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MINISTRY OF HEALTH

PHARMACY AND POISONS BOARD

GUIDANCE FOR INSPECTIONS OF API MANUFACTURERS AND HANDLERS

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Abbreviations

API	Active Pharmaceutical Ingredient
GMP	Good Manufacturing Practice
GDP	Good Distribution Practice
PPB	Pharmacy and Poisons Board
CT	Clinical Trials
QMS	Quality Management System
COA	Certificate of Analysis
QC	Quality Control
EMEA	European Medicines Agency
ICH	International Commission on Harmonization
WHO	World Health Organization
USFDA	United States Food and Drugs Authority
PWS	Primary Working Standards
SWS	Secondary Working Standards
CRS	Chemical Reference Stan

Foreword

This document (guide) is intended to provide guidance regarding good manufacturing practices (GMP) for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the requirements for quality and purity that they purport or are represented to possess. In this guide "manufacturing" is defined to include all operations of receipt of materials, production, packaging, repackaging, labelling, re-labelling, quality control, release, storage and distribution of APIs and the related controls.

In this guide the term "should" indicates recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance. For the purposes of this guide, the terms "current good manufacturing practices" and "good manufacturing practices" are equivalent.

The guide as a whole does not cover safety aspects for the personnel engaged in the manufacture, nor aspects of protection of the environment. These controls are inherent responsibilities of the manufacturer and are governed by national laws.

This guide is not intended to define registration and filing requirements or modify pharmacopoeial requirements. This guide does not affect the ability of the responsible regulatory agency to establish specific registration or filing requirements regarding APIs within the context of marketing or manufacturing authorizations or pharmaceutical applications. All commitments in registration and filing documents must be met.

It is hoped that this guideline will go a long way in assuring the quality of APIs imported and/or manufactured and used in the country and by extension assure the quality of finished pharmaceutical dosage forms manufactured in Kenya.

Thank you.

DR. F.M. SIYOI

CEO, Pharmacy and Poisons Board

GLOSSARY:

Acceptance criteria

Numerical limits, ranges or other suitable measures for acceptance of test results.

API Handlers

Agents, brokers, distributors, repackers or relabellers who deal in APIs other than the original manufacturers

API

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body

API starting material

A raw material, intermediate or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement or produced in-house. API starting materials normally have defined chemical properties and structure.

BATCH

A specific quantity of material produced in a process so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

Batch Number (or Lot Number):

A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined.

Bioburden

The level and type (e.g. objectionable or not) of microorganisms that can be present in raw materials, API starting materials, intermediates or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

Computerized System

A process or operation integrated with a computer system.

Contamination

The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging or repackaging, storage or transport.

Contract manufacturer

A manufacturer performing some aspect of manufacturing 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 predetermined criteria 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 instruction or established standard.

Drug (Medicinal) Product

The dosage form in the final immediate packaging intended for marketing.

Drug Substance

Synonymous to Active Pharmaceutical Ingredient

Expiry Date (or Expiration Date)

The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.

Finished pharmaceutical product (FPP)

ICH: The dosage form in the final immediate packaging intended for marketing (reference Q1A (*4*)). WHO: A product that has undergone all stages of production, including packaging in its final container and labelling. An FPP may contain one or more APIs.

Handlers

This includes agents, brokers, traders, distributors, repackers and relabellers of APIs

Impurity

Any component present in the intermediate or API that is not the desired entity.

Impurity profile

A description of the identified and unidentified impurities present in an API.

In-process control (or process control)

Checks performed during production in order to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or API conforms to its specifications.

Intermediate

A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated.

Manufacture

All operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage and distribution of APIs and related controls.

Material

A general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs and packaging and labelling materials.

Mother liquor

The residual liquid which remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API and/or impurities. It may be used for further processing.

packaging material

Any material intended to protect an intermediate or API during storage and transport.

pharmaceutical substance

See Active pharmaceutical ingredient.

procedure

A documented description of the operations to be performed, the precautions to be taken and measures to be applied, directly or indirectly related to the manufacture of an intermediate or API.

process aids

Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g. filter aid or activated carbon).

process control

See In-process control.

production

All operations involved in the preparation of an API from receipt of materials through processing and packaging of the API.

qualification

Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

quality assurance (QA)

The sum total of the organized arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

quality control (QC)

Checking or testing that specifications are met.

quality unit(s)

An organizational unit independent of production which fulfils both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

quarantine

The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

raw material

A general term used to denote starting materials, reagents and solvents intended for use in the production of intermediates or APIs.

reference standard, primary

A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard can be:

— obtained from an officially recognized source;
— prepared by independent synthesis;
— obtained from existing production material of high purity; or
— prepared by further purification of existing production material.

reference standard, secondary

A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.

reprocessing

Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization

step or other appropriate chemical or physical manipulation steps (e.g. distillation, filtration, chromatography or milling) that are part of the established manufacturing process. Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process and not to be reprocessing.

retest date

The date when a material should be re-examined to ensure that it is still suitable for use.

reworking

Subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API (e.g. recrystallizing with a different solvent).

signature (signed)

See Signed.

signed (signature)

The record of the individual who performed a particular action or review. This record can be in the form of initials, full handwritten signature, personal seal or an authenticated and secure electronic signature.

solvent

An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.

specification

A list of tests, references to analytical procedures and appropriate acceptance criteria that are numerical limits, ranges or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. “Conformance to specification” means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

validation

A documented programme that provides a high degree of assurance that a specific process, method or system will consistently produce a result meeting predetermined acceptance criteria.

validation protocol

A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters and operating ranges, product characteristics, sampling, test data to be collected, number of validation runs and acceptable test results.

yield, expected

The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot- scale or manufacturing data.

yield, theoretical

The quantity that would be produced at any appropriate phase of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production.

INTRODUCTION

OBJECTIVE

Persons or firms intending to engage in importation and/or manufacture of APIs must acquaint themselves with PPB legal requirements and guidelines for importation and manufacture of APIs into the country. This document is intended to guide manufacturers, importers, distributors, agents, brokers, traders, distributors and re-packers or re-labelers

to adhere to GMP and GDP standards to assure quality and purity of APIs as specified for their intended use.

SCOPE

This guidance document covers the following:

- APIs for use in medicinal products
- Sterile APIs
- APIs manufactured by chemical synthesis, extraction, cell culture/fermentation, recovery from natural resources or combination processes.
- API for Clinical Trials (CT) (Investigational medicinal products).

REGULATORY APPLICABILITY

Different APIs are produced through different processes. This will determine level of controls required to achieve compliance. API manufacturers and importers are subject to guidance with regard to trade, possess, repack, relabel, manipulate by any means, distribute or store an API or intermediate. API agents, brokers, traders, distributors, re-packers and re-labelers are subject to this guidance.

Table 1[a]

Application of this guide to API manufacturing

Type of manufacturing	**Application of this guide to steps (shown in grey) used in this type of manufacturing**				
Chemical manufacturing	Production of the API starting material	Introduction of the API starting material into process	Production of intermediate(s)	Isolation and purification	Physical processing, and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API starting material into process	Isolation and purification	Physical processing, and packaging
API extracted from plant sources	Collection of plants	Cutting and initial extraction(s)	Introduction of the API starting material into process	Isolation and purification	Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/ comminuting			Physical processing, and packaging
Biotechnology: fermentation/ cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, and packaging
"Classical" fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging

[a] This table has been taken from the ICH Harmonised Tripartite Guideline: Active Pharmaceutical Ingredients Q7. Current *Step 4* version, dated 10 November 2000.

Quality Management System(QMS)

Manufacturers, agents, brokers, traders, distributors, re-packers or re-labelers should establish, document and implement an effective system of managing quality and purity of APIs. General Principles of QMS of GMP to assure Quality and Purity of APIs are applicable under this guidance.

Personnel

The principles of WHO GMP inspection guideline (TRS 986 annex 2) applies to this guideline.

Premises and facilities

Design and construction

Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants as appropriate.

They should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.

Where the equipment itself (e.g. closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.

The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination.

There should be defined areas or other control systems for the following activities:

— receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection;

— quarantine before release or rejection of intermediates and APIs;

— sampling of intermediates and APIs;

— holding rejected materials before further disposition (e.g. return, reprocessing or destruction);

— storage of released materials;

— production operations;

— packaging and labelling operations; and

— laboratory operations.

Adequate, clean washing and toilet facilities should be provided for personnel. These washing facilities should be equipped with hot and cold water as appropriate, soap or detergent, air driers or single-use towels. The washing and toilet facilities should be separate from, but easily accessible to, manufacturing areas. Adequate facilities for showering and/or changing clothes should be provided, when appropriate.

Laboratory areas and operations should normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements, and the laboratory and its operations do not adversely affect the production process or intermediate or API.

Utilities

All utilities that could impact on product quality (e.g. steam, gases, compressed air, and heating, ventilation and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded. Drawings for these utility systems should be available.

Adequate ventilation, air filtration and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimize risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where APIs are exposed to the environment.

If air is recirculated to production areas, appropriate measures should be taken to control risks of contamination and cross-contamination.

Permanently installed pipework should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipework should be located to avoid risks of contamination of the intermediate or API.

Drains should be of adequate size and should be provided with an air break or a suitable device to prevent back-siphonage, when appropriate. 4.3 Water Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use. 4.31 Unless otherwise justified, process water should, at a minimum, meet WHO guidelines for drinking (potable) water quality. If drinking (potable) water is insufficient to assure API quality, and tighter chemical and/or microbiological water quality specifications are called for, appropriate specifications for physical and chemical attributes, total microbial counts, objectionable organisms and/or endotoxins should be established. Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process should be validated and monitored with appropriate action limits. Where the manufacturer of a non-sterile API either intends or claims that it is suitable for use in further processing to produce a sterile FPP, water used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms and endotoxins

Containment

Dedicated production areas, which can include facilities, air handling equipment and/or process equipment, should be employed in the production of highly sensitizing materials, such as penicillins or cephalosporins. Dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g. certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained. Appropriate measures should be established and implemented to prevent cross-contamination, e.g. from personnel or materials, moving from one dedicated area to another. Any production activities (including weighing, milling or packaging) of highly toxic non-pharmaceutical materials such as herbicides and pesticides should not be conducted using the buildings and/or equipment being used for the production

of APIs. Handling and storage of these highly toxic non-pharmaceutical materials should be separate from APIs.

Lighting

Adequate lighting should be provided in all areas to facilitate cleaning, maintenance and proper operations.

Sewage and refuse

Sewage, refuse and other waste (e.g. solids, liquids, or gaseous byproducts from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely and sanitary manner. Containers and/or pipes for waste material should be clearly identified.

Sanitation and maintenance

Buildings used in the manufacture of intermediates and APIs should be properly maintained and repaired and kept in a clean condition. Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment and materials to be used in cleaning buildings and facilities. When necessary, written procedures should also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging or labelling materials, intermediates and APIs.

Equipment

The principles of WHO GMP inspection guideline (TRS 986 annex 2) applies to manufacturers, agents, brokers, traders, distributors, re-packers or re-labelers

Documentation and records

The principles of WHO GMP inspection guideline (TRS 957 annex 2, section 6) applies to manufacturers, agents, brokers, traders, distributors, re-packers or re-labelers

Material management

There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials. Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials. Materials should be purchased

against an agreed specification, from a supplier or suppliers approved by the quality unit(s). If the supplier of a critical material is not the manufacturer of that material, the name and address of that manufacturer should be known to the intermediate and/or API manufacturer. Changing the source of supply of critical raw materials should be done according to section 13, Change control (TRS 957 annex 2, section 7).

Production and In-process controls

Production operations

Raw materials for manufacturing of intermediates and APIs should be weighed or measured under appropriate conditions that do not affect their suitability for use. Weighing and measuring devices should be of suitable accuracy for the intended use.

If a material is subdivided for later use in production operations, the container receiving the material should be suitable and should be so identified that the following information is available:

— material name and/or item code;

— receiving or control number;

— weight or measure of material in the new container; and

— re-evaluation or retest date if appropriate.

Critical weighing, measuring or subdividing operations should be witnessed or subjected to an equivalent control. Prior to use, production personnel should verify that the materials are those specified in the batch record for the intended intermediate or API.

Other critical activities should be witnessed or subjected to an equivalent control.

Actual yields should be compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges should be established based on previous laboratory, pilot scale or manufacturing data. Deviations in yield associated with critical process steps should be investigated to determine their impact or potential impact on the resulting quality of affected batches.

Any deviation should be documented and explained. Any critical

deviation should be investigated.

The processing status of major units of equipment should be indicated either on the individual units of equipment or by appropriate documentation, computer control systems or alternative means.

In- process sampling and controls

Written procedures should be established to monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs. In-process controls and their acceptance criteria should be defined based on the information gained during the development stage or historical data.

The acceptance criteria and type and extent of testing can depend on the nature of the intermediate or API being manufactured, the reaction or process step being conducted and the degree to which the process introduces variability in the product's quality. Less stringent in-process controls may be appropriate in early processing steps, whereas tighter controls may be appropriate for later processing steps (e.g. isolation and purification steps).

Critical in-process controls (and critical process monitoring), including the control points and methods, should be stated in writing and approved by the quality unit(s).

In-process controls can be performed by qualified production department personnel and the process adjusted without prior quality unit(s)' approval if the adjustments are made within pre-established limits approved by the quality unit(s). All tests and results should be fully documented as part of the batch record.

Written procedures should describe the sampling methods for in-process materials, intermediates and APIs. Sampling plans and procedures should be based on scientifically sound sampling practices.

In-process sampling should be conducted using procedures designed to prevent contamination of the sampled material and other intermediates or APIs. Procedures should be established to ensure the integrity of samples after collection.

OOS investigations are not normally needed for in-process tests that are performed for the purpose of monitoring and/or adjusting the process.

The principles of WHO GMP inspection guideline (TRS 957 annex 2, section 8) applies to contamination control, blending batches of intermediates and APIs and time limits.

Storage and distribution

Warehousing procedures

Facilities should be available for the storage of all materials under appropriate conditions (e.g. controlled temperature and humidity when necessary). Records should be maintained of these conditions if they are critical for the maintenance of material characteristics. Unless there is an alternative system to prevent the unintentional or unauthorized use of quarantined, rejected, returned or recalled materials, separate storage areas should be assigned for their temporary storage until the decision as to their future use has been taken.

Distribution procedures

APIs and intermediates should only be released for distribution to third parties after they have been released by the quality unit(s). APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the quality unit(s) and if appropriate controls and documentation are in place. APIs and intermediates should be transported in a manner that does not adversely affect their quality. Special transport or storage conditions for an API or intermediate should be stated on the label. The manufacturer should ensure that the contract acceptor (contractor) for transportation of the API or intermediate knows and follows the appropriate transport and storage conditions. A system should be in place by which the

distribution of each batch of intermediate and/or API can be readily determined to permit its recall

Laboratory controls

The independent quality unit(s) should have at its disposal adequate laboratory facilities. There should be documented procedures describing sampling, testing, approval or rejection of materials and recording and storage of laboratory data. Laboratory records should be maintained in accordance with section 6.6. All specifications, sampling plans and test procedures should be scientifically sound and appropriate to ensure that raw materials, intermediates, APIs, labels and packaging materials conform to established standards of quality and/or purity. Specifications and test procedures should be consistent with those included in the registration/fi ling. There can be specifications in addition to those in the registration/fi ling. Specifications, sampling plans and test procedures, including changes to them, should be drafted by the appropriate organizational unit and reviewed and approved by the quality unit(s). Appropriate specifications should be established for APIs in accordance with accepted standards and be consistent with the manufacturing process. The specifications should include a control of the 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 should be established and met. If the API has a specification for endotoxins, appropriate action limits should be established and met. Laboratory controls should be followed and documented at the time of performance. Any departures from the above-described procedures should be documented and explained. Any OOS result obtained should be investigated and documented according to a procedure. This procedure should require analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions and conclusions. Any resampling and/or retesting after OOS results should be performed according to a documented procedure. Reagents and standard solutions should be prepared and labelled following written procedures. “Use by” dates should be applied as appropriate for analytical reagents or standard solutions. Primary reference standards should be obtained as appropriate for the

manufacture of APIs. The source of each primary reference standard should be documented. Records should be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations. Primary reference standards obtained from an officially recognized source are normally used without testing if stored under conditions consistent with the supplier's recommendations. Where a primary reference standard is not available from an officially recognized source, an "in-house primary standard" should be established. Appropriate testing should be performed to establish fully the identity and purity of the primary reference standard. Appropriate documentation of this testing should be maintained. Secondary reference standards should be appropriately prepared, identified, tested, approved and stored. The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard should be periodically requalified in accordance with a written protocol.

The principles of WHO GMP inspection guideline (TRS 957 annex 2, section 11)

Validation

Validation policy

The company's overall policy, intentions and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, in-process control test procedures, computerized systems and personnel responsible for design, review, approval and documentation of each validation phase, should be documented.

The critical parameters and attributes should normally be identified during the development stage or from historical data and the ranges necessary for the reproducible operation should be defined. This should include:

— defining the API in terms of its critical product attributes;

— identifying process parameters that could affect the critical quality

attributes of the API;

— determining the range for each critical process parameter expected to be used during routine manufacturing and process control.

Validation should extend to those operations determined to be critical to the quality and purity of the API.

Validation documentation

A written validation protocol should be established that specifies how validation of a particular process will be conducted. The protocol should be reviewed and approved by the quality unit(s) and other designated units.

The validation protocol should specify critical process steps and acceptance criteria as well as the type of validation to be conducted (e.g. retrospective, prospective or concurrent) and the number of process runs.

A validation report that cross-references the validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed and drawing the appropriate conclusions, including recommending changes to correct deficiencies.

Any variations from the validation protocol should be documented with appropriate justification.

The principles of WHO GMP inspection guideline (TRS 957 annex 2, section 12) applies to qualification, approaches to process validation, process validation programs, periodic review of validated systems, cleaning validation and validation of analytical methods.

Change control

A formal change control system should be established to evaluate all changes that may affect the production and control of the intermediate or API.

Written procedures should cover the identification, documentation, appropriate review, and approval of changes in raw materials, specifications,

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analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labelling and packaging materials and computer software.

Any proposals for relevant changes to GMP should be drafted, reviewed and approved by the appropriate organizational units and reviewed and approved by the quality unit(s).

The potential impact of the proposed change on the quality of the intermediate or API should be evaluated. A classification procedure may help in determining the level of testing, validation and documentation needed to justify changes to a validated process. Changes can be classified (e.g. as minor or major) depending on their nature and extent and the effects these changes may have on the process. Scientific judgement should be used to determine what additional testing and validation studies are appropriate to justify a change in a validated process.

When implementing approved changes, measures should be taken to ensure that all documents affected by the changes are revised.

After the change has been implemented there should be an evaluation of the first batches produced or tested under the change.

The potential for critical changes to affect established retest or expiry dates should be evaluated. If necessary, samples of the intermediate or API produced by the modified process can be placed on an accelerated stability programme and/or can be added to the stability monitoring programme.

Manufacturers of the current dosage form should be notified of changes from established production and process control procedures that can impact the quality of the API.

Rejection and reuse of materials

The principles of WHO GMP inspection guideline (TRS 957 annex 2, section 14) applies to rejection, reprocessing, reworking and recovery of materials and solvents and returns

Contracts (manufacturers & laboratories)

All contract manufacturers (including laboratories) should comply with GMP defined in this guide. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability. They should be evaluated

by the contract giver to ensure GMP compliance of the specific operations taking place at the contract sites.

There should be a written and approved contract or formal agreement between the contract giver and the contract acceptor that defines in detail the GMP responsibilities, including the quality measures, of each party which should permit the contract giver to audit the contract acceptor's facilities for compliance with GMP.

Where subcontracting is allowed the contract acceptor should not pass to a third party any of the work entrusted to him or her under the contract without the contract giver's prior evaluation and approval of the arrangements.

Manufacturing and laboratory records should be kept at the site where the activity takes place and be readily available and any changes in the process, equipment, test methods, specifications or other contractual requirements should not be made unless the contract giver is informed and approves the changes.

Agents, brokers, traders, distributors, repackers and relabellers

Applicability

This section applies to any party other than the original manufacturer who may trade and/or take possession of, repack, relabel, manipulate, distribute or store an API or intermediate.

All agents, brokers, traders, distributors, repackers and relabellers should comply with GMP as defined in this guide.

Traceability of distributed APIs and intermediates;

Manufacturers, importers, agents, brokers, traders, distributors, repackers, relabellers should maintain complete traceability of APIs and intermediates that they distribute. Documents to be retained include:

- Identity of original manufacturer
- Address of original manufacturer
- Purchase orders
- Bills of landing (transfer documents)
- Receipt documents.

- Name or designation of API or intermediate
- Manufacturing batch number
- Transport and distribution records
- All authentic certificates of analysis, including those of the original manufacturer
- Re-test/Expiry dates

Quality management

Agents, brokers, traders, distributors, repackers or relabellers should establish, document and implement an effective system of managing quality, as specified in section 2.

Repacking, Relabeling and Holding of APIs and Intermediates

There should be written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release and handling of packaging and labelling materials. Packaging and labelling materials should conform to established specifications. Those that do not comply with such specifications should be rejected to prevent their use in operations for which they are unsuitable. Records should be maintained for each shipment of labels and packaging materials showing receipt, examination, or testing and whether they are accepted or rejected.

Repackaging, relabeling and holding of APIs and Intermediates should be handled as manufacturing process hence done under appropriate GMP controls to avoid mix ups, contamination/cross contamination and loss of API/Intermediate Identity and or purity.

Repacking should be done under appropriate environmental conditions to avoid quality and purity deterioration, contamination and cross contamination.

Stability

Stability studies to justify assigned expiration/retest dates should be conducted if the API/Intermediate is repackaged in different containers other than that used by API/Intermediate manufacturer.

Transfer of Information:

Agents, brokers, distributors, repackers or relabellers should transfer all quality or regulatory information received from an API/Intermediate manufacturer to the customer and from the customer to API/Intermediate manufacturer.

Agents, brokers, traders, distributors, repackers or relabellers who supply API/Intermediate to customer should provide name of original API/Intermediate manufacturer and batch number(s) supplied.

Agents should also provide identity of original API/Intermediate manufacturer to regulatory authority upon request.

The original Manufacturer can respond to regulatory authority directly or through authorized agent.

Handling of complaints and recalls;

Manufacturers, importers, agents, brokers, traders, distributors, re-packers or re-labelers should maintain records of complaints and recalls for all complaints and recalls that are received.

In some cases, Agents, brokers, traders, distributors, re-packers or re-labelers should review complaints with original API manufacturer in order to determine if further action either with customer or regulatory authority or both should be initiated. The investigation should be conducted and documented by appropriate party.

Complaint records should include:

— name and address of complainant;

— name (and, where appropriate, title) and telephone number of person submitting the complaint;

— nature of the complaint (including name and batch number of the API);

— date the complaint was received;

— action initially taken (including dates and identity of person taking the action);

— any follow-up action taken;

— response provided to the originator of complaint (including date on

which the response was sent); and

— final decision on intermediate or API batch or lot.

Records of complaints should be retained in order to evaluate trends, written procedure that defines the circumstances under which a recall of an intermediate or API should be considered and procedure to designate who should handle the recall process and the material should be available

In the event of a serious or potentially life-threatening situation, local, national and/or international authorities should be informed and their advice sought.

Where complaint is referred to original manufacturer records maintained should be include any response received from original manufacturer (including date information received).

Handling of returns:

The agents should maintain documentation of returned API/Intermediates: This should include:

- Name and address of consignment
- API batch number and quantity
- Reason for return
- Use/disposal of returned API.

Specific guidance for Certificate of Analysis (COA)

The following guidance on COA should be met

- Authentic COA should be issued for each batch on request
- Information on name ofAPI/Intermediate including its grade, batch number and date of release should be provided. Expiry date should be provided on the label and COA.
- List tests performed in accordance with compendia or customer requirements, including acceptance limits.
- COA should be signed and dated by authorized personnel in Quality Control (QC). It should show the name, address and Telephone number of original manufacturer. Where analysis is carried out by reprocessor, COA

should show name, address and Telephone number of reprocessor and reference to the name of original manufacturer.

- Where new COA is issued by reprocessor/on behave of reprocessor, it should show name, address and Telephone number of the Lab that performed the analysis. Should also show reference to name and address of original manufacturer and to original batch COA, copy should be attached.

Stability Monitoring of APIs

Stability program on the APIs should be instituted and results used to confirm appropriate storage conditions and expiry/retest date.

Test procedures should be validated.

Samples should be stored in containers simulating market samples.

Normally three new commercial batches of repackaged APIs should be put on stability monitoring program to confirm retest or expiry date. Thereafter at least one batch per year of API repackaged should be placed on stability program to confirm stability.For APIs with short shelf life, testing should be more frequent i.e. monthly for first three months then three monthly

Specific guidance for APIs manufactured by cell culture/fermentation

This section is intended to address specific controls for APIs or intermediates manufactured by cell culture or fermentation using natural or recombinant organisms and that have not been covered adequately in the previous sections. It is not intended to be a stand-alone section. In general, the GMP principles in the other sections of this document apply. Note that the principles of fermentation for “classical” processes for production of small molecules and for processes using recombinant and non-recombinant organisms for production of proteins and/or polypeptides are the same, although the degree of control will differ. Where practical, this section will address these differences. In general, the degree of control for biotechnological processes used to produce proteins and polypeptides is greater than that for classical fermentation processes.

Production of APIs or intermediates from cell culture or fermentation involves biological processes such as cultivation of cells or extraction and purification of material from living organisms. Note that there may be additional process steps, such as physicochemical modification, that are part of the manufacturing process. The raw materials used (media, buffer components) may provide the potential for growth of microbiological contaminants. Depending on the source, method of preparation, and the intended use of the API or intermediate, control of bioburden, viral contamination, and/or endotoxins during manufacturing and monitoring of the process at appropriate stages may be necessary.

Appropriate controls should be established at all stages of manufacturing to assure intermediate and/or API quality. While this guide starts at the cell culture/fermentation step, prior steps (e.g. cell banking) should be performed under appropriate process controls. This guide covers cell culture/fermentation from the point at which a vial of the cell bank is retrieved for use in manufacturing.

Appropriate equipment and environmental controls should be used to minimize the risk of contamination. The acceptance criteria for quality of the environment and the frequency of monitoring should depend on the step in production and the production conditions (open, closed or contained systems).

In general, process controls should take into account:

— maintenance of the working cell bank (where appropriate);

— proper inoculation and expansion of the culture;

— control of the critical operating parameters during fermentation/cell culture;

— monitoring of the process for cell growth, viability (for most cell culture processes) and productivity where appropriate;

— harvest and purification procedures that remove cells, cellular debris and media components while protecting the intermediate or API from contamination (particularly of a microbiological nature) and from loss of quality;

— monitoring of bioburden and, where needed, endotoxin levels at appropriate stages of production; and

— viral safety concerns as described in ICH Guideline Q5A (2)..

Where appropriate, the removal of media components, host cell proteins, other process-related impurities, product-related impurities and contaminants should be demonstrated.

Harvesting, isolation and purification

Harvesting steps, either to remove cells or cellular components or to collect cellular components after disruption, should be performed in equipment and areas designed to minimize the risk of contamination.

Harvest and purification procedures that remove or inactivate the producing organism, cellular debris and media components (while minimizing degradation, contamination, and loss of quality) should be adequate to ensure that the intermediate or API is recovered with consistent quality.

All equipment should be properly cleaned and, as appropriate, sanitized after use. Multiple successive batching without cleaning can be used if intermediate or API quality is not compromised.

If open systems are used, purification should be performed under environmental conditions appropriate for the preservation of product quality.

Additional controls, such as the use of dedicated chromatography resins or additional testing, may be appropriate if equipment is to be used for multiple products.

Viral removal/inactivation steps

See the ICH Guideline Q5A (2) for more specific information.

Viral removal and viral inactivation steps are critical processing

steps for some processes and should be performed within their validated parameters.

Appropriate precautions should be taken to prevent potential viral contamination from pre-viral to post-viral removal/inactivation steps. Therefore, open processing should be performed in areas that are separate from other processing activities and have separate air handling units.

The same equipment is not normally used for different purification steps. However, if the same equipment is to be used, the equipment should be appropriately cleaned and sanitized before reuse. Appropriate precautions

should be taken to prevent potential virus carry-over (e.g. through equipment or environment) from previous steps.

The principles of WHO GMP inspection guideline (TRS 957 annex 2, section 18) applies to cell bank maintenance and record keeping and cell culture/fermentation

APIs for use in clinical trials

Not all the controls in the previous sections of this guide are appropriate for the manufacture of a new API for investigational use during its development. Section 19 provides specific guidance unique to these circumstances.

The controls used in the manufacture of APIs for use in clinical trials should be consistent with the stage of development of the pharmaceutical product incorporating the API. Process and test procedures should be flexible to allow for changes to be made as knowledge of the process increases and clinical testing of a pharmaceutical product progresses from the preclinical stages through the clinical stages. Once pharmaceutical development reaches the stage where the API is produced for use in pharmaceutical products intended for clinical trials, manufacturers should ensure that APIs are manufactured in suitable facilities using appropriate production and control procedures to ensure the quality of the API.

The principles of WHO GMP inspection guideline (TRS 957 annex 2, section 19) applies to quality, equipment and facilities, control of raw materials, production, validation, changes, laboratory controls and documentation.

Quality

Appropriate GMP concepts should be applied in the production of APIs
for use in clinical trials with a suitable mechanism for the approval of each batch.

A quality unit(s) independent from production should be established for the approval or rejection of each batch of API for use in clinical trials.

Some of the testing functions commonly performed by the quality unit(s) can be performed within other organizational units.

Quality measures should include a system for testing of raw materials, packaging materials, intermediates and APIs.

Process and quality problems should be evaluated.

Labelling for APIs intended for use in clinical trials should be appropriately controlled and should identify the material as being for investigational use.

Equipment and facilities

During all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean and suitable for its intended use.

Procedures for the use of facilities should ensure that materials are handled in a manner that minimizes the risk of contamination and cross- contamination.

Control of raw materials

Raw materials used in production of APIs for use in clinical trials should be evaluated by testing or be received with a supplier's analysis and subjected to identity testing. When a material is considered hazardous a supplier's analysis should suffice.

In some instances the suitability of a raw material can be determined before use based on acceptability in small-scale reactions (i.e. use testing) rather than on analytical testing alone.

Production

The production of APIs for use in clinical trials should 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 observations.

Expected yields can be more variable and less defined than the expected yields used in commercial processes. Investigations into yield variations are not expected.

Validation

Process validation for the production of APIs for use in clinical trials is normally inappropriate where a single API batch is produced or where process changes during development of an API make batch replication difficult or inexact. The

combination of controls, calibration and, where appropriate, equipment qualification assures quality of the API during this development phase.

Process validation should be conducted in accordance with section 12 when batches are produced for commercial use, even when such batches are produced on a pilot scale or small scale.

Changes

Changes are expected during development as knowledge is gained and the production is scaled up. Every change in the production, specifications or test procedures should be adequately recorded.

Laboratory controls

While analytical methods performed to evaluate a batch of API for clinical trials may not yet be validated they should be scientifically sound.

A system for retaining reserve samples of all batches should be in place. This system should ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time after approval, termination or discontinuation of an application.

Expiry and retest dating as defined in section 11.6 applies to existing APIs used in clinical trials. For new APIs section 11.6 does not normally apply in early stages of clinical trials.

Documentation

A system should be in place to ensure that information gained during the development and the manufacture of APIs for use in clinical trials is documented and available.

The development and implementation of the analytical methods used to support the release of a batch of API for use in clinical trials should be appropriately documented.

A system for retaining production and control records and documents should be used. This system should ensure that records and documents are retained for an appropriate length of time after the approval, termination or discontinuation of an application.

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