall review and approve all relevant quality documents. The main responsibilities of the independent quality unit(s) shall not be delegated. These responsibilities should be described in writing and include, but not necessarily limited to: release or reject all APIs. Releasing or rejecting intermediaries for use is the control of the manufacturing company that establishes a release or discard system © raw materials, intermediates, packaging, and labelling materials Revision of of batch production and laboratory control of the stages of the criminal process prior to the release of the API for distribution Make sure that the criminal deviations are investigated and resolved Approve all specifications and instruments of production intermediate quality © APIs or medias Ensure that internal audits (self-inspections) are carried out by approving intermediate contract manufacturers © and API, approving changes that could potentially affect mid-quality review © day or API and approving validation and reporting protocols ensuring that quality-related complaints are investigated and resolved by making sure that effective systems are used to maintain and calibrate credible equipment, ensuring that materials are properly tested and that results are reported, ensuring that there are stability data supporting test or validity dates and storage conditions in APIs and/or intermediate © Where appropriate, carry out product quality reviews (as defined in section 2.5) C. Responsibility for production activities (2.3) Responsibility for production activities must be written and must include, but not necessarily limited to: preparation, review, revision, and review. Approval, and distributing the instruments for the production of intermediaries or APIs according to written procedures Produce APIs and, where appropriate, intermediate © in accordance with practical instructions ©- approved, reviewing all the records of the production lots and ensuring that they are completed and signed, making sure that all production deviations are reported and evaluated and that the credit deviations are investigated and that the conclusions are recorded, Making sure production facilities are clean and, where appropriate, disinfected by making sure that the required calibrations are carried out and keeping records, ensuring that the installations and equipment are maintained and records maintained, ensuring that validation protocols and reports are reviewed and approved Evaluate proposed changes in the product, process or equipment making sure that new and, where appropriate, Modified installations and equipment are qualified D. Internal audits (self-inspection) (2.4) To verify compliance with GMP principles for APIs, regular internal audits must be carried out according to an approved schedule. Audit results and corrective actions must be documented and brought to the knowledge of the responsible management of the company. The corrective measures agreed upon must be completed in a timely and effective manner. E. Product quality assessment (2.5) Regular reviews of IPA quality must be carried out in order to verify the consistency of the process. These revisions should normally be conducted and documented annually and include at least, a review of the critical results of the API test in the process and the critical results of API tests A review of all batches that did not meet the established specifications A review of all the credit deviations or non-conformities and related investigations A review of any Changes made in processes or methods © all analgesic; A review of the results of the stability monitoring program A review of all returns related to quality, Complaints and recalls A review of the appropriateness of corrective actions The results of this review should be evaluated and an assessment made of whether the corrective action or any revalidation should be carried out. The reasons for this corrective action should be documented. The corrective measures agreed upon must be completed in a timely and effective manner. III. PERSONNEL (3) A. Quality of staff (3.1) There must be a sufficient number of qualified staff by education, training and/or experience appropriate to perform and supervise the manufacture of intermediaries and API. The responsibilities of all personnel involved in the manufacture of intermediaries and APIs shall be specified in writing. Training should be conducted regularly by qualified persons and should at least include the specific operations that the employee performs and the regarding the duties of the employee. Training records should be maintained. Training should be periodically evaluated. B. Staff hygiene (3.2) Staff must practice good health and health checks. Staff must wear clean clothes suitable for manufacturing activity that are involved and that the dressing room must be changed, if any. If necessary, additional protective clothing should be used, such as hair, face, hand and arming coatings, to protect intermediate and APIs from contamination. Staff should avoid direct contact with intermediaries or APIs. Smoking, eating, drinking, chewing and storing food should be limited to certain designated a reas, personnel who suffer from an infectious disease or have open lesions in the exposed surface of the body should not engage in activities that may result in compromising the quality of the API. Any person nominated at any time (by hand examination © or supervising observation) to have apparent illness or open injuries should be excluded from activities where the health condition may adversely affect the quality of API at © that the condition is corrected or the staff in hand © qualified dic determines that the inclusion of the person would not compromise the insurance or quality of the API. C. Advisers (3.3) advisors advising on the manufacture and control of intermediaries or APIs must have sufficient education, training and experience, or any combination of them, to advise on the subject for which they are being held. Records shall be maintained indicating the name, address, qualifications and type of service provided by these consultants. IV. BUILDINGS AND FACILITIES (4) A. Design and Construction (4.1) Buildings and facilities used in the manufacture of intermediates and API must be located, designed and constructed to facilitate cleaning, maintenance and operation, as appropriate to the type and phase of manufacture. Facilities also © m should be designed to minimise potential contamination. Whenever microbiological specifications for intermediate contaminants have been established © Facilities must also be designed to limit exposure to questionable microbiological contaminants, as appropriate. The buildings and installations must have sufficient space for the orderly deployment of equipment and materials to avoid confusion and contamination. If the equipment itself (e.g. closed or contained systems) provides adequate protection of the material, This equipment can be located outdoors. The flow of materials and personnel through © The building or installation must be designed to avoid confusion or contamination. There must be defined areas or other control systems for the following activities: reception, identification, sampling and quarantine of incoming materials, Quarantine pending release or rejection Quarantine prior to release or discard of intermediaries and after Sampling intermediate materials © Holding bodies and APIs rejected before new disposition (e.g. return, reprocessing or destruction) Storage of released materials Packaging and labelling operations Appropriate laboratory operations and personnel must have clean facilities for washing and toilet toilets. These installations must be equipped with hot and cold water, as the case may be, soap or detergent, air dryers or simple service towels. Washing and toilet facilities must be separated from manufacturing areas but easily accessible. Where necessary, suitable facilities for bathing and/or changing clothes must be provided. Laboratory areas/operations should normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, may be located in production zones, provided that the operations of the production process do not adversely affect the accuracy of laboratory measurements, and the laboratory and its operations do not adversely affect the production process, in between © dio or API. B. Utilities (4.2) All services that may affect product quality (e.g. steam, g. air heating, ventilation and air conditioning) should be qualified and adequately monitored and measures taken when the limits ar e exceeded. Drawings for these utility utilities should be available. Adequate ventilation, air filtration and exhaust systems shall be provided, as appropriate. These systems must be designed and constructed to minimise risks of contamination and cross-contamination and must include atmospheric pressure control equipment © rich, micro-organisms (if necessary), dust, humidity and temperature, as appropriate to the manufacturing phase. Special attention should be paid to the areas where the APIs are exposed to the environment. If air is recirculated in production areas, appropriate measures must be taken to control the risks of contamination and cross-contamination. The permanently installed pipelines shall be adequately identified. This can be achieved by identifying individual lines, documentation, computer control systems, or alternative means. The pipes must be located to avoid risks of contamination of the intermediate or API. The drains shall be of adequate size and shall be supplied with an air burst or with a suitable device to prevent air withdrawal where appropriate. C. It must be demonstrated that the water (4.3) used in the manufacture of APIs © adequate for their intended use. Unless justified otherwise, water must at least satisfy the guidelines of the World Health Organisation (WHO) for the quality of water (potable). If the (potential) water is insufficient to guarantee the quality of the API and more rigorous chemical and/or microbiological specifications in matters © water quality requirements, appropriate specifications for physical/chemical attributes, total microbial count, objective organisms and/or endotoxins shall be established. If the water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process must be validated and monitored with appropriate action limits. In case the manufacturer of an API is not © ril Pretendes or Claims that © suitable for use in later treatments to produce a medicine © ril (medicine), the water used in the final stages of isolation and purification should be monitored and controlled for total microbial counts, questionable organisms and endotoxins. D. Content (4.4) Specific production areas, which may include installations, handling equipment © ground and/or process equipment, should be used in the production of highly sensitive materials such as penicillins or cephalosporins. The use of specific production areas should also © to be considered when dealing with material of an infectious nature or high pharmacological activity or toxicity (e.g. certain steroids or anti-cancer agents in cytotoxic genes), unless validated inactivation and/or cleansing procedures are established and maintained. Appropriate measures should be established and implemented to avoid cross-contamination of personnel and materials moving from one specific a rea to another. N o production activities (including weighing, grinding or packaging) of highly toxic pharmaceuticals, such as herbicides and pesticides, should be performed, using the buildings and/or equipment used in the production of API. The handling and storage of these materials © Highly topical pharmaceuticals should not be separated from APIs. E. proper illumination (4.5) should be provided in all a reas to facilitate cleaning, maintenance and proper operations. F. Sewage and Refuse (4.6) Sewage, refuse and other waste (e.g. solid, liquid or gaseous by-products of the manufacturing industry) in and out of buildings and immediate surroundings must be disposed of safely, in good time and in good health. Waste vessels and/or pipes must be clearly identified. G. Sanitation and Maintenance (4.7) The buildings used in the manufacture of intermediates and APIs must be properly maintained and maintained. and kept in good condition. Written procedures should be established that assign responsibility for sanitation and describe the hours, hands © all cleaning equipment and materials to be used in cleaning buildings and facilities. When When When Written procedures should also be established for the use of rodenticides, insecticides, fungicides, fumigants and appropriate cleansing and disinfection agents in order to avoid contamination of equipment, materials © raw materials, packaging/labelling materials, intermediate products © Dios and API. V. PROCEDURE EQUIPMENT (5) A. Design and construction equipment (5.1) used in the manufacture of intermediate products © Sources and APIs should have a proper design and size and be adequately located for their intended use, cleaning, sanitation (if necessary), and maintenance. Equipment should be constructed so that the surfaces that com e into contact with materials © raw materials, intermediate or APIs do not change the quality of intermediate products © radios and APIs for hello © the official specifications or other established specifications. Production equipment should only be used in its range of skilled operations. The main equipment (e.g. reactors, storage containers) and permanently installed processing lines used during the production of intermediate equipment © Audio or API shall be adequately identified. Any substances associated with the operation of equipment, such as lubricants, heating fluids or soft drinks, should not contact intermediate or APIs to change the quality of APIs or intermediates beyond © the official specifications or other established specifications. Any deviations from this practice must be evaluated to ensure that there are no harmful effects on the fitness of the material for use. Whenever possible, lubricants and oils for food must be used. Whenever necessary, closed or contained equipment must be used. If open or open equipment is used, adequate precautions must be taken to minimise the risk of contamination. A set of current designs must be maintained for chronic equipment and installations (e.g. instrumentation and utility systems). B. Programs and procedures for equipment maintenance and cleaning (5.2) for the preventive maintenance of equipment, including the allocation of responsibilities. Written procedures should be established for the cleaning equipment and its subsequent release for use in the manufacture of intermediaries and API. Cleaning procedures shall contain sufficient data to allow operators to clean each type of equipment in a reproducible and effective manner. These procedures should include: Assignment of responsibility for cleaning equipment hours including, where appropriate, cleaning schedules, a complete description of the hands © all and materials, including dilution of cleaning agents used to clean equipment, where appropriate, Instructions to disassemble and assemble each article of equipment to ensure adequate cleaning tools for the removal or disposal of instruments for identifying previous batches for the protection of clean equipment against contamination before using Inspection of equipment for cleaning immediately prior to use, if, in practice, it determines the maximum period that can occur between the completion of transformation and the cleaning of equipment, where appropriate, equipment and utensils should be cleaned, stored and, where appropriate, disinfected or sterilised to prevent contamination or transfer of material that alters the quality of the intermediate material © dio or API for hello © the official or other specifications established. Where the equipment is assigned to continuous production or production on a campaign basis of successive lots of the same intermediate material © equipment must be cleaned at appropriate intervals to avoid accumulation and transfer of contaminants (e.g. degrading or objectionable from The dedicated equipment should not be cleaned between the production of different materials to avoid cross-contamination. The critters © rivers of acceptance of waste and the choice of cleaning procedures and cleaning agents should be defined and justified. The equipment shall be identified as its contents and cleanliness status by appropriate means. C. Calibration (5.3) Control, weighing, measurement, measurement, and the chronic test equipment to ensure the quality of intermediate or APIs shall be calibrated according to written procedures and an established schedule. If available, equipment calibrations shall be carried out using certified standards traceable. Records of these calibrations must be kept. The current calibration status of the chronic equipment must be known and verifiable. N o instruments should be used that do not meet the criteria © Calibration rivers. Deviations from the approved calibration standards of the instruments should be investigated to determine whether they could have had an effect on the quality of the intermediate or API(s) manufactured with this equipment since the last successful calibration. D. Computerised systems (5.4) related to GMP should be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerised application. Appropriate installation and operational qualifications must demonstrate the suitability of computer hardware and software to perform assigned tasks. Commercially available software that has been qualified does not require the same level of testing. If an existing system has not been validated at the time of installation, a retrospective validation may be carried out if adequate documentation is available. Computerised systems must have sufficient controls to prevent unauthorised access or alterations to data. There must be controls to avoid omissions in the data (e.g. off-line system and non-captured data). There should be a record of any change of data made, the previous entry, which made the change, and when the change was made. Written procedures should be made available for the operation and maintenance of computer systems. If data are to be entered manually, the accuracy of the input must be verified. This can be done by a second operator or by the system itself. Incidents related to computer systems that may affect the quality of intermediaries or APIs or the reliability of the records or results of the tests shall be recorded and investigated. Changes to computerised systems must be made according to an amendment procedure and must be formally authorised, documented and tested. Records must be kept of all changes, including changes and improvements made to hardware, software and any other chronic component of the system. These records must demonstrate that the system is maintained © m in a validated state. If system failures or failures result in permanent loss of records, a backup system shall be provided. A means of ensuring data protection for all computer systems should be established. The data can be recorded by a second medium, hello © m the computer system. VI. DOCUMENTS AND RECORDS (6) A. Documentation and specification system (6.1) All documents relating to the manufacture of intermediaries or APIs shall be prepared, revised, approved and distributed in accordance with written procedures. These documents can be in paper or electronic format. The emission, revision, Survival and withdrawal of all documents must be controlled by the maintenance of the review history. A procedure must be established t o maintain all appropriate documents (e.g. development history reports, scale reports, transfer reports © technique, process validation reports, training records, production records, control records and distribution records. The retention periods of these documents should be specified. All production, control and distribution records must be kept at least one year after the batch's expiry date. For APIs with repeat dates, the registers must be kept for at least three after the lot is completely distributed. When the entries are made in records, these must be made in an indelible manner. © in the spaces foreseen for these inputs, directly after the realization of the activities, and must identify the person making the entrance. Corrections for must be dated and signed and leave the original entry still readable. During the retention period, the original or track records must be readily available at the establishment where the activities described in these registers took place. Records that can be readily recovered from another location electronically or by other means are accepted. Specifications, instrumentations, procedures and records can be kept both as original or as true ones, such as photocopies, microfilm, microfiche or other precise reproductions of the original records. When they are used so © Reduction techniques, such as microfilm or electronic registers, should be readily available adequate recovery equipment and a means to produce a printed screen. There must be established and documented specifications relating to the issues © raw materials, intermediaries, if necessary, API s and materials © raw materials for labelling and packaging. Hello. © In addition, specifications may be appropriate for certain other materials, such as process aids, couplings or other materials used during the production of intermediaries or APIs that may seriously affect quality. The critters © Acceptance rivers must be established and documented for in-process controls. If electronic signatures are used in documents, they must be authenticated and protected. B. Records of cleaning and use of equipment (6.2) Records of use of the main equipment, cleaning, sanitation and/or sterilisation and maintenance must indicate the date, time (if appropriate), product and batch number of each batch processed in the equipment and the person who cleaned and maintained it. If the equipment is dedicated to the manufacture of a n intermediate equipment © Individual equipment records are not required if the intermediate or API lots follow traceable sequence. In cases where the equipment dedicated to © employee, cleaning, maintenance and use records can be part of the batch registration or kept separately. C. Morning records © Raw materials, intermediates, API Labeling and Packaging Materials (6.3) Records must be kept, including: the name of the manufacturer, the identity and quantity of each consignment of materials © raw materials, intermediate materials or labelling and packaging materials for API; the name of the supplier; the control number(s) of the supplier(s), if known, or other identification number; The number awarded at reception; and the date of receipt The results of any test or examination carried out and the conclusions derived from these records that track the use of materials © Raw materials Review and Review of API and MATTERS labels © raw packaging materials to conform to the established specifications The final decision on the subject © rejected raw materials, intermediate © Either API and Master Package Materials (approved) must be preserved for comparison to the issued rungs. D. Master Production and Control Records (6.4) To ensure uniformity between lot and batch, they must be prepared, dated and signed by a person and independently verified, dated and signed by a person in the quality unit(s). The main production instruments must include: the name of the intermediary or API that is being manufactured and a referral of ID document, if applicable A complete list of issues © Raw and intermediate rivers designated by sufficiently specific names o r addresses to identify any special quality characteristics An accurate statement of the quantity or amount of each subject © ris-raw or intermediate © the day to be used, including the unit of measurement. In c a se the quantity is not fixed, the calculation for each size or production rate of the lot shall be included. Variable quantities must be included whenever the location is justified Production and main production equipment to use detailed production instructions, including the following: sequence of process parameters to be used in process parameters and controls with their criteria © rivers of acceptance, if any Limits for the completion of the individual processing steps and/or the total process, where appropriate, expected yield ranges in appropriate processing or time stages, ratings and special precautions to be adopted, or cross-references to these Instructions for the storage of intermediate materials © in order to ensure their suitability for use, including labelling and packaging materials and special storage conditions with deadlines, if any. E. Batch Production Records (Batch Production and Control Records) (6.5) Batch Production Records must be prepared for each intermediate and API and must include full production and control information for each batch. The batch production record should be verified before the issue in order to ensure that the correct version and a readable and accurate reproduction of the appropriate main production instrument. If the batch production record is produced from a separate part of the main document, that document should include a reference to the current main production instrument that is being used. These records shall be numbered with a lot or number of unique identification, dated and signed when issued. In the continuous production, the product's step together with the date and time can serve as unique identifier. © that the final number is assigned. The documentation relating to the completion of each significant stage of batch production records (production records and batch control) shall include: dates and, where appropriate, Identification time of the main equipment (e.g. reactors, dryers, mills, etc.) used to identify the specific lot, including weights, measures and lots of materials © raw materials, intermediaries, or any reprocessed materials used during manufacturing The actual results recorded for the chronic parameters of the process Any sampling carried out Signatures of persons performing and supervising directly or checking each chronic step in the operation Results of trials in the process and laboratory Actual surrender at appropriate stages o r times of description Pack and Title for the representative API or API API API or intermediate rung © dio, if made available commercially, any recorded deviation, its evaluation, the investigation carried out (if any) or referral to that investigation, if the results of the release trials are stored separately, Written procedures should be established and followed for the investigation of credit deviations or non-compliance of a batch of intermediate tests © with the specifications or API. The inquest © rite must cover other lots that may have been associated with the specific fault or deviation. F. Laboratory Control Records (6.6) Laboratory control records shall include complete derived data from all tests carried out to ensure compliance with established specifications and standards, including examinations and tests, as follows: A description of samples received for testing, including name or source of material, Number of the lot or other distinguishing unit, date sampling and, where applicable, quantity and date on which the sample was received for the test A statement or referral per month © any test used A statement of the weight or measurement of the sample used for each test, as described by the hand © whole; Data on or crosswords on the preparation and testing of standards of reference, reagents and standard solutions A complete record of all raw data generated during each test © m of graphs, graphs and laboratory instrumentation spectra, duly identified to show the specific material and the tested batch A record of all the calculations made in connection with the test, including, for example, units of measurement, conversion factors, and equivalence factors A statement of test results and how compare with critters © The signature of the person who carried out each test and the date(s) of the tests were performed The date and signature of a second person showing that the original records were revised for accuracy, accuracy, and respect for established standards should also be kept complete records for: Any changes to one month © every analogue established periodic calibration of laboratory instruments, apparatus, manmeters, and recording devices All stability tests carried out in investigations © Written procedures must be established and followed for the revision and approval of laboratory production and control records in lots, including packaging and labelling, To determine the compliance of the MI or API with the specifications established before a batch is released or distributed. Batch production and laboratory records of control of the critical stages of the process shall be reviewed and approved by the quality unit(s) before a batch of API is released or distributed. Production and laboratory control records of non-process stages may be revised by qualified production personnel or other units in accordance with procedures approved by the quality unit(s). All reports of deviation, investigation and OOS should be reviewed as part of the revision of the batch record before release of the batch. The quality unit(s) may delegate to the production unit the responsibility and authority for releasing intermediates, except those dispatched outside the control of the manufacturing company. 7th. Materials MANAGEMENT (7) General controls (7.1) There shall be written procedures that describe the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials. Intermediary and/or APIs manufacturers must have a system for evaluating critical material suppliers. The materials must be purchased on the basis of an agreed specification from a supplier or suppliers approved by the quality unit(s). If the supplier of a credible material is not the manufacturer of this material, the name and address of that manufacturer must be known by the intermediate manufacturer © dio and/or API. The modification of the material supply source © Credit raw materials should be treated according to Section 13, Change Control. B. Reception and Quarantine (7.2) After receipt and before acceptance, each container or group of material containers should be examined visually for correct labelling (including correlation between the name used by the supplier and the first name, if these are different), damage to the containers, Broken seals and evidence of tampering or contamination. Materials should be kept in quarantine until further notice. © which have been sampled, examined or tested, as appropriate, and released for use. Before the material © Incoming services are to be mixed with the existence (e.g. solvents or existence in silos), must be identified as correct, tested, if any, and released. Procedures should be made available to prevent the undue discharge of materials received in existing existences. If bulk deliveries are made in non-specific oil tankers, there must be guarantees that the oil tanker will not contaminate cross-contamination. The means to ensure this guarantee may include one or more of the following: the cleaning test certificate for checking residual impurities, the audit of the supplier Large storage containers and their distributors, filling and discharging lines shall be adequately identified. Each container or grouping of containers (lots) of materials must be assigned and identified with a distinctive dog, lot or number of reception. This number must be used in the register of the disposition of each lot. There must be a system to identify the condition of each batch. C. Sample and test input material (7.3) At least one test shall be carried out to verify the identity of lot of material, with the exception of the materials described below. The certificate of analysis of a supplier may be used instead of conducting other tests, provided that the manufacturer has a system for assessing suppliers. The approval of suppliers should include an assessment that provides adequate evidence (for example, Quality history) that the manufacturer can consistently provide compliance specifications for the material. Full analysis shall be carried out on at least three batches before reducing internal tests. However, at the minimum, a complete analysis should be carried out at appropriate intervals and in comparison with the analysis certificates. The reliability of the analysis certificates shall be verified at regular intervals. Aid for processing, the materials © dangerous or highly topical raw materials, other materials © Special raw materials or materials © raw materials transferred to another unit under company control need not be tested if the manufacturer's analysis certificate is obtained, showing that these materials © raw materials are in accordance with the established specifications. Visual examination of containers, runes and recording of batch numbers should help determine the identity of these materials. The lack of on-site testing for these materials should be justified and documented. The samples shall be representative of the batch of material from which they are taken. The mom's © all sampling shall specify the number of vessels to be sampled, which part of the vessel to be sampled and the quantity of material to be taken from each vessel. The number of containers to be sampled and the size of the sample shall be based o n a sampling plan that takes into account the criticality of the material, material variability, past supplier quality history and the quantity required for the analysis. Sampling shall be carried out at defined locations and by procedures to avoid contamination of the material sampled and contamination of other materials. The containers from which the samples are taken should be opened carefully and then recovered. They must be marked to indicate that a sample has been taken. D. The storage (7.4) of materials must be handled and stored in such a way as to avoid degradation, contamination and cross-contamination. Materials stored in fibre batteries, bags or boxes should be stored on the floor and, where appropriate, properly spawned to allow cleaning and inspection. Materials should be stored in conditions and during a period that does not impair their quality, It should normally be controlled so that the oldest stock is used first. Certain materials in appropriate containers may be stored outdoors, provided that the identification of legable permanence rubles and containers a r e adequately cleaned before opening and use. Rejected materials must be identified and controlled under a quarantine system designed to prevent their unauthorised use in production. Reassessment (7.5) Materials should be reassessed, where appropriate, to determine their suitability for use (e.g. after prolonged storage or exposure to heat or humidity). Eighth. PRODUCT AND PROCESS CONTROLS (8) A. Production operations (8.1) MATTERS © raw materials for intermediate production © day and API should be weighted or measured in appropriate conditions that do not affect their suitability for use. Weighing and measuring devices should have an appropriate accuracy for the intended use. If a material is subdivided for later use in production operations, The container receiving the material must be suitable and must be identified in such a way that the following information is available: name and/or name of the material receiving or number of weight control or measurement of the material in the new container Re-evaluation or test date, if any, scientific consideration, Measurement, or subdivision operations shall be witnessed or subject to equivalent control. Before use, production personnel must verify that the materials are specified in the batch record for the intermediate or API intended. Other Credits must be witnessed or subject to equivalent control. Actual yields should be compared to expected yields in the designated stages of the production process. Expected yields at appropriate intervals should be established on the basis of past laboratory, pilot or manufacturing data. Income gap with credible process steps should be investigated to determine their impact or potential impact on the quality resulting from the affected batches. Any deviation must be documented and explained. Any credible deviation must be investigated. The processing status of the main equipment units should be indicated either in the individual equipment units or through © adequate documentation systems, IT control systems or alternative means. Repressed or reformulated materials should be adequately controlled to avoid unauthorised use. B. Time limits (8.2) If time limits are specified in the main production instrumentation (see 6.40), these deadlines must be met to ensure the quality of intermediate and APIs. Deviations shall be documented and evaluated. The deadlines may be inadequate when process to a target value (e.g. pH adjustment, hydrogenation, drying to a specification ©- determined) because the conclusion of the reaction or processing stages are determined by sampling and testing in the process. Intermediaries held for further processing should be stored in appropriate conditions to ensure their adequacy in use. C. Written procedures for sampling and control in the process (8.3) should be established to monitor progress and control the performance of the stages of the process processing that cause variability in the quality characteristics of intermediates and API. The in-process controls and their critique © Acceptance rivers must be defined on the basis of information obtained during the development phase or on the basis of historical data. The critters © rivers of acceptance and type and extension of tests may depend on the nature of the intermediate product © of the reaction or process phase, and of the degree to which the process introduces variability in product quality. Less rigorous in-process controls may be appropriate in the early processing stages, while tighter controls may be suitable for later processing steps (e.g. isolation and purification steps). CREDIT CONTROLS OF THE PROCESS (and CREATIC MONITORING OF THE PROCESS), including control points and hands © all must be indicated in writing and approved by the quality unit(s). Process controls can be carried out by qualified personnel in the production department and the process adjusted without approval. © by unit or quality units if adjustments are made within own limits ©- established by the quality unit(s). All tests and results shall be fully documented as part of the batch record. The written procedures should describe the mother © all sampling for materials in process, intermediate and API. Sampling plans and procedures shall be based on scientifically sound sampling practices. Sampling in process shall be performed using procedures designed to avoid contamination of the sampled material and other intermediaries or APIs included in the sample. Procedures should be established to ensure the integrity of samples after collection. Normally, they are not necessary enquiries © extra-specific rites (OOS) for process tests that are performed for process monitoring and/or process adjustment. D. Intermediate mixing lots or APIs (8.4) For the purposes of this document, the mixture © defined as the process of combining materials within the same specification to produce a homogeneous intermediate © Or API. The process mix of individual batch fractions (e.g. collecting various centrifuge loads from one single crystallisation batch) or combinations of fractions of several batches for further processing © considered to be doing part and the production process and not © considered a mixture. The lots the specification must not be mixed with other batches for the purpose of complying with specifications. Each batch incorporated into the mixture must have been manufactured using an established process and must have been tested individually and found to satisfy appropriate specifications before mixing. Acceptable blending operations include, but are not limited to: mixing small lots to increase batch size of flows (i.e. relatively small quantities of isolated material) of lots of the same intermediate material © The blending processes must be adequately controlled and documented, and the blended batch must be tested for compliance with the established specifications, if any. The batch recording of the blending process should allow traceability back to the individual batches that compose the mixture. Whenever API's physical attributes are chronic (e.g. APIs intended for use in sound forms o f oral dosage or suspensions), blending operations must be validated to show the homogeneity of the combined batch. Validation should include the test of critical attributes (e.g. particle size distribution, faucet mass density and density) that can be affected by the mixing process. If the mixture can adversely affect stability, stability tests of the blended final lots shall be carried out. The period of validity or repetition of the blended batch shall be based on the date of manufacture of the oldest tails or the oldest batch of the mixture. E. Contamination Control (8.5) Residual materials can be transported to successive lots of the same intermediate material © or API, if there is proper control. Examples include remnants adhering to the wall of a microniser, residual layer of humid crystals remaining in a centrifuge basin after discharge, and incomplete discharge of fluids or crystals from a processing vessel after transfer of material to the next step of the process. Such transport shall not result in the transport of degradants or microbial contamination that may adversely alter the API impurity profile established. Production operations must be conducted in such a way as to prevent contamination of intermediaries or APIs by other materials. Caution must be taken to avoid contamination when EPAs are handled after purification. IX. PACKAGING AND IDENTIFICATION LABELING OF API AND INTERMEDIATE (9) A. General (9.1) There must be written procedures that describe the reception, identification, quarantine, sampling, examination and/or testing, release and handling of packaging and labelling materials. The packaging and labelling materials must conform to the established specifications. Those who do not comply with these specifications must be rejected to prevent their use in operations for which they are not adequate. Records shall be kept for each consignment of rubles and packaging materials indicating receipt, examination o r test and accepted or rejected. B. Containers of packaging materials (9.2) must provide adequate protection against the deterioration or contamination of the intermediate or API that may occur during the recommended transport and storage. The containers must be cleaned and, if indicated by the nature of the IA or API, must be hygiened to ensure that they are suitable for their intended use. These containers must not be reactive, additives or absorbers to change the quality of the intermediate product © dio or API for hello © m of specified limits. If the containers are r e-used, they must be cleaned in accordance with documented procedures and all previous rungs must be removed or disfigured. C. Issue and Control Label (9.3) Access to the storage areas of the article must be limited to authorised personnel. Procedures should be established to reconcile the quantities of subtitles issued, used and returned and to assess the discrepancies detected between the number of labelled vessels and the number of subtitles issued. Such discrepancies must be investigated and the investigation © rite must be approved by the quality unit(s). All excess runes bearing lots o r other batch-related printing must be The returned rungs must be kept and stored in such a way as to avoid confusion and provide an adequate identification. Obsessive and outdated rungs must be destroyed. Printing devices used to print subtitles for packaging operations should be controlled to ensure that all brands conform to the printing press in the batch production record. Printed rungs issued for a batch must be carefully examined to obtain an adequate identity and compliance with the specifications contained in the main production record. The results of this examination shall be documented. A printed rung representative of those used shall be included in the batch production register. D. Packaging and labelling operations (9.4) procedures designed to ensure the use of correct materials and controls must be documented. Labelling operations must be designed to avoid confusion. There must be physical or spatial separation o f operations involving other intermediaries or APIs. The runes used in intermediate containers o r API s must indicate the name or name of the identification unit, batch number and storage conditions when such critical information is to ensure the quality of the intermediate or API. If the material management system or API is intended to be transferred outside the control of the manufacturer's material management system, the name and address of the manufacturer, the quantity of contents, special transport conditions and any special legal requirements must also © to be included in the title. In the case of intermediaries o r API with expiry date, the expiry date shall be indicated in the title and in the certificate of analysis. In the case of intermediaries o r API with a date of repetition, the date of repetition shall be indicated in the rung and/or in the analysis certificate. Packaging and labelling facilities must be inspected immediately before use in order to ensure that all materials not necessary for the next packaging operation have been removed. This examination must be documented in the production records in batches, in the installation fee o r other documentary system. Intermediates or packaged and labelled APIs must be examined to ensure that the containers and packaging in the lot have the correct title. This examination should be part of the packaging operation. The results of these examinations must be recorded in production or batch control records. The intermediate containers © Dios or APIs which are transported outside the manufacturer's control shall be sealed so that, if the seal is breached or not, the recipient is alerted to the possibility that the contents have been changed. X. STORAGE AND DISTRIBUTION O (10) A. Storage facilities for all materials under appropriate conditions (e.g. controlled temperature and humidity, when needed). Records of these conditions must be kept if they are credible for maintaining the material characteristics. Unless there is an alternative system to prevent the unintentional or unauthorised use of materials in quarantine, rejected, returned or collected, the separate storage a reas should be assigned to their temporary storage at once. © The decision on their future use. B. Distribution procedures (10.2) API and intermediate © Only products must be released for distribution to third parties after they have been released by the quality unit(s). API s and intermediaries may be transferred under quarantine to another unit under company control, when authorised by the quality unit(s) and where appropriate controls and documentation are in place. APIs and intermediaries should be transported in a way that does not adversely affect their quality. Special conditions for the transport or storage of an API or an intermediary must be indicated in the title. The manufacturer shall ensure that the contract receiver (contractor) for the transport of API or intermediate knowledge © Knowledge and follow proper transport and storage conditions. There must be a system through © s from which the distribution of each batch of intermediate material © ERA and/or API may be promptly determined to allow collection. 11th. LABORATORS (11) A. General controls (11.1) The independent quality unit(s) must have appropriate laboratory facilities. Procedures describing sampling, testing, approval or rejection of samples shall be documented. and recording and storage of laboratory data. Laboratory records shall be maintained in accordance with Section 6.6. All specifications, sampling plans and test procedures must be scientifically sound and adequate to

ensure that the materials are © raw materials, intermedictors, API and rubles and materials © raw packaging materials are in accordance with established quality and/or purity standards. The test specifications and procedures shall be consistent with those included in the register/storage. There may be specifications for hello © of the record/store constants. The specifications, sampling plans and test procedures, including amendments, shall be drawn up by the appropriate and revised organisational unit and approved by the quality unit(s). Appropriate specifications for APIs shall be established in accordance with accepted standards and in accordance with the manufacturing process. Specifications should include control of impurities (e.g. organic impurities, inorganic impurities, and residual solvents). If the API has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms must be established and complied with. If the API has a specification for endotoxins, must be established and complied with limits of appropriate action. Laboratory checks shall be followed up and documented at the time of performance. Any deviations from the procedures described above shall be documented and explained. Any result outside the specification obtained must be investigated and documented according to a procedure. This procedure should include analysing data, assessing the existence of a significant problem, assigning tasks to corrective actions and conclusions. Any resale and/or recount after the OOS results shall be carried out in accordance with a documented procedure. Reagents and standard solutions must be prepared and labelled according to written procedures. The use by dates shall be applied, where appropriate, to analog reagents or standard solutions. Primary reference standards for the manufacture of API shall be obtained if necessary. The source of each primary reference standard must be documented. Records of each primary standard of storage and use shall be maintained in accordance with the recommendations of the supplier. Normally, the primary reference standards obtained from an officially recognised source are used without testing if stored in accordance with the recommendations of the supplier. If a primary reference standard is not available from an officially recognised source, an internal primary standard must be established. Appropriate tests shall be carried out to fully determine the identity and purity of the primary reference standard. The appropriate documentation of this test should be maintained. Secondary reference standards must be adequately prepared, identified, tested, approved and stored. The appropriateness of each secondary reference lot must be determined before first use, compared to a primary reference standard. Each consignment of secondary reference should be periodically qualified according to a written protocol. B. Test of Intermediators and APIs (11.2) for each batch of intermediate material © Appropriate laboratory tests shall be carried out to determine compliance with the specifications. A profile of impurities describing the identified and unidentified impurities present in a peak batch produced by a specific controlled production process should normally be established for each API. The impurity profile must include identity or some qualitative analog name (e.g. retention time), the range of each observed and the classification of each identified impurity (e.g. inorganic, g. organic, solvent). The impurity profile normally depends on the production process and origin of the API. Ordinarily, impurity profiles are not necessary for animal or herbal APIs. herbal. The considerations are covered by the ICH Q6B Guideline. The impurity profile should be compared at appropriate intervals with the impurity profile in the regulatory submission or compared to historical data to detect API changes resulting from changes in the issues © In the operational parameters of the equipment or in the production process, raw materials must be tested in each batch of intermediate material. © in the case of specified microbial quality. C. Validation of analogue procedures See section 12. (11.3) D. Certificates of analysis (11.4) shall be issued authentic certificate of analysis for each batch of intermediate material © dio or API, on request. Information o n the name of the intermediary or the API shall be provided, including, where appropriate, its degree, batch number and release date on the certificate of analysis. In the case of intermediaries o r API with expiry date, the expiry date shall be indicated in the title and in the certificate of analysis. In the case of intermediaries o r API with a date of repetition, the date of repetition shall be indicated in the rung and/or in the analysis certificate. The certificate must list each test performed according to the requirements of the client or the compendium, including the acceptance limits, and the results in no way © rich obtained (if the test results are in no way © rich). Certificates must be signed and dated by authorised quality unit(s) personnel and must indicate the name, address and telephone number of the original manufacturer. Where the analysis has been carried out by a repackaged or reprocessing agent, the certificate of analysis shall indicate the name, address and telephone number of the relauncher/reprocesser and indicate the name of the original manufacturer. If new certificates are issued by or o n behalf of reimbursements/reprocessers, agents or brokers, these certificates shall indicate the name, address and telephone number of the laboratory that performed the analysis. They must also © to include a reference to the name and address of the original manufacturer and to the original batch certificate, the doggy of which must be attached. E. Monitoring IPA stability (11.5) An ongoing documented test programme should be established to monitor the stability characteristics of IPA, and the results should be used to confirm appropriate storage conditions and retain or expire dates. The test procedures used in the stability tests shall be validated and shall indicate stability. The stability samples shall be stored in containers simulating the market container. For example, if the API is marketed in bags inside fibre drums, stability samples can be packed in bags of the same material and in small scale drums of similar or identical material composition to market drums. Normally, the first three lots of commercial production should be placed in the stability monitoring program to confirm the new or expiration date. However, in cases where data from previous studies show that API is expected to remain stable for at least two years, less than three batches can be used. After that, at least one batch per year of manufactured API (unless none are produced that year) should be added to the stability monitoring program and tested at least annually to confirm stability. For APIs with short shelf life, the tests must be done more frequently. For example, for biotech/biological organisms and other API with a term of validity of one year or less, stability samples must be obtained and tested monthly in the first three months, and at intervals of three months after that period. When data exist that confirm that API stability is not compromised, the elimination of test intervals can be considered (e.g. nine-month tests). If appropriate, the conditions for preserving stability should be compatible with the ICH guidelines in terms of © laugh at stability. F. Expiry and update date (11.6) Whenever it is intended to transfer an intermediary out of control of the manufacturer's material management system and an expiration date or again or again Information on stability support should be available (e.g. published data, test results). The validity or repetition period of the API should be based on an evaluation of the data resulting from stability studies. The common practice © use a repeat date, not an expiration date. The expiration or repeat dates of the preliminary API may be based on pilot lots if (1) the pilot lots use one hand © all manufacturing and procedure simulating the final process to be used on a commercial scale of manufacture and (2) the quality of API represents the material to be made on a commercial scale. A representative sample shall be taken for the purpose of conducting a new test. G. Reservation/retention samples (11.7) Packaging and retention of reservation samples are intended for a future potential assessment of the quality of API lots and no future stability tests. Reservation samples duly identified from each batch of API shall be kept for one year after the batch validity period allocated by the manufacturer, or for three years after the batch is distributed, whichever is longer. For API s with test dates, similar spare samples should be kept for three years after the batch is completely distributed by the manufacturer. The spare sample must be stored in the same packaging system as the API. © stored or in an equivalent or more protective sample than the marketed packaging system. Sufficient quantities should be maintained to perform at least two complete compilation analyses or, where no pharmacopoeia monograph is available, two complete specification analyses. 12th. VALIDATION O (12) A. Validation Policy (12.1) Global company policy, intentions and validation approach, including validation process validation, cleaning procedures, methods © all analytical, process control test procedures, computerized systems and persons responsible for design, revision, approval, and documentation of each validation phase, shall be documented. Critical parameters/attributes should normally be identified during the development phase or from historical data, and the necessary ranges for the reproductive operation should be defined. This should include: Defining the API in terms of its CRITICAL attributes of the product Identify process parameters that may affect the credit quality attributes of the API by determining the range for each critical parameter of the process that is expected to be used during routine manufacturing and validation of the control of the process process should extend to these operations determined to be critical to the quality and purity of the API. B. Validation Documentation (12.2) A written validation protocol specifying how the validation of a given process will be made should be established. The Protocol shall be reviewed and approved by the quality unit(s) and other designated units. The validation protocol must specify the critical steps of the process and critique © the type of validation to be conducted (e.g. retrospective, prospective, competitor) and the number of executions of the process. A validation report that the cross-references of the validation protocol should be drawn up, summarizing the results obtained, commenting on any observed deviations and drawing appropriate conclusions, including recommending amendments to correct deficiencies. Any changes to the validation protocol must be documented with an appropriate justification. C. Qualification (12.3) Before commencing process validation activities, the appropriate qualification of chronic equipment and ancillary systems must be completed. The qualification © usually held through © the realization of the following activities, individually or in combination: quality of the project (DQ): documented verification that the proposed design of the installations, or systems © adequate for the intended design Quality of the facility (IQ): documented verification that the equipment or systems, as installed or modified, comply with the approved design of the manufacturer and/or usage requirements Operational quality (QO): documented verification that the equipment or systems, as installed or modified, comply with the planned operation ranges foreseen Quality of performance (QP): documented verification that the equipment and auxiliary systems, as linked together, can perform efficiently and reproducibly based on the hand © the process validation approaches (12.4) Validation of the process (PV) are documented proof that the process, operated within the established parameters, can perform effectively and reproducibly to produce an intermediary or API that satisfies its specific and primary quality attributes ©- determined. There are three approaches to validation. © the preferred approach, but there are situations where other approaches can be used. These approaches and their applicability are discussed here. The prospective validation should normally be performed for all API processes defined in 12.1. The prospective validation of an API process must be completed before the commercial distribution of the final product manufactured from this API. Concomitant validation can be performed when replicate production test data are not available because only a limited number of API lots have been produced, API lots are produced infrequently, or API lots are produced by a validated process that has been modified. Before completion of concurrent validation, batches can be released and used in the final drug product for commercial distribution, based on thorough monitoring and testing of API batches. An exception can be made to retrospective validation of well-established processes that were used without significant changes in API quality due to changes in terms of © Raw materials, equipment, systems, installations or production process. This validation approach can be used whenever: Credit quality attributes and parameters of the process have been identified that have been identified © adequate rivers and controls in the process There were no significant process/product failures attributable to causes that are not operator errors or equipment failures not related to the impairment profiles of the equipment were established for the existing batches selected for retrospective validation API should be representative of all batches produced during the review period, including all batches that do not comply with the specifications, and must be sufficient in numbers to demonstrate the consistency of the process. Retained samples can be tested to obtain data to retrospectively validate the process. E. Process Validation Program (12.5) The number of validation processes must depend o n the complexity of the process or the magnitude of the process change being considered. For prospective and simultaneous validation, three consecutive successful production lots should be used as a guide, but there may be situations where the additional processes are justified to prove process consistency (e.g. complex API processes or API processes with prolonged completion deadlines). For the purpose of retrospective validation, data from 10 to 30 consecutive batches should be examined in general to assess the consistency of the process, but less batches may be examined if justified. The critical parameters of the process should be monitored and monitored during process validation studies. Process parameters not related to quality, such as controlled variability to minimize energy consumption or equipment use, need not be included in process validation. Process validation should confirm that the impurity profile of each API is within the specified limits. The impurity profile must be comparable or superior to the historical data and, where appropriate, to the profile determined during the development of the process or to the batches used in basic classical studies and toxicokinetics. F. Periodic revision of validated systems and processes (12.6) should be a periodic review check that they are still operating in a timely manner. In case no significant changes have been introduced into the system or process, and a quality review confirms that the system or process is constantly producing material that meets its specifications, There is normally no need for revalidation. G. Cleaning validation (12.7) Cleaning procedures should normally be validated. In general, cleaning validation should be directed at situations or steps in the process where contamination or transport of materials represents the greatest risk to API quality. For example, in early production it may be unnecessary to validate the procedures for cleaning equipment in which the waste is removed by subsequent purification steps. The validation of cleaning procedures should reflect the actual patterns of use of the equipment. If several APIs or intermediaries are manufactured in the same equipment and the equipment is cleaned by the same process, a representative intermediary or API may be selected for cleaning validation. This selection should be based on the solubility and difficulty of cleaning and on the calculation of residue limits based on potency, toxicity and stability. The cleaning validation protocol shall describe the equipment to be cleaned, procedures, materials, acceptable cleaning levels, parking meters to monitor and control, and © All analgesic. The protocol must also © to indicate the type of samples to be taken and how they are collected and labelled. Sampling should include scrubbing, cleaning or working © all alternative (e.g. direct extraction), as appropriate, to detect insoluble and soluble waste. The mom's © all the sampling used must be able to measure quantitatively the levels of residue remaining in the surfaces of the equipment after cleaning. Swab sampling may be impractical when the contact surfaces of the product are not easily accessible due to design limitations and/or process of the equipment (e.g. interior superflues of hoses, transfer tubes, reserve reactors with small ports or handling sensitive materials, and intricate small equipment such as micronizers and microfluindros). Mom should be used © All anals validated with sensitivity to detect residues or contaminants. The detection limit for each hand © Any analogue must be sufficiently sensitive to detect the accepted level of the residue or contaminant established. The level of recoveries reached in the mother should be established © whole. The residue limits must be practical, achievable, verifiable and based on the most harmful waste © River. The limits may be established on the basis of the known pharmacological, toxicological or physiological activity of the API or its most harmful component. The cleaning/sanitation studies of equipment should focus on microbiological and endoxic contamination for the processes in which © There is a need to reduce the total microbiological count or the endotoxins in the API, or other processes in which this contamination may be of concern (e.g. APIs not sterile used for the manufacture of products are © kings). Cleaning procedures should be monitored at appropriate intervals after validation in order to ensure that these procedures are effective when used during routine production. The cleaning of the equipment can be monitored through © Analytical tests and visual examinations, whenever possible. Visual inspection may allow the detection of gross contamination concentrated in small a reas which could otherwise be undetected by sampling and/or analysis. H. Mother Validation © All analgesic (12.8) The hands © All analogues must be validated unless the mother © all used is included in the relevant pharmacopoeia or other recognised standard reference. The adequacy of all hands © all of the test used must, however, be in actual usage and documented conditions. Should be validated mom © all to include consideration of the characteristics included in the ICH guidelines on the validation of the mother © All analgesic. The degree of analytical validation carried out should reflect the purpose of analysis and the stage of the API production process. Appropriate Appropriate Anatic equipment should be considered before starting the validation of the hands © All analgesic. Complete records of any modification of a hand must be maintained © every analogue validated. These records should include the reason for the change and the appropriate da t a t o verify that the change produces such precise and faithful results as the mother © all established. XIII. CHANGE CONTROL (13) A formal change control system shall be established to assess any changes that may affect production and control of the intermediate or API. The written procedures should provide for identification, documentation, proper revision and approval of changes in the issues. © raw materials, specifications, mother © all analogues, installations, support systems, equipment (including computer equipment), processing phases, labelling and packaging materials and computer software. Any relevant BPF change proposals should be prepared, reviewed and approved by the appropriate and revised organisational units and approved by the quality unit(s). The potential impact of the proposed change on the quality of the interim or API shall be assessed. A classification procedure can help determine the test level, validation and documentation needed to justify changes to a validated process. Changes can be classified (e.g. as smaller or larger) depending on the nature and extent of the changes, and the effects these changes can have on the process. The scientific judgment must determine that additional testing and validation studies are adequate to justify an amendment to a validated process. In implementing the approved amendments, measures must be taken to ensure that all the documents affected by the amendments are reviewed. After the application of the change, an evaluation of the first batches produced or tested under the change should be carried out. If necessary, intermediate or API samples produced by the modified process can be placed in an accelerated stability program and/or can be added to the stability monitoring program. Manufacturers of current dos e formulae should be notified of changes in production procedures and control of established processes that may affect the quality of the API. XIV REJECTIVE AND REVIEW OF MATERIALS (14) A. Rejection (14.1) Intermediators and APIs that do not comply with the specified specifications shall be identified as such and quarantined. These intermediaries or APIs may be reprocessed or reformulated as described below. The final disposition of the rejected materials must be recorded. B. Reprocessing (14.2) Introduction of an interim API © day, including one that does not conform to the standards or specifications, Return to the process and reprocessing, repeating a step o f crystallization or other appropriate steps of quantum or physical manipulation (e.g. distillation, filtration, chromatography, milling) that are part of the established manufacturing process © generally considered acceptable. However, if this reprocessing is used for most batches, this reprocessing should be included a s part of the standard manufacturing process. © considered part of the normal procedure. This is not © considered reprocessing. The introduction of material not reacting back to a process and the repetition of a chemical reaction © considered reprocessing unless part of the established process is done. This reprocessing must be preceded by a careful evaluation to ensure that the quality of the intermediate product © dio or API not © adversely affected due to potential formation of by-products and materials with excessive reaction. C (14.3) Before a decision is taken to reformulate batches that do not conform to established standards or specifications, an investigation should be carried out into the reason for non-compliance. Batches that have been reformulated To be subjected to an evaluation, test, appropriate stability test, if warranted, and documentation demonstrating that the reformulated product © of equivalent quality is produced by the initial process. The concurrent validation © often the validation approach appropriate to the recasting procedures. This allows a protocol to define the recasting procedure, how it will be executed, and the expected results. If there is only one batch to be reformulated, a report can be written and the batch released once the © considered acceptable. The procedures shall provide for the comparison of the impurity profile of each reformulated batch with the batches manufactured by the established process. Case the hands © all routine analgesics are unsuitable to characterize the reformulated batch, must be used in hand © all additional. D. Recovery of materials and solvents (14.4) Recovery (e.g. from maternal or filtered liqueur) from reagents, intermediate or API © deemed acceptable, provided that there are approved procedures for recovery and the materials recovered satisfy the specifications appropriate for their intended use. Solvents can be recovered and reused in the same processes or in different processes, provided that recovery procedures are controlled and monitored to ensure that solvents comply with appropriate standards before reusing or blending with other approved materials. Fresh and recovered solvents and reagents can be combined if the appropriate tests have demonstrated their suitability for all manufacturing processes in which they can be used. The use of recovered solvents, maternal fluids and other recovered materials should be properly documented. E. Intermediate (14.5) devolutions © returned books or APIs shall be identified as such and quarantined. If the conditions under which the returned middlemen or APIs have been stored or sent before or during their surrender or during the conditions of their containers give rise to doubts about their quality, the returned middlemen or APIs shall be reprocessed, reformulated or destroyed as appropriate. Records of intermediate should be maintained © returned all the cards or APIs. For each return, the documentation must include: Name and address of the mediator or or recipient's API, batch number and quantity returned Reason for use or disposal of the returned XV or API. COMPLAINTS AND RECALLS (15) All quality-related complaints received orally or in writing must be registered and investigated in accordance with a written procedure. The register of complaints should include: Name and address of the complainant Name (and, where appropriate, title) and telephone number of the person lodging the complaint (including name and batch number of API) Date of reception of the complaint (including da t e and identity of the person making the action); Any follow-up measures taken Response provided to the reporting author (including response to the date sent) Final decision on the intermediate batch © either the API batch or batch of complaints must be maintained to assess trends, frequencies related to the product and gravity, with a view to taking additional and, where appropriate, immediate remedial action. There should be a written procedure defining the circumstances in which the devolution of an intermediary or API should be considered. The collection procedure should designate who should participate in the evaluation of information, how a collection should be initiated, who should be informed about the collection and how the reserve material should be handled. In the event of a serious or potentially dangerous situation for life, local, national and/or international authorities should be informed and their advice requested. XVI. Contract manufacturers (INCLUDING LABORATORIES) (16) All contract manufacturers (including laboratories) must comply GMP defined in this orientation. Special attention should be given to preventing cross-contamination and maintaining traceability. Companies must evaluate any contractors (including laboratories) to ensure compliance of GMP Specific operations that take place at the premises of the contractor. There must be a written and approved contract or a formal agreement between an undertaking and its contractors which sets out in detail the responsibilities of GMP, including quality measures, of each party. A contract must allow a company to audit the premises of its contractor for compliance with GMP. Where the subcontracting is authorised, the contractor shall not pass on to third parties any of the works entrusted to him under the contract without the actual valuation. © via and prior approval © via the company. Production and laboratory records shall be kept at the place where the activity takes place and shall be readily available. Changes in process, equipment, hands © All testing, specifications or other contractual requirements must not be carried out unless the contractor is informed and approves the changes. 17th. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, E RELABELLERS (17) A. Applicability (17.1) This section applies to any other party other than the original manufacturer who can market and/or take possession, repackaging, relabel, manipulate, distribute or store an API or intermediate. All agents, brokers, traders, distributors, reimbursements and confidence agents must comply with the GMP defined in this Guideline. B. The traceability of API and distribution intermediaries (17.2) Agents, brokers, traders, distributors, reimbursements or trusted agents must maintain complete traceability of APIs and intermediaries they distribute. Documents to be kept and available include: Identity of the original manufacturer Address of the original manufacturer Purchase orders Boarding notes (transport documentation) Reception documents Name or API name or batch number of the intermediate manufacturer © The analysis, including that of the original manufacturer Retest or expire the term C. Quality Management Agents (17.3), brokers, traders, distributors, reimbursements or clock agents shall establish, document and implement an effective quality management system as specified in Section 2. D. The repair, retransmission and arrest of API and intermediaries (17.4) Repair, reimbursement and retention of API and intermediaries should be carried out under appropriate GMP controls, as stipulated in this Guideline, in order to avoid confusion and losses of API or intermediate identity or intermediate identity © day or purity. The repair should be carried out in appropriate environmental conditions to avoid contamination and cross-contamination. E. Stability studies (17.5) shall be carried out to justify the duration of validity granted or the date of repetition of the tests, if either the API or the intermediate is reimbursed in a different type than that used by the API or the intermediate manufacturer. © Hate. F. Transfer of information (17.6) Agents, brokers, distributors, reimbursements or trusted agents must transfer all the quality or regulatory information received from an API or intermediate manufacturer to the customer, and from the customer to the API or intermediate manufacturer. The agent, the broker, the trader, the distributor, the repurchaser or repairman providing the API or the intermediary to the customer shall provide the name of the original API or intermediate manufacturer and the batch number(s) supplied. The agent must also © m provide the identity of the original API or intermediate manufacturer © regulatory authorities, upon request. The original manufacturer can respond directly or via © its authorised agents to the regulatory authority, in function of the legal relationship between the authorised agents and the original API or intermediate manufacturer © Hate. (In this context, authorised refers to the one authorised by the manufacturer.) Specific guidelines for the certificate of analysis included in section 11.4 must be met. G. Handling of complaints and complaints (177) brokers, traders, distributors, reimbursements or retread agents shall keep records of complaints and censuses, as specified in section 15, for all complaints and records that come to their meeting If the situation warrants, agents, brokers, traders, distributors, reimbursements or relabelers shall review the complaint with the original API or intermediate manufacturer © to determine whether there has been any further action, either with other customers who may have received this API, either intermediate or with the regulatory authority, or both, should be initiated. Investigation of the cause of dencience or dencience must be conducted and documented by the appropriate party. Where a report is referred to the original API or to the intermediate manufacturer © dio, the register kept by agents, brokers, traders, distributors, reimbursements or brokers shall include any response received from the original API or the intermediate manufacturer © dio (including date and information provided). H. Treatment of devolutions (17.8) should be treated as specified in section 14.5. Agents, brokers, traders, distributors, repackers or relabelers must keep the API documents and returned intermediaries. 18th. SPECIFIC GUIDENCE FOR APPIS MANUFACTURED BY CELL CULTURE/FERMENTS O (18) General (18.1) Section 18) is intended to address specific API or intermediate API controls manufactured by cell culture or fermentation using natural or recombinant organisms and which have not been adequately covered in the cells previous sections. It is not intended to be an isolated section. Generally, the principles of GMP apply in the other sections of this document. It should be noted that the principles of fermentation for classical processes of small-scale production © and for processes using recombinant and non-recombinant organisms for the production of proteins and/or polyps © Great are the same, although the degree of control is different. If it is practical, this section will address these differences. In general, the degree of control of biotech processes used in the production of proteins and polyps © Fine © above the standard fermentation processes. The term biotechnological process (biotechnology) refers to the use of dog © squids or organisms that have been generated or modified by recombinant DNA, hybridoma or other technology to produce APIs. APIs produced by biotechnological processes usually consist of substances with high molecular weight such as proteins and polyps. © Great, for which © certain low molecular weight APIs, such as antibiotics, amino acids, vitamins and carbohydrates, also © m can be produced by recombinant DNA technology. The level of control of these types of API © similar to that used in classical fermentation. The term classical fermentation refers to processes that use existing microorganisms in nature and/or modified by hand © all conventional (e.g. irradiation or mutation) © (c) to produce APIs. The APIs produced by classical fermentation are usually low molecular weight products such as antibiotics, amino acids, vitamins and carbohydrates. The production of cellular culture or fermentation APIs involves biological processes, such as dog farming © squid or extracting and purifying materials from living organisms. Note that there may be additional steps in the process, such as physical modification © mica, which are part of the manufacturing process. © The raw materials used (social media, buffer components) can provide the potential for growth of microbiological contaminants. In function of the source, mother © any preparation and intended use of the API or intermediate © day, it may be necessary to control biological load, viral contamination and/or endotoxins during manufacture and process monitoring at appropriate stages. Appropriate controls should be established at all stages of manufacturing to ensure intermediate quality © day and/or API. As this orientation begins in the cell culture/fermentation phase, previous steps (e.g. bank) must be carried out under appropriate process controls. This guideline covers cell culture/fermentation from the point where a vial of the cell seat © Wow. © adequate equipment and environmental controls must be used to minimise the risk of contamination. © Acceptance rivers to determine environmental quality and monitoring frequency must depend on the production step and production conditions (open, closed or contained systems). In general, process controls should take into account: maintenance of the dog bank © Working cells (if appropriate) inoculation and expansion of culture Control of critical operational parameters during fermentation/cell culture Monitoring of cell growth process, viability (for most cell culture processes) and productivity, if any, Harvesting and purifying procedures that remove dogs © squid, cellular waste and components of the media while protecting the interim or API from contamination (especially of a microbiological nature) and loss of monitoring of the quality of biocargon and, if necessary, Endotoxin levels at appropriate stages of production Viral Safety Concerns as described in the ICH Guideline Q5Quality of biotechnological products: Assessment of viral safety of biotechnology products Derived from human or animal cell lines, if any, Removal of social media components, host cell protection, other impurities related to the process, impurities and product-related contaminants must be demonstrated. B. Maintenance and maintenance of cell bank records (18.2) Access to cell banks must be limited to authorised personnel. Mobile banks should be kept in storage conditions designed to maintain viability and avoid contamination. Records should be kept of the use of the vials from the dog banks © calamari and storage conditions. If applicable, the dog seats © squids should be periodically monitored to determine the appropriateness of use. See ICH Q5D Quality of biotechnological products: Derivation and Characterisation © Cells used for the production of biotechnological/biological products for a more complete discussion of the cell banking. C. Culture/nutrition of C © Cells (18.3) Whenever cell substrates, social media, tampons and gases should be added © closed or contained systems must be used whenever possible. If the inoculation of the initial vessel or subsequent transfers or additions (social media, buffers) are carried out on open vessels, controls and procedures should be in place to minimise the risk of contamination. If the quality of the API can be affected by microbial contamination, manipulations using open vessels must be carried out in a biosecurity office or in an equally controlled environment. Staff should be properly dressed and take special precautions in crop handling. Credit operational parameters (e.g. temperature, pH, agitation rates, gas additions, pressure) must be monitored to ensure consistency with the established process. Cell growth, viability (for most cell culture processes), and, where appropriate, productivity as well © m should be monitored. Chronic parameters vary from process to process, and for classical fermentation, certain parameters (cell viability, for example) may not need to be monitored. Cell culture equipment should be cleaned and sterilized after use. Where appropriate, fermentation equipment should be cleaned, disinfected or sterilized. Culture media should be sterilized before using, where necessary, to protect the quality of API. Appropriate procedures should be established to detect contamination and determine the course of the to take. Procedures should be made available to determine the impact of contamination on the product and to decontaminate the equipment and return it to a condition to be used in subsequent batches. External organisms observed during fermentation processes shall be identified as appropriate and the effect of their presence on the quality of the product shall be assessed if necessary. The results of these evaluations must be taken into account in the disposition of the material. Records of contamination events should be maintained. Shared equipment (multi-product) can justify additional testing after clean-up between product campaigns, as appropriate, to minimise the risk of cross-contamination. D. Harvesting, isolation and purification (18.4) Harvesting steps, either to remove dog © Cell cells or components, either to collect cellular components after interruption, must be carried out in equipment and areas designed to minimise the risk of contamination. Harvesting and purification procedures that remove or inactivate the producer organism, cellular waste and social media components (while minimizing degradation, contamination and quality loss) must be adequate to ensure that the AI is recovered with consistent quality. All equipment must be properly cleaned and, if necessary, hygienised after use. Several successive lots can be used without cleaning if the intermediate quality © day or API is not compromised. If open systems are used, purification must be carried out in appropriate environmental conditions to preserve the quality of the product. Additional controls, such as the use of specific chromatography resins or additional tests, may be appropriate if equipment for multiple products is to be used. E. Viral removals/decommissioning steps (18.5) See ICH Guidance Q5Quality of Biotechnological Products: Assessment of Viral Safety of Biotechnological Products by Canine Derivatives © Human or animal origin cells for more specific information. The viral and inactivation steps of removal are critical processing steps for some processes and should be carried out within their validated parameters. Appropriate precautions must be taken to avoid potential viral contamination since the removal/inactivation phases. ©- viral until © Pastoral. Therefore, open treatment should be carried out in separate areas of other treatment activities and have treatment units in place. © Ground separated. The same equipment is not © normally used for different stages of purification. However, if you want to use the same equipment, the equipment should be properly cleaned and hygied before re-use. Appropriate precautions should be taken to prevent the potential v rus from being transported (e.g. via © (s) of equipment or environment) from previous steps. 19th. API s FOR USE IN CLINICAL TRIALS (19) A. General (19.1) Not all controls in previous sections of this orientation are adequate for the manufacture of a new API for experimental use during its development. The 19th (19) section provides specific guidelines for these circumstances. The controls used in the manufacture of APIs for use in classical trials should be consistent with the development phase of the product incorporating the API. Process and test procedures should be flexable to predict changes, as knowledge of the process increases and the classic testing of a medicine progresses from practical stages. ©- Classics. Once the development of medicines reaches the stage at which API © Manufacturers must ensure that API s are manufactured in appropriate facilities, using appropriate production and control procedures to ensure the quality of API. B. Quality (19.2) Appropriate GMP concepts should be applied in the production of APIs for use in classical trials with an appropriate batch approval mechanism. An independent production unit(s) for approval or rejection of each batch of API for use in classical trials shall be established. Some of the test functions normally performed by the quality unit(s) can be performed within other units Quality measures should include a matchmaking test system © raw materials, materials © raw packaging, intermediate and API. Process and quality problems should be assessed. Labelling for APIs intended for use in classical trials should be adequately controlled and should identify the material as being for experimental use. C. Equipment and (19.3) During all stages of classical development, including the use of small-scale or laboratory facilities for the manufacture of lots of APIs for use in classical trials, procedures ensuring calibration should be established, cleaning and fitting of equipment to their intended use. The procedures for using installations must ensure that materials are handled in a way that minimises the risk of contamination and cross-contamination. D. Control of the issues © raw materials (19.4) Math © raw materials used in the production of APIs for use in classical trials should be evaluated by © tests or received with an analysis by a supplier and subjected to identity tests. When a material is © considered dangerous, the analysis of a supplier should be sufficient. In some cases, the fit of a story © raw laughter can be determined before use based on acceptability in small-scale reactions (i.e. use tests) rather than isolated analog tests. E. Production (19.5) Production of APIs for use in classical trials must be documented in laboratory notebooks, batch records or by other appropriate means. These documents should include information on the use of production materials, equipment, processing and scientific observation. The expected yields can be more variable and less defined than expected yields used in commercial processes. N o research is expected on variances in income. F. Validation (19.6) Validation of the process for the production of APIs for use in classical trials © normally inappropriate, when a single batch of API © produced or when process changes during API development make replication difficult or inaccurate batch. The combination of controls, calibration and, where appropriate, equipment qualification ensure the quality of the API during this development phase. Process validation should be carried out in accordance with Section 12, when lots are produced for commercial use, even when these lots are produced in pilot or small scale. G. Changes (19.7) Changes are expected during development, such as knowledge © acquired and production © Enlarged. All changes in production, specifications or test procedures shall be properly recorded. H. Laboratory checks (19.8) Though the hands © All analogues performed to evaluate a batch of API for classical trials may not yet be validated, must be scientifically sound. There must be a system for retaining reserve samples from all batches. This system shall ensure that a sufficient quantity of each sample is retained during an appropriate period of time after approval, termination or interruption of an application. The expiration and repeat date, as defined in section 11.6, applies to existing APIs used in classical trials. For new API, section 11.6 does not normally apply in early stages of classical trials. I. Documentation (19.9) There must be a system that ensures that information obtained during the development and manufacture of APIs for use in classical trials is documented and available. The development and application of the hands © all analogues used to support the release of a batch of API for use in classical trials must be properly documented. A system for retaining records and production and control documents shall be used. This system shall ensure that records and documents are kept for an appropriate period of time after approval, termination or suspension of an application. GLOSSARY (20) Critical © acceptance rivers: limits in no way © rich, intervals or other appropriate measures for the acceptance of test results. Ingredient Active Pharmaceutical (API) (or medicated substance): Any substance mixture of substances intended to be used in the manufacture of a medicine (medicine) and that when used in the production of a medicine, become an active ingredient of the medicine. These substances are intended to provide a pharmacological activity or other direct effect on diagnosis, healing, attenuation, treatment or prevention of illness or to affect the structure and function of the patient. API Starting material: A morning © ris-prima, intermediate © day or API that © used in the production of an API and that © embedded as a significant structural fragment in the API structure. An API starting material can be a parent article © a material purchased from one or more suppliers under contract or commercial contract, or produced at home. API base materials are normally of quantum properties and structure defined. Batch (or batch): A specific quantity of material produced in a process or healthy © process series, so that it is expected to be homogenous © or within the specified limits. In the case of continuous production, a batch can correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the quantity produced in a fixed time range. Batch number (or lot number): A unique combination of numbers, letters and/or symbols identifying a lot (or lot) and from which the history of production and distribution can be determined. Biocargo: N o and type (e.g. objectionable or not) of micro-organisms that may be present in the field © raw materials, materials © API, intermediate or API raw materials. Bioavailability should not be considered as contamination unless the levels have been exceeded or defined target organisms have been detected. Calibration: A demonstration that a particular instrument or device produces results within the specified limits, in comparison to the results obtained by a screening referral or standard over an adequate range of measurements. Computer system: A group of associated hardware and software components designed and assembled to perform a specific function or function group. Computerised system: A process or operation integrated with a computer system. Contamination: The unwanted introduction of impurities of a chemical or microbiological nature, or of a material nature © foreign laughter, in a story © ris-prima, intermediate © day or API during production, collection, packaging or repackaging, storage or transport. Contract manufacturer: A manufacturer that performs some aspect of production on behalf of the original manufacturer. Critical: Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within critique © rivers first ©- determined to ensure that the API meets its specification. Cross-contamination: Contamination of a material or product with another material or product. Deviation: Departure from an approved instrument or established standard. Medicine: The posologic formulation in the immediate final packaging intended for marketing. Expiration date (o r Expiration date): The date placed in the container/rungs of an API indicating the period during which the API is expected to be allowed within the established shelf life specification, if stored in defined conditions and after which it is not to be used. Impurity: Any component present in the interim or API that is not the desired entity. Impurity Profile: A description of the identified impurities and not identified in an API. In-Process Control (or Process Control): Controls made during production to monitor and, where appropriate, adjust the process and/or to ensure that the interim or API meets its specifications. Intermediator: A material produced during the steps of processing an API that undergoes new molecular changes or purification before becoming an API. Intermediaries may or may not be isolated. (Note: this guideline refers only to the intermediaries produced after the point that a company defined a s the point at which the production of API begins.) Batch: See lot lot lot lot lot lot lot lot lot lot lot manufacturing: All operations of material reception, production, packaging, repackaging, labelling, replacement, control of Release, storage and distribution of API and related controls. Material: A general term used to designate the raw product (COUGHING) © raw materials, reagents, solvents), process aids, intermediate, APIs and packaging and labelling materials. Mother Liquor: The residual fluid that remains after the crystallization or isolation process. A mother's liquor may contain unused materials, intermediate, API levels and/or impurities. It can be used for further processing. Packaging material: Any material intended to protect an intermediate material © or an API during storage and transport. Procedure: A documented description of the operations to be carried out, the precautions to be taken and the measures to be applied directly or indirectly related to the manufacture of an intermediate product © or an API. Process aids: materials, excluding solvents, used as aid in the manufacture of an intermediate product © an API that does not participate themselves in a quantum or biological reaction (e.g. filtering aid, activated carbon). Process Control: see In-Process Control. Production: All the operations involved in preparing an API from the reception of materials through © processing and packaging of API. Qualification: The action of proving and documenting that the equipment or auxiliary systems are properly installed, working properly, and actually leading to the expected results. Qualification is part of validation, but the individual steps of qualification alone do not constitute validation of the process. Quality Assurance (QA): The total sum of the arrangements organised in order to ensure that all EPAs are of the quality required for their intended use and that quality systems are maintained. Quality control (CSF): Verification or testing of compliance with specifications. Quality Unit: An organizational unit independent of production that fulfils both quality assurance and quality control responsibilities. This can be in the form of separate QA and QC units or one individual or group, depending on the size and structure of the organization. Quarantine: The status of materials physically isolated or by other effective means pending a decision on their subsequent approval or rejection. © Raw rias: A general term used to designate materials © raw materials, reagents and solvents intended for use in the production of intermediaries or APIs. Reference standard, Primary: A substance that has been demonstrated by a vast array of analog tests to be authentic material that must be of high purity. This standard can be: (1) obtained from an officially recognised source, (2) prepared by independent manufacture, (3) obtained from existing high purity production material, or (4) prepared by further purification of the existing production material. Reference standard, secondary: a established quality and purity substance, as demonstrated in comparison to a primary reference standard, used as a reference standard for routine laboratory analysis. Conclusion: Introduction of an API or intermediate © day, including one that does not conform to the standards or specifications, go back to the process and repeat a step o f crystallization or other appropriate steps of quantum or physical manipulation (e.g. distillation, filtration, chromatography, milling) that are part of the established manufacturing process. The continuation of a process step after a process control test showed that the step is incomplete. © considered part of the normal process and not © reprocessing. Validity date: The date on which a material must be re-examined to ensure its use. Request: To submit an interim API © the day or API that do es not conform to the standards or specifications of one or more processing steps that are different from the manufacturing process established to obtain acceptable intermediate quality © day or API (e.g. recrystalize with a and different). Signature (signed): See definition for signature. Signed (signature): Registration of the individual who has carried out a certain action or revision. This record may be initial, complete handwritten signature, personal stamp or secure electronic signature. Solvent: Solvent: Inorganic or organic liquid used as a vehicle for preparing solutions or suspensions in the manufacture of an intermediate vehicle © or an API. Specification: A list of tests, references to analytical and critical procedures © Appropriate acceptance rivers that are no limits © rich, ranges or other critters © rivers for the described test. Establishs the critter set © rivers that a material must obey to be considered acceptable for its intended use. Compliance with the specifications means that the material, when tested according to the analogue procedures listed, meets the criteria © rivers of acceptance listed. Validation: A documented program that provides a high degree of assurance that a process, m o m © any specific system or system will consistently produce a result that satisfies critique © rivers of acceptance first ©- determined. Validation Protocol: A written plan showing how the validation will be conducted and defining the criteria © Acceptance rivers. For example, the protocol for a manufacturing process identifies the processing equipment, the critical process parameters and/or operating ranges, the product characteristics, the sampling, the test data to be collected, the number of validation tests and the accepted test results. Income, expected: amount of material or percentage of theoretical income expected at any appropriate stage of production based on laboratory, pilot or manufacturing data. Income, rich: The amount that would be produced at any appropriate stage of production based on the amount of material to use, in the absence of any loss or error in actual production. 1 This Guideline was developed within the working group of experts (Q7A) of the International Conference on Harmonisation of Requirements © Medicines Registration Technics for Human Use (ICH) and was consulted by the regulatory parties in accordance with the ICH process. This document was approved by the Commission © ICH Director in Stage 4 of the ICH process, November 2000. In Phase 4 of the process, the final design for adoption is recommended to the regulators of the European Union, Japan and the United States. The numbers in the subheadings reflect the organisational breakdown in the document approved by the Commission © Director of ICH at stage 4 of the ICH process in November 2000. FDA/Center for Drug Evaluation and Research Last Updated: September 24, 2001 Originator: OTCOM/DLIS HTML by PKS Submit comments on this guidance document electronically via docket ID: FDA-2013-S-0610 specific Electronic Submissions Intended for FDA's Dockets Management Staff (i.e., Citizen Petitions, Draft Proposed Guidance Documents, Variances and other administrative record submissions) If unable to submit Online comments, please send comments written t o: Dockets Management Food and Drug Administration 5630 Fishers Lane, Rm 1061 Rockville, MD 20852 All comments must be identified with the title of the Orientation.

we make you sure. 4C Consulting provides an extensive range of strategic consulting and advisory services that lead to sustainable business excellence. We work closely with small and large businesses, understand their strength, manage their risk through futuristic strategies and ensure business continuity through sustainable process improvement. Disclaimer. This GMP audit checklist is intended to aid in the systematic audit of a facility that manufactures drug components or finished products. The adequacy of any procedures is subject to the interpretation of the auditor. Therefore, ISPE and the GMP Institute accept no liability for any subsequent regulatory observations or actions stemming from the use of this audit checklist. Nov 30, 2021 · Download checklists for ISO 22000 Audit of your Food Safety Management System (FSMS). Comprehensive ISO 22000 Audit Checklist. ISO 22000:2005 Compliance Audit. ISO 22000:2018 Compliance Audit. Use iAuditor to prepare for, implement and assess your FSMS for ISO 22000 certification. Aug 26, 2020 · The QSR, also commonly called Current Good Manufacturing Practice regulations, was established and is maintained by the U.S. Food and Drug Administration (FDA). The FDA is in the process of harmonizing U.S. quality system requirements with ISO 13485, and plans to issue a notice of proposed rulemaking in October 2020. For the time being ... The approval, maintenance and audit of excipient suppliers should be based on quality risk management, in accordance with GMP Part I, 5.29 and the EU guidelines on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use. Gene Synthesis is a reliable and cost-effective method for obtaining customized DNA constructs with 100% sequence accuracy. As a powerful molecular biology tool, DNA synthesis is rapidly becoming a crucial part of research workflow and has transformed modern biology. CloneAmp HiFi PCR Premix is designed for use with the In-Fusion Cloning system due to its exceptionally accurate and efficient DNA amplification. The 2X master mix contains enzyme, optimized buffer, and dNTPs, allowing rapid setup of PCR reactions and facilitating high-throughput applications for multiple cloning samples. Article 35 Drugs used for clinical trials shall be manufactured in facilities in compliance with the Good Manufacturing Practice for Pharmaceutical Products (GMP). ... and a template of the informed consent form, etc. ... and submit a certificate of analysis for drug registration to the Center for Drug Evaluation of the State Food and Drug ... The DoC is based on supporting documentation which documents the reasoning on the safety of a plastic food contact material, and which must be provided to enforcement Authorities on their request. The supporting documentation also provides an important link to the manufacturer's responsibility under GMP (Commission Regulation (EC) No 2023/2006). May 25, 2016 · Documentation and Records for GMP Compliance . GOOD MANUFACTURING PRACTICES. GMP is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use. GMP is aimed primarily at diminishing the risk inherent in any pharmaceutical production. Sep 17, 2018 · These questions and answers (Q&As) provide an overview of the European Medicines Agency's (EMA) advice on issues that are typically addressed in discussions or meetings with marketing authorisation holders in the application phase.. This guidance should be read in conjunction with the rules governing medicinal products in the European Union, volume ... Qualified Persons A qualified person shall be in possession of a diploma, certificate, or other evidence of formal qualifications awarded on completion of a university course of study, or a course recognized as equivalent by the Member State concerned, extending over a period of at least four years of theoretical ... NOTE: The order of the products printed on the certificate will be the same order of the products entered in Section 4 or on the product template upload file. Grouping a Product(s) to a Facility(ies) Products can be grouped to one, some or all of the facilities to be printed on the certificate.

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