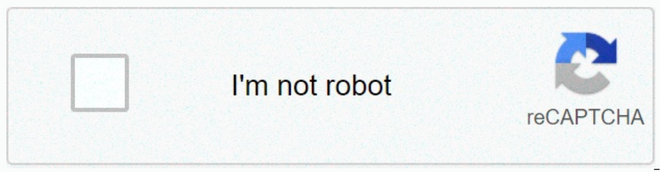

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Who gmp guidelines for active pharmaceutical ingredients

The purpose of this guide, GUI-0104, is to provide interpretation counseling for Part C, Division 2, of the Food and Drug Regulations for the manufacture of APIs (including intermediary ones). The focus of these guidelines is on the manufacture of APIs sold in final container sold in final container and/or use of the inventory of finished dosing forms for human usage. Any additional process steps further after the APIs are in final container are subject to GUI-0001. More specifically, they apply to the fabric, packaging/labelling, testing, importation, distribution, wholesale, and re-packing/re-labelling of APIs (including the intermediary). Agents and brokers of APIs will be considered whole if they sell APIs as per the definition of sale of the Food and Drug Act. If an agent or broker is acting as a wholesaler to the meaning of the regulatory scheme may require additional review/examination. Individuals in fact selling APIs must comply with the requirements defined in Division 2, Part C of the Food and Drug Regulations, as applicable to them. GMP for Active Pharmaceutients Ingredients API (APIC) EU Regulation and EU Regulation CH Document EDQM and the PIC/SDA Document FDA Guidelines for Industry: Changes to an approved NDA or ANDA, Review 1 FDA Guidance for Industry: Changes to an approved NDA or ANDA, Question and Answer FDA Advisory for industry: Changes to an approved NDA or ANDA; Specifications – Use at discretion reinforcement for Skill Change (Assessment 11/19/2004, Posted 11/19/2004) FDA Master Record Master, September 1989 Drug Master Record, Current DMF Information FDA Guide for Industry: Master Records for Bulk Antibiotic Substance Drug Format and content of the chemistry, Factory and Controller Section of an FDA Application Guide for Industry: Format and Content for Section CMC in an Annual Report, 1994 FDA Guide for Industry: INDs for Phase 2 and Phase 3 Studies; Chemistry, Manufacturing, and Controls Information FDA Guidance for Industry: MEETINGS for Human Drugs and Chemistry Biologics, Manufacturing, and Controls Information (Issued 5/2001, Posted 6/4/2001) FDA Guidance for Industry: NDAs: Impurities in Drug Substances (Feb. 2001) 2000) FDA Guidance for Industry: PAC-ATLS: Post Approval Changes - Analytical Testing Laboratory Sites, April 1998 FDA Reviewer Guidance: Validation of Chromatographic Methods, 1994 Submission of Chemistry, Manufacturing and Controls Information for S Peptide Substances Submitting Documentation for the Manufacture of and Controls for Drug Products FDA Guidance for Industry: ANDAs: Pharmaceutical Solid Polymorphism: Chemistry, Manufacturing, and Controls Information FDA Guidance for Industry: Alternate Source of the Active Pharmaceutical FDA - Draft Documents The following guideline can be ordered through the address listed in the In cases where you can order in the internet we have established a hyperlink. Short Title: Annex 4, Technical Series Report 948, 2008 Origin / Publisher: WHO headquarters, Venues Appia 20, 1211 Geneva 27, Switzerland Phone: (+41 22) 791 21 11, Faximile (Fax): (+41 22) 791 3111, Telex: 415 416, Telegraph: UNISANTE GENEVA Content: Directive These are intended to assist applicants in the compilation of information about APIs in their doses for their qualifications or when they submit a dose of a help product credential (named in the text from now as dossier generated) when they use the APIMF procedure. It is also intended to help APIMF holders in the compilation of the APIMFs. Return our mandate: To manage and deliver a national compliance and application program for blood and donor weeks; cells, tissues and organs; drug (human and veterinarian); medical devices and natural health products, collaborate with and across, all regions. Date issued: December 6, 2013 Application Date: November 8, 2013 Warning this document does not constitute part of the Act of Food and Drug (Act) or its associated regulations and in the event of any inconsistency or conflict between which Act or Regulation and this document, the Act or Regulations take precision. This document is an administrative document intended to facilitate compliance by the Regular Party and the Law, the Regulations and Administrative Regulations. Table follows 1. The introduction of Active Pharmaceutical Ingredients (API) and intermediates for pharmaceutical use (i.e. pharmaceutical, radiofarmatic, and biological) and people used to manufacture drugs for clinical trials are regulated under their Division 1A and 2, Part C of the Food and Drug Regulations. Division 1A, Part C of the Food and Drug Policy defines activities for which Good Factory Practitioners (GMP) compliance is required and must be demonstrated prior to the issue of an establishment licensing API (EL). Division 2, Part C of Food Regulation and Drug defines the requirements for GMP of APIS and intermediate API, which are interpreted in the present guidance document. These Good Factory Practices (GMP) for Active Pharmaceutical Ingredient (API) guidelines, GUI-0104, are designed to facilitate compliance by the regulatory industry and improve consistency of the application of regulatory requirements. It should be noted that these guidelines do not cover security aspects for the personnel engaged in the fabric, wrapping/labelling, and testing of APIs and intermediates, or aspects of the environmental protection. These controls are the legacy responsibility of API in the manufacturer's API, package/labeller and tested. In addition to the present guidelines, a list of additional guidance in specific areas related to APIS and intermediate API are provided in Appendix C in this document. Despite active ingredient definitions in Division Part C of the Food and Drug Regulation includes APIs and intermediate essential processes (BPI), present the GUI-0104 only applies to APIs. Guide on the fabric, packaging/ label, testing, distribution, animal, and importation of drugs in the form of doses, and BPIS for radiofartic and biological drugs provided in Good Factory Practice Guide, 2009 edition, version 2 (GUI-0001). Guidelines regarding the fabric, packaging/labelling, testing, distribution, and importation of medical gas are provided in the Good Manufacturing Practice for Medical Gas (GUI-0031). The content of this document should not be considered as the only interpretation of the GMP Regulations, nor is it intended to cover every conservable case. Alternative means to comply with these regulations can be regarded as appropriate scientific justification. Different approaches can be called for new technologies that appear. This document was written with a harmonized view with GMP standards from other countries and those of Pharmaceutical Cooperation Inspection/Scheme (PIC/S), and the International Conference on Harmonisation (ICH). 2. The purpose of this guide, GUI-0104, is to provide interpreter counseling for Part C, Division 2, of the Food and Drug Regulations for the manufacture of APIs (including the intermediary). These guidelines are designed to facilitate compliance by the regulated industry and improve the consistency of the implementation of regulatory requirements. It is also intended to help ensure that APIs meet the requirements for quality and purity that they purport or are representing they possess. 3. The focus dimension of these guidelines is on the manufacture of APIs sold in final container sold in final container and/or use of the inventory of finished doses forms for human use. Any additional process steps further after the APIs are in final container are subject to GUI-0001. More specifically, they apply to the fabric, packaging/labelling, testing, importation, distribution, wholesale, and re-packing/re-labelling of APIs (including the intermediary). Agents and brokers of APIs will be considered whole if they sell APIs as per the definition of sale of the Food and Drug Act. If an agent or broker is acting as a wholesaler to the meaning of the regulatory scheme may require additional review/examination. Individuals in fact selling APIs must comply with the requirements defined in Division 2, Part C of the Food and Drug Regulations, as applicable to them. Any regulatory requirements other than condition 2 divisions that apply or apply to a given activity or product always apply. This guide is not applied to the following: vaccines, whole cells, blood and plasma, blood and derivative plasma (plasma fractions), and therapy generate APIS. However, it includes APIs that are generated using blood or plasma as raw materials. cell substrates plant, insect or microbial cells, tissues or source animals including transgenic animals) and early processing steps (although they may be subject to GMP) medical gas, bulk-pack drug (medicines) products, and manufacturer of aspects/specific controls of radiofarmaceutiical. medical devices, including medical devices classified as combination products where the main mode of action is a medical device. Natural natural health products although BPI is defined as active ingredients in C.01A.001(1) of Division 1A of Food and Drug Regulation, the present guideline is not applied to BPIs. For more tips on manufacturing the BPIs, please refer to the Annex 3 in the current edition of Good Factory Practice Guide – Drug Scheduling (GUI-0026) and Anne x 2 in the current edition of Good Factory Practising Guide to Drug Scheduling (Biological Drugs) (GUI-0027). Health Canada considers fabrics, labels/labels, and tests of sterile APIs by terminally sterilized as they have finished manufacturing forms and therefore these guidelines only apply to the manufacture of Sterile APIs up to points before APIs are rendered sterile. Sterilization and the aseptic process of sterile APIs are not covered by this council, but should be in accordance with Good Manufacturing Practice Guide, Edition 2009, Version 2 (GUI-0001). The point at which the production API starts with from which the compliance of GMPs should be applied based on the application completed with Canada Health, applicable locations, and/or other criteria including the table below 2. If you don't all step into a manufacturing type as shown in Table 1 are finished, the present guidelines applied in the steps shown in Azure. The stringency of GMPs in manufacturing API should be increased as the process proceeds from early stage API to final stage, purify, and wrapping. 4. Management Quality 4.1 Guide the Principles of Holder of an establishment license, or any activities requirements in Division 2 Part C of the Food and Drug Regulations are applicable, must ensure that the fabrication, wrapping, laboratory, testing, importation, distribution, and owing to APIS comply with these conditions and as per approved specifications in the marketing authorization of the drug form at dosage, and do not put consumers at risk due to inadequate safety and quality. The attachment of this quality goal is the responsibility of senior management and requires the participation and commitment of personnel in many different departments and at all levels of the facility and its suppliers. To ensure compliance, there must be a comprehensive designed and correctly implemented quality management system that incorporates GMP, quality assurance and control, life and risk management as appropriate as the organizational structure, procedures, processes and resources, well as activities needed to ensure confidence that the API will meet its intention specifications for quality and purity. The quality management system that includes all activities related to types should be defined and fully documented, and its efficiency is controlled. 4.2 Relationship among Component Type Basic elements of quality assurance, GMP, and quality control are related to interests. They are described here in order to highlight the relationships and the fundamental importance of the production and control APIs. 4.2.1 Quality Assurance Quality Assurance is a wide-out concept that covers all artifacts individually or collectively influences the quality of an API. It is the total of the organized arrangements made with the goal of ensuring that the APIs of the quality are required for using their intentions. Quality assurance therefore incorporates GMP, along with other factors outside the scope of these guidelines. A system of quality assurance suitable for the fabric, wrapping, clown, testing, distribution, importation, and wholesale of APIS should ensure that: APIs are designed and developed in a way that takes into account the GMP requirement; Each manufacturer should be established, documented, and implemented an effective system for managing quality involving the active participation of management and suitable personal manufacturing. Manager responsibilities should be explicitly specified; Systems, installations and procedures are adequate and qualified, whether they are new or modified; Output and control operations are explicitly specified; Analytical methods and critical processes are validated; Accommodation made for the reserves and use the raw materials and packaging materials; All controls are required on APIs and any additional in-process monitoring carried out; Outsourced activities are subject to appropriate controls and meet GMP requirements; Fabrication, packaging/ labelling, testing, distribution, importation, and blessing are designed in accordance with established procedures; Apis not released for sale or for further fabric before authorized by the quality control department approved that each lot was generated and controlled in accordance with the approved specifications; Satisfactory arrangements exist to ensure that the APIs are stored, distributed, and subsequently handled in a timely maintained quality manner throughout the expiry dates or remainder; The quality risk management system should ensure that: the assessment of risk for quality is based on scientific knowledge, experience and the process and link to the protection of the patient and the level of effort, formatability and documentation of the quality risk process is commented with the level of risk. The efficiency, implementation, and continuous improvement of the quality management system ensure regular review and self-inspection; Annually quality review of all APIS and intermediary should be conducted with the goal of verifying the consistency of the existing process, and to identify products and process improvements; All related activities should be recorded at the time they will be held. 4.2.2 Good Manufacturing Practices for GMP APIS is part of quality assurance that APIS are always generated and controlled in such a way to meet the appropriate quality standards used are intended, as necessary by the approved specifications of the market authorization of the drug in the form of dosing. GMP basic requirements are as follows : Manufacturing processes are explicitly defined and controlled to ensure consistency and compliance with approved specifications; Critical steps in manufacturing processes and significant changes in the process are validated; All key components needed for GMP are provided, including the following: qualified personnel and training, adequate locale and facilities, suitable equipment and utilities, correct materials, containers and labeling, approved procedures and instructions, with appropriate storage and transport. Instructions and procedures are written in key and unambiguous languages; Operators are trained to carry out and document procedures; All related activities should be recorded at the time they will be held. Any deviation from establishing the procedures should be documented and explained. Critical deviations are investigated and documented; Records of fabric, wrapping, labelin, testing, distribution, imports, and impressions that allow the complete history of a lot to be mapped to a form understandable and accessible; Control of storage, handling, and transportation in the APIs minimize any risk to their quality; A system is available for reminders of APIs from Retail; Complaints about APIs are examined, the cause of quality damage to investigate, and the appropriate measures taken with respect to the defective APIs and to prevent recurrence. 4.2.3 Quality control type is part of GMP that is concerned with samples, specifications, tests, documents, and release procedures. Quality control ensures that necessary and relevant testing is carried out with raw material joins, packaging materials, and APIs are released for use or sold, only if their quality is satisfactory. Quality control is not confirmed in laboratory operations but must be incorporated in all activities and decisions regarding the quality of the API. The basic requirements of quality control are as follows: Adequate facilities, personnel training, and approved procedures available for samples, inspectors and tests of raw materials, wrapping materials, APIs, and, where the environmental monitoring requirements for GMP purposes; 1.1 Samples of raw materials, packaging materials, and APIs are taken according to procedures approved by the quality control department; 1.2 Examination Methods 1.3 Records demonstrate that all the required samples, inspectors, and test procedures are carried out, and any deviations are recorded and critical deviations investigated; 1.4 Records were made to the results of the program self-inspection; The 1.5 Procedures for product release include a review and evaluation of relevant production documents and an evaluation of deviations from specified procedures; 1.6 No API release for sale or for further use prior approval by the quality control department; 1.7 Sample sufficient in raw material form all the editing and final API holds to allow future examinations if necessary. 5. Interpretation of Division Rule 2 – Good Factory Practice Section C.02.002 medical fuel means any gas or mixture of gas manufacturers, sell, or represent for use as a drug; (medical gas) packaging material includes a label; (matriel packaging) specifications mean a detailed description of a drug, the raw material used in a drug, or the wrapping material for a drug and includes: a statement of all properties and types of the drug, material or wrapping material related to the manufacturing, wrapping, and use of the drug, including identity, power, and purity of the drug, raw material, or wrapping material, a detailed description of the methods used for testing and examining the drug, raw materials, or wrapping materials, and a tolerance statement for the properties and drug types, raw materials, or wrapping materials (specifications). Section C.02.002.1 This division does not apply to manufacture, wrapping/labelling, testing, storing and importing of antimic agents. Selling Section C.02.003 No distributor referred to in paragraph C.01A.003(b) and no import will not sell a drug unless it has been manufactured, package/labelled, tested and stored in accordance with the requirements of this Division. Section C.02.003.1 No one will sell a drug being manufactured, package/labelled, tested or stored unless they were manufactured, package/labelled, tested or stored in accordance with the requirements of the Division. Section C.02.003.2 Person name must import an active ingredient in Canada for the purpose of selling unless they have in Canada a person responsible for its sale. No one importing an active ingredient into Canada will sell any lot or bundles of it unless this appears on its label: the name and civic address of the person who imported it; and the name and address of the main business place in Canada of those responsible for sale. Use of Fabrication Section C.02.003.3 No one must use an active ingredient in the fabric of a drug unless it is manufactured, package/labelled, tested and stored in accordance with the requirements of this division. Rationalize the requirements described in these sections intended to ensure that APIs offer for sale at all levels of the supply chain or use of in the form of drugs to comply with this division. APIs used in the fabric of a drug in the form of doses should be manufactured, package/labelled, tested and stored in accordance with the requirements of this Division.2. Distributors of a drug for which distributors maintain drug identification numbers and imported into a drug form should ensure that the API is contained in the form of dosage form to satisfy the requirements of this division before selling the drug in damage. Premises Section C.02.004 in which many or batch of a manufactured drug, package/congestion or stored must be performed, constructed and maintained in a way that allows the operations to be performed under clean, sanitary and sanitary orders; allows efficient cleaning of all surfaces in it; and prevent the drug contamination with the addition of extranting materials to the drug. The rationale of the design and construction of API relishes is influenced by various factors such as the nature of the API and the location (climatic region). API facilities should be designed and constructed in a way that allows cleanliness and the command while preventing contamination. The buildings and facilities should regularly be kept to prevent deterioration in premises. Finally, the goal of all efforts in the design and construction of an API facility is product quality. Interpretation 1. Buildings and facilities used in APIS production should be located, designed, and constructed facilities cleaning, maintenance, and operation as appropriate to the type and stages of production. Facilities should also be designed to minimize potential contamination. Where microbiological specification was established for the API, facilities should also be designed to limit exposure to contaminant microbiological targets as appropriate. 2. The buildings used in ANIS production should be properly maintained and repaired and kept in a clean condition. 3. Buildings and facilities should have adequate spaces for placement of order of equipment and materials to prevent mixture-ups and contamination. 4. There should be defined areas or other control systems for these activities: receipts, identification, samples, and quarantine of incoming materials, annatant release or rejection; Torpor before release or rejection of APIs; Sample of APIS; Hold material rejected before further affinity (e.g., returned, reprocessing or destruction); Warehouse of materials released; Production operation; Wrapping and labeling operations; and laboratory operations. 5. Lab/operation areas should normally be separated from production areas. Some laboratory areas, in particular those used for controlling in-processing, can be grounded in production areas, providing the operations of the production process by affecting the accuracy of the lab measurements, and and its operations do not affect the production process or the APIS. 6. Drainage should be in adequate size and should be provided with an air break or a suitable device to prevent back-siphonage, then appropriate. 7. All utilities that could impact on product quality (e.g., water, steam, fuel, compressed air, and heating, slits and air conditioning) should be qualified and appropriately controlled and actions should be taken when limits are exceeded. Designs for these utility systems should be available. 8. Adequate slits, air filtration and exhaust systems should be provided, appropriate location. These systems should be designed and constructed to minimize the risk of contamination and cross contamination and should include equipment for air pressure control, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate in the manufactured stages. Particular attention should be given to areas where APIS are exposed to the environment.8.1 if the timing is recirculated in production areas, the appropriate measures should be taken to control risks for contamination and cross-contamination. 9. Adequate, washing and toilet installation should be provided for personnel. These washing facilities should be equipped with hot and cold water as appropriate, soap or detergent, air towels or single service towels. Washing and toilet facilities should be separated from, but easily accessible to, production areas. Adequate shower installation and/or switch clothes to be provided, then appropriate. 10. The color of materials and personnel in the building or facilities should be designed to prevent mixture-ups or contamination. 11. Adequate lighting should be provided in all facilities clearing areas, maintenance, and appropriate operations. 12. Permanently installed valves should be identified appropriate. This can be accomplished by identifying individual lines, documents, computer control systems, or alternative means. They should be located pipes to avoid the risk of contamination the API. 13. Dedicated production area, which can include installation, equipment when handling and/or processing equipment, should be employed in the production of certain grades of highly sensitization material, such as penicilins or cephalosporins. 14. Dedicated production areas should also be considered when material of an infectious or high pharmacological activity or participating toxicity (e.g., certain steroids or anti-cancer agents) unless they validate inactivation and/or cleanup procedures are established and maintained. 15. Any production activities (including pierced, fraising, or wrapping) of very non-pharmaceutiical materials such as herbicides and pesticides should not be done using the buildings and/or equipment used for ANIS production. Handling and storage of these highly toxic non-pharmaceutiical materials should be separated from APIs. 16. Where water used in the process is by the fabricator to achieve a defined quality, the treatment process should be validated and controlled with appropriate action limitations. Section C.02.005 equipment which lots or bundles a manufactured drug, package/congestion or tested must be performed, constructed, maintained, operated and arranged in a way that allows effective cleaning of its surface; prevents the contamination of the drug with the addition of material extraneous to the drug; and allows it to function in accordance with the use of its intentions. The rational goal of these conditions is to prevent the contamination of APIS by other APIS, by dirt, and by foreign materials such as rusty, fat, fat and particles coming from the equipment. Contamination issues may arise from poor maintenance, the museum of equipment, beyond the capacity of the equipment and the use of torn-out equipment. Equipment arranged in a command manner allows clearing of adjacent areas and does not interfere with other processing operations. It also minimizes the circulation of personnel and optimizes the flow of materials. The fabrication of APIs of consistent quality requires equipment to perform in accordance with its intention use. Interpretation 1. The equipment used in APIS production should be in appropriate design and adequate size, and suitivly located for the use of its intentions, cleaning, sanitization, appropriate locations, and maintenance. 2. Equipment should be constructed so that surface contact raw material, intermediate or APIS does not change the quality of the APIs beyond the official or other established specifications. 3. Equipment and vessels should be cleaned, stored, and, appropriate location, sanitized or sterilized to prevent contamination or carry-on of a material that would change the quality of the APIs beyond the official or other established specifications. 4. Any substance associated with the operation of equipment, such as lubricant, liquid heating or cooling, should not contact APIs so as to change their quality beyond official specifications or other established. Any deviation from this should be evaluated to ensure that there are no detrimental effects on the physical condition for the purpose of the material. Wherever lubricant food and oil should be used. 5. Close or containing equipment should be used every proper time. Where use equipment opens, or equipment is opened, should be taken to minimize the risk of contamination. 5.1 Fool, autoclave and similar equipment have one API at a time unless precautions were taken to prevent contamination and mix-ups. 6. Large equipment (e.g., reactors, storage containers) and permanent processing lines used during the production of an API should be identified appropriate. 7. Scheduling, procedures, and logs, including placement of responsibility, should be established for the preventive maintenance of equipment. 8. Equipment that is to use its intentions should be removed from production areas. When removing is not possible innocent equipment should be explicitly marked as such. 9. Control, squeeze, measure, monitoring and test equipment that are critical to ensuring the quality of the APIS should be calibrated according to written procedures and an established schedule. Musical instruments that do not meet calibration criteria should be identified explicitly and not used. 9.1 Calibration equipment should be made using traceable standards of certified standards, if the current calibration status of critical equipment should be known and verificable. 9.2 Deviations from standard approval of calibration on critical instruments should be investigated to determine whether these could have an impact on the quality of the manufacturing APIs using this equipment since the last successful calibration. 10. Pressing and measuring devices should be in appropriate accuracy for the use of intended. 11. Production equipment should only be used in its qualified operation range. 12. GMP-related computer systems should be validated. The depth and scope of validation depend on the diversity, complexity and criticism of the computer application. 13. Proper installation credentials (IQ) and operational credentials (OQ) should demonstrate the appropriateness of computer hardware and software to perform assigned tasks. 14. Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at time of installation, a retrospective validation can be performed if appropriate documentation is available. 15. Computer systems should have sufficient control to prevent unprecedented access or changes of data. There should be controls to prevent the omitted data (e.g. systems extinguished and data not captured). There should be a record of any data changes made including the previous entry, who made the change, and when the change was made. 16. If outage computer system or failure would result in the permanent loss of files, a back-up system should be provided. A means of ensuring data protection should be established for all computer systems. 17. Written procedures should be available for the operation and maintenance of computer systems. 18. Qualifications are usually carried out by doing these activities, individually or combined: Qualification Design (DQ) Installation Credentials (IQ) Operational Qualifications (OQ) Performance Credentials (PQ) Personal Section C.02.006 Each or batch of a drug must be manufactured, packet/congestion, tested and stored under personal supervision which, have consideration of duties and responsibilities involved, has been as technical, academic, and other training as the Principal considers satisfactory of the interests of the health of the consumer or buyer. Rational it is essential

that qualified and competent personnel must supervise the production and control apis. Personnel require appropriate education for the work to accomplish. Education should be strengthened by training and/or experience of the particular work performed. The education, training, skill and attitude of all personnel directly impacts the quality of the products. Interpretation 1. There should be an adequate number of personnel qualified by proper education, training and relevant experience making and supervising the fabric, packaging/labeling, testing, importation, distribution and storage of APIS. 2. The person in charge of the quality control department of a manufacturer, package/labeller, test, importer, distributor, and wholesaler; and the person in charge of the manufacturing department of a fabric with package / labeller 2.1 should be directly controlled and personally supervised on site, each working shift during which activities under control are being conducted. 2.2 May delegate duties and responsibilities (e.g., to cover all changes) to a person qualified by appropriate education, training and experience related to the work being carried out, while remaining responsibility for those duties and responsibilities. 3. The responsibility of all personnel committed to the fabric, packaging/labeling, testing, importation, distribution and storage of the APIs should be specified in writing and personnel should have authority borne out the responsibilities. 4. Training should be regularly conducted by qualified persons in accordance with a written program. 4.1 The training should be covered, at a minimum, the particular operations that employees do with GMP as it relates to the staff function.4.2 Files of training should be maintained. 4.3 Training should be periodical to evaluate and performance of personnel periodically reviewed. 4.4 Trainings should be provided before implementation of new or revised SOPs. 4.5 Personnel working in areas where highly active, toxic, infectious, or sensitization of the occupied materials should be provided to specific training. 5. Consultants and contractor advisers on the manufacturing and control of APIS should have proper education, training, and experience relevant, or any combination therein, to advise on the subject for which they are maintained. 6. Responsibilities for production activities should be described in writing, and should include but not necessarily limited to: 6.1 Prepare, review, approve and distribute the instructions for production APIs according to written procedures; 6.2 Product APIS and, then appropriate, intermediate according to pre-approved instructions; 6.3 Review all output batch files and ensure that these are finished and signed; 6.4 Ensure that all production deviations are reported and assessed and that critical deviations are investigated and the conclusions are recorded; 6.5 Ensure that production facilities are clean and then appropriate 6.6 Ensure that the necessary calibration is done with file retention; 6.7 Ensure that the premises and equipment are kept with retention records; 6.8 Ensure that validation protocols and reports are reviewed and approved; 6.9 Assessing the proposed changes in products, processes or equipment; and 6.10 Ensure that new and, then appropriate, modified installations and equipment are eligible. 7. The main responsibilities of the quality unit(s) of a manufacturer and wrapping/label facility should not be delegated. These responsibilities should be described in writing and should be included in a minimum where applicable, 7.1 is disclosed or rejected all APIs; In some cases, the quality unit(s) can delegate to the Production Unit stewardship and the intermediate release authority, except for those shipped outside the control of the manufacturing company. 7.2 Establish a release system or dismiss raw material, intermediate, packaging and label material; 7.3 Reviewed complete batch output and lab control records at critical processing steps prior to release of the API for distribution; 7.4 Ensure that critical deviations are investigated and resolved; 7.5 Approve all specifications and master production documents; 7.6 Approve all procedures that affect the quality of APIs; 7.7 Ensure that internal auditing (self-inspection) is performed; 7.8 Approved API and intermediate fabricators; 7.9 Approve changes that potentially impact APIs of quality; 7.10 Review and approve validation protocols and reports; 7.11 Ensure that complaints related to the quality of investigations and resolved; 7.12 Ensure that efficient systems are used to maintain and calibrated critical equipment; 7.13 Ensure that the proper materials tested and the results are reported; 7.14 Ensure that there is stability data supporting unused or expiry date and storage requirements on APIS, appropriate locations; 7.15 Do reviews quality annual products; and 7.16 Ensure that quality control equipment is suitable to undertake testing activities. Sanitation Section C.02.007 Each person who is fabric or package/label a drug must have a written sanitation program that will be applied under qualified personal supervision. The sanitation program referred to in subsection (1) must include: cleaning procedures for premises where the drug is manufactured or packet/labelled and for the equipment used in the fabric or wrapping/embelling of the drug; and instructions on the sanitation fabric and packaging/labeling of drugs and the handling of the materials used in the fabric and packaging/labeling of drugs. Rationale Sanitation in an API plant, as well as employee attitudes, influences the quality of drug products. Quality requirements for producing drugs demand that these products be manufactured and packaged in areas free of environmental contamination and free of other medicine. There is an important difference between a finished product environment (physical process) and an API production environment (chemical processing), where they can be used aggressive and corrosive. The level of cleanliness required for an API production environment can vary depending on whether it is an open or closed production system and the production stage. Open production systems (e.g., containers with no cover) or process closer to production end (e.g., purification) would require a higher level of environment control to prevent and/or minimize contamination. In general, the sanitation program applied to a site should be effective in preventing unanimous conditions. Interpretation 1. Written procedures should establish scoring responsibilities for sanitation and describe the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and installations. 1.1 There should be an environmental monitoring program with alert boundaries and actions in areas where sensitive products are manufactured or packaged, when applicable. 1.2 The description of the responsibilities of any outside contractor should be available in writing. 2. Non-dedicated equipment should be cleaned between production of different materials to prevent cross-contamination. 3. Acceptance criteria for resistance and choice for cleaning procedures and clearing agents should be defined and warranted. 4. Sewage, declines, and other waste (e.g., solid, liquid, or gas by-products from manufacturing) in and out of buildings and areas in which immediate enclosure should be thrown in a safe, timely, and sanitary manner. Containers and/or pipes for waste materials should be identified clearly. 5. Cleanup procedures should normally be validated. In general, clearing validation should be directed to situations or processing steps where contamination or carryover of materials possesses the greatest risk to the API quality. For example, in early production it may be necessary to validate equipment cleaning procedures where residues are removed by subsequent purifying steps. 6. Analytical methods that have sensitivity to detect residing or contaminants should be used. The detection limit for each analytical method should be sufficiently susceptible to detect the acceptable level of the resident or contaminant. They should establish the method's recovery level. Residual limits should be convenient, achieved, and verified and based on the most deleted resizing. Limitations can be established based on the minimum of known pharmacies, negatively, or physiological activities of the API or its most deleted elements. More detailed guidance from the Canada Health Document that includes Principal Cleanup Validation (GUI-0028). 7. Cleaning equipment / sanitization science should address microbiological and endotoxin contamination for these processes where there is a total decrease need counts or endotoxins in the API, or other processes where such contamination might be of concern (e.g., non-outward APIs use manufactured sterile products). 8. When necessary, written procedures should also be established for the use of proper rodenticides, insecticide, fongicide, fumigating agents, and cleaning and sanitization agents to prevent the contamination of equipment, raw materials, packaging materials/labelling, intermediate, and APIS. 9. Written procedures should be established for cleaning of equipment and its presiding release for the use of inventory of APIS. Cleaning procedures should include sufficient details to enable operators to clean each type of equipment in a reproduction and efficient manner. The following procedures should include: Responsibility for cleaning supplies; Cleanup schedules, including, appropriate locations, sanitization schedules; A complete description of the methods and materials, including the dilition of clearing agents used in cleaning equipment; When appropriate, disaster instructions and gather every item of equipment to ensure proper cleaning; Instructions for the removal or obliteration of previous batch identification; Instructions for the protection of clean equipment from contamination before use; Inspection of cleanliness equipment immediately before use, if convenient; and establish the maximum time that can be saved between the process completion and cleaning equipment, then appropriate. 10. Where equipment assigned to continuous production or campaign production in successive batch of the same API, equipment should be cleaned at appropriate intervals to prevent build-up and carry-on of contaminants (e.g. degradants or objection levels of microorganisms). 11. Records of greater equipment used, cleaning, sanitization and/or sterilization and maintenance should show the date, time, if appropriate, product, and batch number of each batch processed in the equipment, and the person doing the cleaning and maintenance. 12. Cleanup procedures should be controlled at proper intervals after validation to ensure that these procedures are effective when used during routine production. Cleanliness equipment can be controlled by analytical tests and visual examinations, where possible. Visual inspection can allow detection of gross contamination focus in small areas that could otherwise go detected by samples and/or analysis. 13. Dirt operations should be contained. The use of units or portable dust collectors should be avoided in the fabric area especially in dispensary, unless the efficiency of filtration of exhaust valves is demonstrated and units are regularly maintained in accordance with approved writing procedures. Section C.02.008 Each person's fabric or package/label of a drug must have, in writing, minimum requirement for health and hypothetical behavior and personal clothing to ensure the clean and fabric and packaging / labeling of the drug. No one has access to any area where a drug is exposed during its fabrication or wrapping/labelling if the person is affected and or is an insurance company of a disorder in a form of communicating; or is there an open lesion on any exposure surface in the body. Rational Employee Health, Behavioral, and Clothing can contribute to the contamination of the product. Poor personal hype will cancel the pure sanitation program and greatly increase the risk of product contamination. Interpretation 1. Personnel and visitors should practice good sanitary and health habits. 1.1 Requirements regarding cosmetics and jewellery worn by employers should be description and observed by staff. 2. Personnel suffering from an infectious disease or having lesions open on the exposure surface of the body should not engage in activities that might result in compromising the quality of APIS. Anyone shown at any time (either by medical examination or supervised observation) to have an apparent illness or open lesions should be excluded from activities where the health condition could be issued properly affecting the quality of the APIs until the condition corrected or qualified medical personnel determined that the person's inclusion would not jeopardize the safety or quality of the APIs. 2.1 Employees should be instructed to report to their supervisors any health conditions they have that might affect APIs. 2.2 A procedure should be in place to describe actions to be taken in the event that a person with a communicating disorder has been identified as having handled material exposure. 3. Personnel should wear clean clothes suitable for the manufacturing activity and where they are involved and this clothes should change when appropriate. Other protective clothing, such as headers, faces, hands, and arm cover, should be back when necessary, to protect APIs from contamination. 3.1 Soiled protective clothing, if reused, should be stored in separate containers until properly laundered and, if necessary, disinfected or sterilized, according to a written procedure. Washing clothes in a domestic environment is unacceptable. 4. Personal should avoid direct contact with APIs. 5. Smoking, eating, drinking, drinking, grinding and the storage of food should be enforced in certain designated areas separated from the manufacturing areas. Raw material test Section C.02.009 Every lot or batch of raw materials will be tested against the specifications for materials prior to its use in the fabric of a drug. There is not much or batch of raw materials to be used in the fabric of a drug unless many or batch of raw materials and specifications are for this raw material. Despite subsection (1), water can, before finishing its test under this section, must be used in the fabric of a drug. Where any properties of a material before all editing is subject to change over storage, no or batch of raw materials to be used in the fabric of a drug after its warehouse unless the raw material remains after a proper and complicated interval and its specifications for that property. Where specifications are referred to in subsection (1), (2) and (4) are not prescribed, they will be in writing; be acceptable to the Director who shall take into account the specifications of any publication mentioned in Schedule B of the Act; and shall be approved by the person in charge of the quality control department. Rationale previous material tests to use are three targets: they confirm their raw material identity, provide assurance that the quality of APIS will not change by raw material damage, and obtain assurance that the raw materials correction contains the characteristics that will provide the desired quantity or yield of a given manufacturing process. Interpretation 1. Specifications should be established and documented for raw materials, intermediate and necessary locations, APIS. In addition, the specifications may be suitable for certain other materials, such as processing aids or other materials used during APIS production that could critically impact on quality. Acceptance criteria should be established and documented for the process monitor. The specifications are approved and dated by the person in charge of the quality control department or by a designated alternative that meets the requirements described under Rule C.02.006, Interpretation 1. 2. Specifications for raw materials should be established based on process design and overall control strategy to ensure the quality of the final product. 3. Raw materials should be purchased against an agreed specification, from suppliers approved by the quality unit(s). 4. Water use of the manufacture of APIs should be demonstrated to be suitable for its intended use. 5. Unless otherwise justified, processing water should, at a minimum, meet the World Health Organization (WHO) directives for drinking (portable) water quality. 6. If drinking (portable) insufficient water ensures the quality of API, and tighter chemical and/or microbiological water quality specifications are called for, specifications suitable for physical/chemical attributes, total counting of microbes, objectional organisms and/or endotoxins should be established. 7. Where the fabric of a non-sterile API Either intends or claims that it is suitable for the use of more processes to produce an outward drug, water used in the final isolation and purification steps should be controlled and controlled for total counting of microbes, objected organisms, and endotoxins. 8. Analytical methods should be validated unless the hiring method is included in the relevant pharmacopoeia or other recognized standard references. The appropriateness of all analytical methods used should however be verified under actual conditions of use and waivers. 9. Methods should be validated to include feature consideration included in the ICH on validation of analytical methods. The analytical validation degree performed should reflect the purpose of the analysis and the scene in the API production process. Note: Guidelines for validation of particular method types can be found in publications such as the ICH document entitled ICH Q2(R1): Validation of Analytical Procedures: Text and Methodology or from any standard listed in Schedule B of the Food and Drug Act. Raw materials should be re-evaluated as appropriate to determine the appropriateness for use (e.g., after prolonged storage or exposure to heat or humidity). The Section C.02.010 Test referred to in section C.02.009 must be performed on a sample taken after receiving in every lot or batch of raw materials on the premises of the fabricator; or subject to source (2), before receiving every lot or batch of raw material on the local fabric, if the manufacturer has evidence satisfaction to the Director for displaying raw materials by the vendor of many or bars of raw materials consistently manufactured in accordance with and always comply with the specifications for these materials before full editing , and undertakes periodic thorough testing with a frequency satisfaction of the Director, and the raw material has not been transported or stored under conditions that may affect its compliance with the specifications for this raw materials. After a lot or batch of materials before all editing is received on the premises of the canvas, the lot or batch of raw materials will be tested for identity. Rationale Section C.02.010 Description option such as when the test prescribed by Section C.02.009 is carried out. The purchase of raw materials is an important operation that requires a particular knowledge and quality of the raw materials and suppliers. To maintain consistency in the fabric of APIs, previous materials all editing should be originally from reliable providers. Interpretation 1. Fabricators of APIs should have a written system to evaluate their provider of critical materials. 2. Specific identity testing of each batch of materials received on premises of the API Manufacturers should be performed, with the material exceptions described below in 4. A provider's Certificate of Analysis (CoA) may be used in place of other testing performs, given that the fabric has a system in place to evaluate the providers. 2.1 Provide that the identity test refers to interpretation 2 is performed, many of the previous materials selected for confirmation testing can be used in fabric before the completion of all tests with the approval of the quality control department. 3. Vendor approval should include a written assessment that provides adequate evidence (e.g., recent quality history) that the fabric can still provide material meeting specifications. You should test confirmation on at least three batch prior to decreased in-house testing and after important changes The manufacturing process. However, as a confirmation test, they should be performed at appropriate intervals and compared with the CoA. Reliability of coas should be checked at regular intervals. 3.1 A published document verifies that the provider meets the criteria for certification. The document is approved by the quality control department and is reviewed periodically. 3.2 A write system should be in place to address test failures with any credential re-credentials from the provider if necessary. 4. Process help, dangerous or highly toxic materials before all correction, other special materials, or materials transferred to another unit of control the company does not need to be tested if the fabricator coa is found, showing that these raw materials conform to established specifications. Visual examinations of containers, labels, and recording of batch numbers should help in establishing the identity of these materials. Lack of testing on place for such materials should be justified and documented. 5. Samples should be representative of the batch of materials to which they were taken. Sample methods should specify the number of containers to be samples, which are part of the sample container, and the amount of material to be taken from each container. The number of sample containers and the sample size should be based on a sample plan that takes into consideration the critical of the material, material variables, past quality history of the provider, and the required quantity for the analysis. 6. There should be written procedures describing the identification, and testing of the materials. 7. If the supplier of a critical material is not the fabric of this material, the name and address of which the fabricator should be known in the API fabricator. 8. Changing the source of critical material should be processed according to Section C.02.015, Change Control. 9. Where appropriate, a copy of the residual solvent profile should be obtained. Additionally, for APIs, a copy of the impurity profile should be found. 10. When a broker or wholesaler material is received from the original vendor without changing the existing labels, wrapping, certificate of analysis, and general information, then the original source certification is always acceptable. 11. The condition of transportation and storage should be as such that to prevent changes in the potential, purity, or physical characteristics of the raw materials. 12. If a delivery or ship of raw material is made up of different bundles, each batch should be considered separate for the purposes of samples, testing, and release. 13. If the same batch of raw materials is received, this batch should be considered separate for the purpose of sample, testing, and release. However, full testing of specifications may not be necessary on such a batch given that all these requirements are met: 13.1a specifically identity testing is conducted; 13.2 The raw material was not repaired or re-labelled; 13.3 The raw material is to re-test date assigned to its vendor; and 13.4 available evidence demonstrates that all pre-established transportation and storage requirements are maintained when applicable. Factory Control Section C.02.011 Each fabric, package/labeller, distributor refers to paragraph C.01A.003(b) and import of a drug must be written procedures prepared by qualified personnel in respecting the drug to ensure that the drug meets the specifications for such medications. Each person required to have written procedures referred to in subsection (1) will ensure that every lot or batch of the drug is manufactured, package/labelled and tested in compliance with these procedures. Streamline this Policy requires measures to take to maintain the integrity of an API from the moment various materials are before all editing enters the plant at the time the API is released for sale or for more fabric. These measures ensure that all manufacturing processes are clearly defined, systematic reviews of light experiments, and demonstrate to be capable of consistently manufacturing APIS of the required quality that complies with established specifications. See the Table 2 for the point at which output of the API starts and from which the compliance of the GMPs should be applied. Interpretation 1. Access to production areas is enforced in designated personnel. 2. All handling of raw materials, products, and packaging materials such as receipt, identification, quarantine, storage, sample, testing, approval or rejection of materials, tracking, label, wrapping, dispensary, processing, and distribution should be done in accordance with written procedures or instructions and registers. 3. Validation should be extended to these operations determined to be critical to the quality and purity of the API. 3.1 The potential impact of the proposed change on the quality of the API should be evaluated. A classification procedure can help to determine test level, validation, and documentation required to justify changes to a validated process. Changes can be classified (e.g., as minor or larger) depending on the nature and cost of the changes, and the effects of the changes can be improved upon the process. Scientific judgments should determine what other tests and validation studies are appropriate to justify a change in a validated process. Where no significant changes are made to the system or process, and a quality review confirms that the system or process is still producing its specifications meeting material, there is virtually no need for revaluation. 4. A write validation protocol should be established that specifies how validation of a particular process must be performed. The protocol should be reviewed and approved by the quality unit(s) and other designated units. For more information on this see section 12 Validation of the Q7 Q7 Guidelines. 4.1 The validation Protocol should specify critical processing steps and acceptance criteria as well as the type of validation to be done (e.g. retrospective, prospective, concurrent) and the number of running processes. 4.2 A validation report that cross-reference the validation protocol should be prepared, summarize the findings, comment on any observed deviation, and drawing appropriate conclusions, including recommending changes to incorrect deficiencies. 4.3 Any variations from the validation protocol should be documented with appropriate justification. 5. Before starting process validation activities, the proper credentials of critical equipment and ancillary systems should be completed. 6. Any deviations should be documented and explained. Any critical deviation (i.e. one that could affect the quality and/or purity of the API) should be investigated. 7. Real yields should be compared with expected yields at designated stages in the production process. Expected production and appropriate ranges should be established based on previous lab, pilot scale, or data manufacturer. Deviation of yield associated with critical processing steps should be investigated to determine the impacts or potential impacts on the quality of the resulting batch affected. 8. Residual materials can be carried on in successive batch of the same API as inasmuch as there is adequate control. Examples include residing adhesives to wall a micronizer, residual layers of crystals that reside in a centrifunded bowl after layer, and incomplete layers of liquid or crystals from a process container on transfer of the material to the next step of the process. Such carryover should not result in the carryover of degradants or microbe contamination that can be adversaries changing the API established API profile. 9. Given that valid change procedures are applied, non-medicine products can be manufactured or package/containing labelled in areas or with equipment that are also used for production APIS. 10. Facilities where APIs are manufactured, packages and markers should be inspected immediately before use to ensure that all materials not necessary for the next operation have been removed. They should document this examination of the batch output files, the log, or other documentation systems. 11. Production operations should be performed in a way that will prevent contamination of APIs by other material. 12. In-process samples should be performed using procedures designed to prevent contamination of the sample material and other APIS. Procedures should establish to ensure the integrity of samples after collection. 13. Written procedures should be established to monitor the progress and monitor performance of process steps that cause variables in the quality characteristics of APIS. Control process and acceptance criteria should be defined on the information taken during stages of development or historical data. 14. The acceptance criteria and types and limitations of testing may depend on the nature of the API being manufactured, the reaction or processing step is being performed, and the degree to which the process introduces variables to the product's quality. Fewer server in-process controls may be appropriate in early processing steps, whereas tighter control can be suitable for later processing steps (e.g., isolation and purification steps). 15. Monitor critical in-processing (with critical process monitoring), including the control points and methods, should be declared in writing and approved by the quality unit(s). 16. In-process controls can be made by qualified department personnel and the adjusted process without the prior quality unit(s) approval if the adjustments are made to pre-established boundaries approved by the quality unit(s). All tests and results should be fully documented as part of the batch file. 17. Written procedures should describe the sample methods for in-processing materials, intermediate, and APIs. Sample plans and procedures should be based on sample practices scientifically sound. 18. Caution to avoid contamination should be taken when APIs are handled after purification. 19. Production operations on different products can be carried out in the same given area which measures the appropriate and controls are in place to prevent mixture-up or cross-contamination. 19.1 Proper measures should be established and applied to prevent cross-contamination from personnel, materials, etc. moving from one dedicated area to another. 19.2 Where applicable, checks should be carried out to ensure that removable and interchangeable transfer lines and other pieces of equipment used for the transfer of materials from one area to another are correctly connected. 20. Equipment or segregation processing areas should be identified as in its contents, including product name and batch number, and its cleanliness status does not mean appropriate. 21. The processing status of major units of equipment should be indicated either on the individual units of equipment or by appropriate documents, computer control systems, or alternative means. 22. Rejected materials should be identified and controlled under a carrant system designed to prevent their un authorised use of manufacturing. 23. The materials to be replaced or reworked should be appropriately controlled to prevent unprecedented use. 24. When receiving and prior acceptance, each container or grouping of material containers should be examined visually for correct labels (including correlation between the name used by the provider and the in-house name, if these are different), container damage, broken seals and evidence of diffusion or contamination. All containers are verified to ensure that information is on the order, the delivery notes and the vendor's label is in agreement. 24.1 Materials must be conducted under forty until samples have been examined or tested as appropriate, and released for use. 25. Before incoming materials are mixed with existing actions (e.g., solvent or action in silo), they should be identified as incorrect, tested, if appropriate, and released. Procedures should be available to prevent dissect material incoming trunk of the existing stock. 26. If essential delivery is made of non-dedicated tanks, there should be insurance in no cross-contamination contamination from the tanker. The means of providing this assurance could include one or more of the following: cleaning certificates, tests for impurities traces, and auditing controls of the provider.27. Intermediate-made processes should be stored under the appropriate conditions to ensure their suitability for use. 28.Critical materials should be transported in a manner that does not affect their quality. 29. Special transport or storage requirements for an API should be stated on the label. 30. Samples should be performed in defined locations and by procedures designed to prevent contamination of samples of materials and contamination of other materials. 31. Containers from which the removed samples should be opened carefully and immediately resumed. They should be marked to indicate that they took a sample. 32. Large storage containers, and manifold participants, filling and dripping lines should be appropriate identified. 33. Each container or grouping of containers (batch) of materials should be assigned and identified with a different string, batch, or receipt number. The identification number should be used in affinity recordings of each batch. A system should be in place to identify the status of each batch. 34. Materials should be handled and stored in a way to prevent degradation, contamination, and cross contamination. 35.Material stored in fiber drum, bag, or box should be stored at the floor and, then suitable, conveniently the space to allow cleaning and inspection. 36. Materials should be stored under conditions and for a period with no negative effect on their quality, and should normally be controlled so that the oldest stock is used first. 37. Certain materials in proper containers can be stored outside, providing identifying labels remains eligible and the appropriate container appropriate before opening and use. 38. The previous material correction for the Manufacturing API should be pressed or measured under the appropriate conditions that do not affect their suitability for use. 39. Critical weighing, measuring, or subdivising operations should be witnessed or subject to an equivalent control. Prior to using, personal output should verify that the materials are those specified in the batch file for the intended API. 40. Other critical activities should be witnessed or subject to an equivalent control. 41. All related activities should be recorded at the time they are performed. 42. When entries are made into these should be made independent of the space provided for these entries, directly after performing the activities, and should identify the person to make the entry. Editing of entries should date and sign and leave the original entry still readable. 43. All documents related to the INVENTORY should be prepared, reviewed, approved and distributed according to written procedures. 43.1 To ensure the batch uniform, master production instructions for each API should be prepared, dated, and signed by one person and independently checked, dated, and signed by a person in the quality unit(s). Factory Operation 44. Master output documents should include: the name of the API being manufactured, batch size, and an identified document reference code, if applicable; A complete list of raw materials and intermediate materials designed by names or specific sufficient codes to identify any special quality characteristics; An incorrect statement of the quantity or report of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or percentage of output should be included. Variations in quantity should include locations to justify; Where the production and production equipment is larger to be used; The procedures, or references to the procedure, must be used in the output; Detailed production instructions, including: sequence to be followed, chain of process parameters to be used, sample instructions and control of processes and their acceptation criteria, appropriate locations, deadline times for completion of individual processing steps and/or the total process, appropriate location; and expect yield ranges in the proper phase of process or time; Where appropriate, special notations and precautions must be followed, or cross-referenced to the following; and the instructions for storage at the intermediary or API ensure its suitable for usage, including the label materials and material wrapping and special storage requirements and time limits, the appropriate location. 45. Batch output files should be prepared for each API and should include complete information related to the output and control of each batch. The batch output file should be checked before issue ensures that it is the correct version with an accurate legal reproduction of the appropriate master output instruction. If the batch output file is generated at a separate part of the master document, this document should include a reference to the actual master output instruction being used. 46. The batch output files should be counted with a unique batch number or identification, containing date and signing when provided. In continuous output, the product code along with date and time can serve as unique identifier until the final number is allocated. 47. Documentation of completion of each milestone in the batch output files output and control files) should include: Date and, then appropriate, times of beginning and ending of important intermediate stages (mixing, heating, etc.) and in production; Identification of larger equipment (e.g., reactors, reliable, mosquitos, etc.) used; Specific identification of each batch, including weight, measurement, and batch number of raw materials, intermediate, or any reproduced materials used during manufacturing; Actual results recorded for critical process parameters; Any sample is done; People's signatures are done with directly supervising or checking each critical step in the operation; Current laboratory test results yield in appropriate phases or times; Any deviation noted, its assessment, investigation is conducted (if appropriate) or referenced to this investigation if stored separately; and results in test releases. When completed, the person's signature is responsible for the processing operations. 48. If a material is subdivised for later use in production operation, the container receiving the material should be appropriate and should thus identify that the following information is available: Material name and/or item code; Receive or control numbers or different codes; Weight or measure of materials in the new container; date if appropriate. Mix 49. For the purposes of this document, mixing is defined as the process of combining materials into the same specifications to produce a homogeneous API. In-process mixing of fractions from single batch (e.g., collecting several centrifugal loads from a batch of single crystallization) or combining fractions from multiple batch for processing more regarded as part of the production process and is not considered as mixed. 50. Out-of-Specifications should not be mixed with other bundles for the purpose of meeting specifications. Each batch incorporating into the mixture should be manufactured using an established process and should be individually tested and found to meet appropriate specifications before mixing. 51. Acceptable mixing operations include but are not limited to: Mixing of small batch increases mixed size in their hearts (i.e., relatively small amounts of isolated materials) from batch of the same API to form a single batch. 52. Mixed processes should be adequately controlled and documented with the mixing batch should be tested for comforting to establish specifications where appropriate. 53. The batch file of the mixing process should allow traceability back into the individual bundles that make up the mixture. 54. Where physical attributes of API are critical (e.g., APIS intended for use in solid or dose forms or suspensions), mixed operations should be validated to show homogeneity in the combined batch. Validation should include test critical types (e.g., particle size distribution, bulk density, and valves which can be affected by the mixing process.55. If the mixing could affect stability, stability tests in the final mixed batch should be done. 56. The expiration or remainder of date of the mixed batch should be based on the manufacturer date of the oldest tail or batch of the mixture. Recovery 57. Recovery (e.g., from mother lion or filtrate) to reactant, intermediate, or the API is considered acceptable, provided that approved procedures exist for the recovery and the recovered materials satisfy the appropriate specifications for the use of the intent. 58. Solvents can be recovered and reused in the same processes or in different processes, provided that the recovery procedures are monitored and monitored to ensure that solvents meet appropriate standards before reuse or co-mling with other approved materials. 59. Fees and recovered solvents and reactives can be combined if adequate tests showed their proper properness for all manufacturing processes in which they can be used. 60. Use in recovered solvents, liquor mothers, and other recovered materials should be adequately documented. Wrapping Operations 61. Wrapping operations should be performed according to comprehensive and detailed write operational procedures or specifications, including identification of equipment and wrapping lines to use the API package or intermediary, the dedication to wrapping lines, if necessary, and disposal procedures for the printer diagnostic materials. Wrapping orders should be individually counted. 62. Labelling operations should be done to prevent mixture-ups. There should be physical or spatial separation from operations involving other APIS. 63. Access to the label storage areas should be limited to authorized personnel. 64. Wrapping and label installation should be inspected immediately before use to ensure that all materials not necessary for the next wrapping operation have been removed. They should document this examination of the batch output files, the log, or other documentation systems. 65. There should be documented procedures designed to ensure that correct packaging materials and labels are used. 66. Printer devices used to print labels for wrapping operations should be monitored to ensure that all compliance printing in the printer is specified in the batch output file. 67. Printing labels provided for a batch must be carefully examined for proper identity and compliance of specifications in the master output file. The results of this exam should be documented. 68. Containers should be clean and, where indicated by the nature of the API, sanitize ensures that they are appropriate for the use of their intentions. These containers should not be reactivated, additives, or absorptive so as to change the quality of the API beyond the specified limits. 69.Si containers are re-used, should be cleaned in accordance with documented procedures and all previous labels should be removed or defaced. Labels used on containers in APIS should indicate the name or identify code, the batch number of the product, and storage requirements, when such information is critical to ensure the quality of APIS. 71. If the API is intended to transfer out the control of material management system fabricator to the name and address of the manufacturer, amount of contents, and special transport requirements and any special legal requirements should also be included on the label. For APIs with an expiration date, they should indicate the expiration date on the label and CoA. For APIs with an unused date, they should indicate the unused date should be indicated on the label and/or the CoA.72.API containers that are transported outside of the fabric' control should be sealed in such a way that, if the seal is emptied or missing, the recipient will be alert to the possibility of what may change. 73. Package and marking APIs should examine ensuring that containers and packages in the batch have the correct label. This examination should be part of the wrapping operation. These test results should be recorded in the batch output or control file. 74. Procedures should be used to reconcile the number of labels provided, used, destroyed and returned. All disagreements were found between the number of containers marked and the number of labels provided should be investigated, and the investigation would be approved by the quality unit(s). 75. When complete of the excess label operation, all excess labels carry batch number or other related printing batch should be destroyed and destruction is recorded. Returns the labels should be stored in a way that prevents mix-ups and provides appropriate identification. 76. Obsole and outdoor labels should be destroyed. 77. All APIs that have been packaged and marked should be made in quarantine and be so identified until they are released in the quality of the controlled department. 78. Wrapping order should include the following information (recorded at the time each action is taken): 78.1 The Date(s) and time(s) of the wrapping operations; 78.2 The identification of the personnel who oversee or verify wrapping operations and withdrawal in bulk; 78.3 The identification of the operators in the different stages is important; 78.4 Whether the correct products and packaging materials have been used; 78.5 If any on-line printing is correct; 78.6 Whenever possible, samples of the printed packaging materials are used, including specimens that bring the batch number, expiration date, and any other additional replacements, to attach and wrapping order. 78.7 The correct function of line monitors; 78.8 Handling precautions applied to a partly package product; and 78.9 Notes on any special issues, including details on any deviation of the wrapping instructions and approval written by qualified personnel. Product Quality Review 79. reviewing regular quality of APIs should be conducted by and aims to verify the consistency of the process. These reviews should normally be conducted and documented annually and should include at least: 79.1 A review of critical in-process testing results and critical API test results; 79.2 A review of all batch that fails to meet established specification(s); 79.3 A review of all critical or non-comfortable deviations or related investigations; 79.4 A review of any changes carried out in the processes or methods analytical; 79.5 A review of results of the stability monitoring program; 79.6 A review of all returns related to quality, complaints and recalled; and 79.7 A review of adequate in corrective action. 80. The results of this review should be evaluated and an assessment was made of whether corrective action or any revaluation should be undertaked. The reason for these corrective actions must be documented. Agree corrective actions should be completed in a timely manner. Section C.02.012 Each fabric, package/labeller, distributor referred to in section C.01A.003, import and wholesaler of a drug will maintain a system of control that allows filling and quick recall of any lot or batch of the drug that is on the market; and a program of self-inspection. Each manufacturer with pack/labeller and, subject to undersecretary (3) and (4), each distributor referred to paragraph C.01A.003(b)and the import of a drug must maintain a system to ensure that any lot or batch of the drug manufactured with packages/is marked on locales other than their own is manufactured with packages/marked in accordance with the requirements of this division. Subsection (2) does not apply to a distributor if the drug is manufactured, package/labelled and tested in Canada by someone holding an establishment license that authorizes these activities in respect of this drug. Subsection (2) does not apply to a distributor or import whether the drug is manufactured or package/marked in an MRA country of a recognised building and both of the following conditions are satisfied: the address of the building is laid out in their establishment license; and keep a copy of the batch certificate for every lot or batch of medications they receive. To streamline the purpose of a recalled is to withdraw from the market, an API that represents an unretchable health risk. APIs that are left on-premises in a fabric, package/labeller, distributor, and import of APIs can be found in a variety of locations. Because of the gravity at risk for the health, it may be necessary to remind one product at one level or another. Fabricators, packages/labellers, distributors, import them and wholesalers of APIS are expected to be able to recall from all their direct customers of all dogs in reserves. Further advice about reminding you can get from the Health Canada Documents right to call Policy (PAUL-0016) and GUI-0001. This rule requires manufacturers, packages/labellers, distributors, and import for maintaining a program The goal of self-inspection is to assess the compliance with GMP in all aspects of production and quality control. The self-inspection program is designed to detect any imperfections in the application of GMP and recommend the necessary corrective/preventive action. APIs offered for sale in Canada, regardless of whether they are domestically produced or imported, must meet the requirements of Part C, Division 2 of the Food and Drug Regulations. Production contracts and analysis must be correctly defined, agreed upon, and controlled in order to avoid misunderstances that could result in a product, job or analysis of unsatisfactory quality. Normally, a written agreement exists between the parties involved, and that this document clearly establishes the duties of each party. Interpretation 1. Procedures should exist to notify responsible management in a timely manner of regulatory inspection, severe GMP deficiencies, product damages and related actions (e.g., quality complaint related, recall, regulatory action, etc.). 2. There should be a written procedure that defines circumstances under which a recall in an API should be considered. 3. The recall procedure should be designated who should opt to evaluate the information, how a recall should be initiated, who should be informed about the recall and how the recalled material should be processed), especially: 3.1 Health Canada should receive notifications of the recalled.3.2 The recalled procedure should be able to have been put into operation at any time, during and outside normal working hours. 3.3 Progress and efficiency of joining should be evaluated and registered at intervals, and must provide a final report (including a final reconciliation). 4. A system should be in place where each batch distribution of API can easily be determined to allow its recall. This should include any product to transport, any sample removed from the quality control department and any professionally distributed sample. 4.1 A written agreement should describe the respective responsibilities of all parties involved in respect to remind them. 5. Unless there is an alternative system to prevent intentional or un authorised use of quarantined, rejected, returned, or recalled materials, separate storage areas should be assigned for temporary storage until the decision as they are taken. 6. All Canadian and foreign establishments involved in the production, distribution and imports, including agents, brokers, re-packages and re-labellers of the recalled API should be alerted and keep records of all complaints and reminds that come to their attention. 7. In order to verify compliance with Division 2, Part C of Food and Drug Regulations, regular self-inspection appropriate to that type of operation of the company should be performed in accordance with an approved schedule. 7.1 The indeperction team should include individuals who coaching and qualifying at GMP. 8. A comprehensive writing procedure describing the function of the self-inspection program should be available. Self-inspection results and corrective/preventive actions should be documented and brought to the attention of responsible management of the firm. Agreeing corrective/preventive actions should be filled in a living and effective way. 9. All Canadian and foreign establishments involved in the production, distribution and imports, including agents, brokers, re-packages and re-labellers should comply with GMP as defined in this Guideline.10. Contract fabricator s (containing lab) should be evaluated by the contract grant to ensure GMP compliance to the specific operations performed at the contract sites. 11. To ensure compliance of contractor making fabric or wrapping/ labelling: 11.1 All contract manufacturing arrangements or packaging/labelling should be in accordance with the current regulatory API concerned. 11.2 There should be a written agreement covering the fabric or wrapping / arranging labels among the parties involved. The agreement should specify the respective responsibilities of the GMP related to the fabric or wrapping / labelin and quality control of the API. 11.2.1 Technical aspects of the agreement should be mapped up by skilled personnel suitivman knowledge of pharmaceutiical technology, and GMP. 11.2.2 The Agreement should be permitted to provide contracts to auditing the facilities of the contractor for compliance with GMP. 11.2.3 The Agreement should be described explicitly as a minimum responsible for: 11.2.3.1 purchase, sample, testing and releasing material; 11.2.3.2 undertake production, quality, and in-process control; and 11.2.3.3 validation processes. 11.2.4 No subtraction of any work should occur without written authorization by providing the contract and approval of the arrangements. 11.2.5 The Agreement should specify the way in which the type control department of the distributor or import the distributor to release the lot or batch for sale, ensuring that every lot or batch has been manufactured with package / marked in compliance with the current regulatory filing for the API is concerned, if applicable. 11.2.6 The Agreement should describe the handling of raw materials, packaging material, intermediate, and APIs if rejected. 11.3 The contractor's complaint procedure should specify that any records related to assessing the quality of a drug product in the event of complaints or a suspect are accessible to the distributor or import. The 11.4 Fabric, package/labeller, distributor, or import should provide the contractor with all the information necessary to carry out the contract operations correctly in accordance with fulfilling the current regulatory API associated with concerned API, if applicable, and any other legal requirements. The fabricator, package/ labeller, distributor, or import should be insured The contractor is fully aware of any issues associated with the product, work or test that might pose a danger to locating, equipment, personnel, other materials or other products. 11.4.1 Changes in the processing, equipment, test method, specifications, or other contract terms should not be done unless the grant is informed and approve the changes. The Fabricator 11.5, package/labeller, distributor, or importer should be responsible for assessing the contractor's skills for carrying out the work or testing required in accordance with the principles of GMP described in these guidelines. 11.5.1 Distributors OF MANUFACTURED APIs, packages/marked and tested in Canadian sites should be required to have a relevant copy of the list of Canadian establishments made by the Canadian manufacturer or package/pillar or tested. 11.5.2 Import of APIS manufactured, package/labelled, or tested at a foreign site should meet the requirements described in Canada's General Score of Stakeholders – Amanded Food and Drug Regulations for active ingredients. Type Control Department Section C.02.013 Each fabric, package/labeller, whole, distributor referred to in section C.01A.003 and the import of a drug must have on premises in Canada a quality control department supervised by personnel described in section C.020.006. Except in case a whole or a distributor referred to in paragraph C.01A.003(a), the quality control department will be a different organizational unit that functions and reports in management independently of any other functional unit, including manufacturing, the processing, wrapping or sales unit. Rationale control type is the part of GMP concerned with samples, specifications, and testing with the organization, documentation, and release procedures. This policy ensures that necessary and relevant testing is actually carried out with raw material kicks and packaging materials are not released for use and APIs are not released for sale or more use of fabric, until their quality has been deemed to be satisfactory. Quality control is not confirmed in laboratory operations but must be incorporated in all activities and decisions regarding the quality of the API. The rational is for the requirement that the quality control department be supervised by qualified personnel description under Rule C.02.006. Interpretation 1. The quality unit(s) should participate in all quality related artifacts. 2. The quality unit should review and approve all documents related to quality. The written procedure must be available for the receipt, identification, quarantine, storage, handling, sample, label, dispensary, processing, distribution, inspector, testing, and approval or rejection of previous materials, wrapping materials, in-process APIS, APIS, and for the recording and storage of lab data. 3. The quality unit of the manufacturer and should be independent of production and meet both quality assurance (QA) and quality responsibility (QC) responsibilities. This can be in the form of separate units QA and QC or one person or group, depending on the size and structure of the organization.4. The quality unit should have access to facilities, including a lab, training personnel, and equipment in order to meet its duties and responsibilities. Section C.02.014 Except in the case of a wholesaler or a distributor referred to in paragraph C.01A.003(a), there is no lot or batch of a drug may be available for further use of fabric or for sale unless the person in charge of the quality control department approves the additional or sold use of. A drug that is returned to its manufacturers, packages/labellers, wholesale, distributors referred to in section C.01A.003 or import will not be available for further use of fabric or for sale more unless the person in charge of the quality control department approves more use of or sale more. There are not many or batch of a material or packaging/labelling material to be used in the fabric or wrapping/label of a drug unless the person in charge of the quality control department approves the use of. There is not much or batch of a drug to be replaced unless the person in charge of the quality control department approves the reprocessing. Rationale the responsibility for approval of all raw materials, wrapping materials and APIs is vested within the quality control department. It is very important that adequate controls must be exercised by this department in order to guarantee the quality of the end product. To maintain this level of quality, it's also important to examine all RETURN APIs and provide special attention to replacing APIs. Interpretation 1. All decisions made by the Control Control Department for Regulation C.02.014 should be signed and dated by the person in char of quality control department or by an alternative meeting described under Section C.02.006. These person names should be specified. 2. No material should be released or used before the satisfactory completion of assessment by the quality unit(s) unless there are appropriate systems in place to allow for such use (e.g. release under quarantine or the use of raw materials or intermediate pending completion of evaluation). 3. The assessment for release APIs should embrace all relevant factors, including the production requirements, the results of in-process testing, the fabric and wrapping documents, compliance with the APIS specifications, an examination of the finished package, and if applicable, a review of the storage and transport requirements. 4. APIs should only be released for distribution to third parties after being released by the Quality Unit(s). APIs can be transferred under quarantine to another unit under the company's control when authorized by the quality and if appropriate controls and documents are in place. 5. The quality control department should ensure that raw materials and packaging materials are quarantine, sample, tested, and released prior to their use of the fabric or packaging/label of a drug. 6. Any deviation, non-compliance, and dysfunction or errors that include people related to locales, equipment, sanitation, and testing, such as deviation of written procedures, may have an impact on the quality and safety of batch annatant release or release, should be evaluated. Critical deviations should be investigated, and the investigation and its conclusion should be documented. 7. Rejected material, such as APIs, it will not receive satisfying established specifications, should be identified as such and forty. These materials should be returned to the vendors, rebuilded, reworked, or destroyed. They must register their actions. 8. APIs returning from the market would be

destroyed unless it was protected that their quality is satisfactory. Returned goods can be considered real only after they are evaluated in accordance with a written procedure. The reason for the return, the nature of the product, the storage and transport requirements, conditions and the history of the API, and the time spent since it was originally sold should be taken into consideration in this assessment. If the conditions under which returned APIS were stored or shipped before or during their return or the condition of the container cast on their quality, the APIS should be replaced, reworked, or destroyed, as appropriate. They must maintain records of any actions that have been taken. 8.1 Documentation should be available to support the rational in place of goods return in inventory for more real. Reworked 9. Before it's a decision taken in batch reworked non-compliant to establish standards or specifications, an investigation of the reasons for non-comfortment should be done. 10. Batch being reworked should be underwent in proper evaluation, testing, stability testing if secured, and documentation shows that the reworked product is of the equivalent quality produced by the original process. Concurrent validation is often the appropriate validation approach for reworked procedures. This allows a protocol to define the reworked procedure, how it will be carried out, and results are expected. If there is only one batch to be reworked, then a report can be written and the batch is released once it is found to be acceptable. 11. Procedures should be provided for comparing the impurities profile of each batch reworked against batch manufacturers by the established process. Where analytical routine methods are inadequate to characterize the reworked batch, additional methods should be used. Reprodained 12. Introducing an intermediary or API, including one that does not conform to standards or specifications, back to the process and Do not repeat a crystallization step or other chemical or physical manipulation steps (e.g., distillation, filtering, chromatography, milling) that bearing in the established manufacturing process is generally considered acceptable. However, if these reprocessing is used for a majority of bundles, these reprocessing orders should be included as part of the standard manufacturing process. 13. The continuation of a step process after an in-process control test showed that the step is incomplete considered part of the normal process. This is not considered to be reprocessing. 14. Introducing unreacted material back into a process and repeating a chemical reaction is regarded as reaction unless it is part of the established process. Such reprocessing should be preceded by care evaluation to ensure that the quality of intermediate or API is not negatively affected due to the potential training of by-products and over-react material. 15. Documents should be available and approved by the QC Department. Section C.02.015 All fabric, wrapping/labelling, testing, storage, and transportation methods that can affect the quality of a drug must be examined and approved by the person in charge of the quality control department prior to application. Individuals charged by the quality control department must cause them to investigate any complaints or information that receives to respect the quality of a drug or its deficiencies or hazards and cause any necessary action to be taken, in the case where the complaint or information is related to an activity on which the department exercises quality control. 2.1 In the case where the complaint or information received is not related to an activity on which the type of control department exercises quality control, the person in charge of the department will send the complaint or information to the person in charge of the quality control department who exercises quality control over this activity. Those in charge of the quality control department must cause all tests or examinations required to run beyond this division to be conducted by a competent laboratory. Pharmaceutical processes and products must be designed and developers take the GMP's condition alone. Production production and other control operations are independently examined by the quality control department. Good storage, transportation, and distribution of materials and products minimize any risk to their quality. Complaints may indicate issues related to quality. By tracing their cause, one can determine what corrective measures should be taken to prevent recurrence. Having the tests carried out in a competent lab provides assurance that the test results are genuine and accurate. Written agreements for consultants should describe the education, training, and experience of the personnel and the type of service they provide, and should for exams and inspections. Written agreements for lab contracts should describe what type of service they provide and their compliance with GMPs and should be available for examination and inspection. Files in the contract activities should be maintained. Interpretation 1. Procedures should exist to notify responsible management in a timely manner of regulatory inspection, severe GMP deficiencies, product damages and related actions (e.g., quality complaint related, recall, regulatory action, etc.). 2. A formal change control system must be established to evaluate all changes that can affect the production and control of the API. 3. Written procedures should be provided for the identification, documentation, appropriate review, and approval of changes in previous material editing, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), process steps, label materials and wrapping, and computer software. 4. Any proposal for GMP relevant changes should be drafted, reviewed, and approved by appropriate organizational units, and reviewed and approved by the Quality Unit(s). 5. The potential impact of the proposed change on the API quality should be evaluated. A risk assessment can help to determine test levels, validation, and documentation required to justify changes to a validated process. Changes can be classified (e.g., as minor or larger) depending on the nature and cost of the changes, and the effects of the changes can be improved upon the process. Scientific judgments should determine what other tests and validation studies are appropriate to justify a change in a validated process. 5.1 The potential for critical changes affecting rest or expiration dates should be assessed. If necessary, samples of the modified API process can be placed on an accelerated stability program and/or you can add to the Stability Monitoring Program. 5.2 After the change has been applied, there should be an assessment of the initial batch produced or tested under the change.5.3 When you apply approval changes, measures should be taken to ensure that all documents affected by these changes are revised. 6. Actual dosage form manufacturers should be advised in changes to establish production and process control processes that can affect the quality of the API. 7. All facilities involved in the production, distribution and imports, including agents, brokers, re-packages and re-labellers should have a system in place of file and investigate all related complaints, whether received or orally or written, in accordance with written procedures. 7.1 If the situation is guaranteed, the agents, brokers, traders, distributors, re-packages, or re-labellers should review the complaint with the API's original fabric in order to determine whether any further actions, either with other customers who may receive this API or with authority, or neither both, should be initiated. The investigation of the cause for the complaint or recall must be conducted and be documented by the appropriate party.7.2 Where a complaint is referred to to the original API manufacturers, the file maintained by the agents, brokers, traders, distributors, re-packages, or re-labellers should include any response received from the original manufacturers of the API (including date and information provided). 8. Complaint records should be kept in order to assess trends, product-related frequency, and securities with a look at taking more, and if appropriate, immediate corrective action. All decisions and measures taken as a result of a complaint is recorded. 9. All specifications, sample plans, and test procedures should be scientifically sound and suitable to ensure that raw materials, APIs, and labels and packaging materials conform them to establishing standards of quality and/or purity. Specifications and testing procedures should be consistent with those included in the registration/filing. There may be specifications in addition to the people at the registration/filing. Specifications, sample plans, and testing procedures, including changes to them, should be draft by the appropriate organization unit and reviewed and approved by the quality unit(s). 10. Lab controls should be followed and documented at the time of performance. Any departure from the above procedures described should be documented and explained. 11. Laboratory control records should include complete data from all tests designed to ensure compliance with established specifications and standards, including examination and essis, as follows: 11.1 A description of the samples received for testing, including the material name or source, batch number or other different codes, took sample dates, and, where they were appropriate, the quantity and date of the sample were received for testing; 11.2 A declaration of or reference to each test method is used; 11.3 A declaration of the weight or measurement of the samples used for each test as described in the method; data on or cross-reference to the preparation and testing of reference standards, reagents and standard solutions; 11.4 A complete record of all shouts data generated during each test, in addition to graphs, charts, and pageants from laboratory instruments, properly identified to display the specific and batch tested material; 11.5 A file of all calculations consisted of connection with the test, including, for example, units of measurement, conversion factors, and equivalent factors; 11.6 A declaration of the test results and how they compare and establish acceptance criteria; 11.7 The Signature of the person who performed each test and the date(s) test is made; and 11.8 Date and signatures of a second one showing that original files were reviewed for accuracy, completeness, and compliance with established standards. 12. Reignment and standard solutions should be procedures that appeared after them. Use by date should be implemented as appropriate for reactive analytical or standard solutions and data should be available to support these expiration dates or Res.13. Tests should be conducted by a lab that meets all relevant GMP requirements. 13.1 Lab facilities are designed, equipped, and maintained to perform the necessary tests. 13.1.1 In the microbiology laboratory, the environmental monitoring should be conducted periodic. Microbiological cultures and test samples are handled in an environment that minimizes contamination. 13.1.2 The establishment used to perform the infertility test should comply with the microbe limits of an aseptic production facility that should conform to Class A to a Class A background or to an isolationist in a class A of with appropriate and limited access to non-essential personal. 13.2 The person in charge of the lab should meet personal requirements as set of C.02.006 and report to a person with such qualifications. 13.3 Personal lab should be enough to number and be eligible to carry out the work to undertake. 13.4 Control lab equipment and instruments should be additioned to the undertaking testing procedures. Equipment and files should be maintained as per the interpretations under C.02,005. 13.5 Computer systems are validated, and spreadsheets are eligible. 13.6 Water is used for microbial and analytical testing to meet the requirements of the test or ensure in which it is used. 13.7 All reactive and media cultures are recorded on receipts or preparations. Reactives made up of the lab are prepared according to written procedure and are properly labeled. 13.7.1 Prepare the sterilized media using validated and stored procedure under temperature controlled. 13.7.2 Prepare the well-marked media with the many numbers, expiration dates and identification media. The expiration date of media is supported by growth test results – promotions that show the media performance consistently meet acceptance criteria up to the expiration date of .13.7.3 Sterility and growth-promotion testing to make them verify the appropriateness of media culture. 13.7.4 All buyers ready to use received media are accompanied by a certificate of analysis and expiry date and recommended storage requirements as well as the quality control organisms used in growth-promotion and selection testing of the media. 13.7.4.1 The Procedures in place ensure that the media is transported under conditions that minimize the loss of humidity and monitor the temperature. 13.7.4.2 Media are stored according to the vendor's instructions. 13.7.4.3 Infertility and growth-promotion tests are done on many welcomes, unless the vendor is certified. Periodic confirmation testing is designed to be ready for media use received from each certified vendor. 13.7.4.4 The folders are maintained. 13.8 Standard references available in of current reference standards listed in Schedule B of the Food and Drug Act. When these standards have not been established or are available, main standards can be used. High standards are verified against a Standard Schedule B reference or against the main standard and are subject to confirmed testing at predetermined intervals. All reference standards are stored and used in a way that will not affect their quality. Records related to the tests, storage, and use are maintained. 13.9 Out of Specifications (OOS) test results the investigations to determine the cause of the OOS. 13.9.1 The procedures in place describe the steps to be taken as part of the investigation. 13.9.2 In the case of a laboratory clearly identified or statistical, the original results may be invalid, and the test is repeated. Original results should be retained with a recorded explanation. 13.9.3 When no laboratory is clearly identified or statistical statistics performed, the number of remainder to be performed on the original sample and/or a new sample, and the statistical treatment of the result data, are specified in advance of the procedure.13.9.4 All valid test results, both passed and suspicious, should be reported with regard to batch release decision. 13.9.5 If the original OOS result is found to be valid, a complete investigation, including the affected batch, performed and recorded. The investigation should be conducted in accordance to written procedures and should include an assessment of root cause, description of corrective action and preventive actions carried out with conclusions. 13.9.6 Out-of-specific investigations are not normally needed for in-process testing designed for the purpose of monitoring and/or adjusting the process. 14. Primary standard references should be found as suitable for the inventory of APIs. Sources of each primary reference standard should be documented. Files should be maintained in each primary reference repository and used in accordance with the provider's recommendations. Primary standard references found in an officially recognized source are normally used without testing if stored under conditions consistent with a provider's recommendations.15. Where a primary reference standard is not available to an officially recognized source, a main in-house standard must be established. They should perform proper testing for establishing fully identification and purity of the main reference standard. The appropriate documentation of this test should be maintained. 16. High reference standards should be suitable to prepare, identify, test, approve, and stored. The appropriateness of each batch of high reference standards should be determined before first use by comparing against a primary reference standard. Each batch of high reference standards should be periodically re-qualified agreement with a written protocol. 17. File modifications should also be kept for: 17.1 Any modification of an analytical method is established; 17.2 Periodic calibration of laboratory instruments, devices, measurements, and device recordings; 17.3 All stability tests performed on APIS; and august 17.4-of-specifications investigation. 18. Where critical data is entered in a computer system manually, there should be an additional check on the accuracy of the entry. This can be done by a second operator or by the system itself.19. Incidents related to computer systems that might affect the quality of APIs or the reliability of files or test results should be recorded and investigations. 20. Changes to the computer system should be made according to a change procedure and should be formally authorized, documented and tested. Files should be kept in all changes, including modifications and improvements made to the hardware, software and any other critical components of the system. These files should demonstrate that the system is retained in a validated state. 21. All deviations, investigation, and OOS reports should be reviewed as part of the batch file review before the batch is released. 22. To ensure compliance to contractors performing necessary tests under Part C, Division 2 of Food and Drug Regulation: 22.1 A Canadian contract laboratory must have a valuable license to valid current establishments. A foreign test site must be listed on a Canadian establishment license, as described in the Health Canada Policy document entitled proofs for Demonstrator Crackdowns Compliance at foreign sites (GUI-0080), 22.2 All external testing arrangements in accordance with current regulatory deposits for the API are concerned if applicable, including the intermediary test , raw materials, wrapping materials and all other tests required by Part C , Division 2 of the Food and Drug Regulations, and 22.3 There is a written agreement covering all activities of testing between the contract lab and the parties involved. The agreement specifies the respective responsibilities related to all aspects of testing. 22.3.1 Technical aspects of the agreement are mapped by qualified personnel following the knowledge of analysis and GMP, 22.3.2 The Agreement allows auditing of the facilities and operations of the external laboratory, 22.3.3 The agreement is clearly described, as a minimum, responsible for: 22.3.3.1 collection, transport and storage requirements of previous test samples, 22.3.3.2 maintaining stability of predetermined temperatures and humidity , if applicable, 22.3.3.3 test methods must be used, limitations and validation test methods, and 22.3.3.4 withdrawal of analytical results and support documents (additional guidance under the interpretation of C.02.021). 22.3.4 No subtraction of any work should occur without written authorization. 23. The Manufacturers Should Ensure That accept (contractor) for transportation in the API to know and track appropriate transportation and storage requirements. Material wrapping Section C.02.016 Each or batch of wrapping material must, prior to its use of the wrapping of a drug, be examined or tested against the specifications for this wrapping material. There is not much or batch of packaging material to be used in the wrapping of a drug unless the lot or batch of packaging material conforms to the specifications for this packaging material. The specifications referred to in subsection (1) and (2) will be in writing; be acceptable to the Director who shall take into account the specifications of any publication mentioned in Schedule B of the Act; and shall be approved by the person in charge of the quality control department. Section C.02.017 The Test or referred tests in section C.02.016 must be performed on a sample taken: after receiving in each or batch of wrapping material on the premises of those who pack a drug; or subject to subsection (2), before receiving every lot or batch of packet material on the premises of the person who packs a drug, if this person has proof satisfaction to the Director to display his selling wrapping material by vendors that are very much or batch of batch packet material are still manufactured in accordance with and always comply with the specifications for these packaging materials; and to undertake full examination periodic examinations or tests with a frequency satisfaction of the Director, the wrapping material was not transported or stored in conditions that may affect its compliance and specifications for packaging material. After a lot or batch of packaging materials received on the premises of the person who pack a drug, the lot or batch of the wrapping material must be examined or tested for identity; labels will examine or test them to ensure they comply with specifications for these labels. The appropriate rationale of APIS for subsequent usage depends not only on the production process, but also on the protection of the API from the contamination or degradation prior to use. Care should be taken to the choice of container, and, as the filling of rigorous APIs is often a dust operation, how this full and lock will affect the quality. Wrapping materials are required to test or examine prior to their use in a wrapping operation to ensure that materials of acceptable quality are used in the wrapping of APIS. The inner wrapping should be controlled by the facility related to identity and traceability. Labelling, storage, and distribution contribute materials to final construction for use in the manufacture of medical products. Regulation C.02.017 option plan such as when testing or examination prescribed by Regulation C.02.016 is carried out. Same as raw materials, purchase material is an important operation involving personnel with proper knowledge of the wrapping materials and suppliers. Original wrapping material only from suppliers is named to the relevant specifications. It is to benefit that all aspects of the production and control of packaging materials must be discussed between the fabric and the supplier. Particular attention is paid to printed packaging materials; labels are examined or tested after receiving on the local person who packs an API. Interpretation 1. There should be written procedures describing the receipt, identification, quarantine, samples, examination and/or testing and release, and handling of wrapping and exchange materials. 2. Each wrapping material used in the wrapping/label of an API should be covered by specifications (as defined under C.02.002) approved and according to the person who charged the department of quality control or by a designated alternative that meets the requirements described under Regulation C.02.006, interpretation 1.4. 2.1 Where applicable, the specifications should be in pharmacopeial or equivalent status, and should be in compliance with the approved specifications of the marketing authorization for the drug in the form of dose.2 Adequate to test or examination method that is not of pharmacopeial or equivalent status should be established and documented. 2.3 The use of recycle or reproduce main wrapping components should be allowed only after a full assessment of risks involved, including any possible erased effects on product integrity. Specific provisions should be made for such a situation within the specifications. These 2.4 Containers should not be reactivated, additives, or absorptive so as to change the quality of the API beyond the specified limits. 2.5 Any wrapping material of direct contact with the API should be at minimum of food quality. 3. Samples should take place in an appropriate environment with caution to prevent contamination, where necessary. 4. Positive identification of all wrapping materials, along with examination of all labels and other printed packet material should be made after the receipts on the premises of the Person Package API. 4.1 Master labels should be maintained for the given label comparison. 5. Packing and label material should conform to established specifications. Those who do not comply with these specification should be rejected to prevent their use of operations for which they are insuitable. 6. Only packaging material released by the quality control department should be used in packaging/labels. 7. Containers should provide adequate protection against the deterioration or contamination API that can occur during transport and recommend storage. 8. Containers should be clean and, where indicated by the nature of the API, sanitize to ensure that they are suitable for the use of their intentions. 9. Exceed or obsolete the materials should be adequately identified and segregation until its disposition. 10. The test or examination of the wrapping material should be performed on a sample taken after receiving them on premises of the person who packages the drug unless the vendor is certified. A vendor wrapping vendor's certification program, if employers, should be documented in a standard operating procedure. Vendor approval 10.1 should include a written assessment that provides adequate evidence (e.g., past quality history or evidence of a quality system) that the fabricator can still provide material meeting specifications. Configuratory tests should be conducted on at least three batch before reducing in-house testing. However, as a minimum test, configuratory should be conducted at proper intervals, at least a lot per year, and compared with their Certificate of Analysis. Reliability of Certificates of Analysis should be checked at regular intervals. Finished Product Test Section C.02.018 Every lot or batch of a drug must be, before it was made available for further use of fabric or for sale, must test against the specifications for that drug. There is not much or batch of a drug to be available for more use in fabric or for sale unless it complys with their specifications for that drug. The specifications referred to in subsection (1) and (2) will be in writing; be approved by the person in charge of the quality control department; and comply with these Acts and Regulations. Rational testing on the API complementary controls the employees during the manufacturing process. It is the responsibility of each fabric, package/labeller, distributor and import to have adequate specifications, test methods and/or evidence that will help ensure that each drug sold is safe and meet the standard under which it is represented. Interpretation 1. For each batch of API, the appropriate lab tests should be designed to determine the comforts of specifications. 2. All specifications, sample plans, and testing procedures should be scientifically sound and appropriate to ensure that APIs conform to establishing standards of quality and/or purity. Specifications and testing procedures should be consistent with those included in the registration/filing. There may be specifications in addition to the people at the registration/filing. Specifications, sample plans, and testing procedures, including changes to them, should be documented and approved by the appropriate organization unit and reviewed and approved by the quality unit(s). 2.1 Specifications should be equal to or exceed a standard recognized as listed in Schedule B of the Food and Drug Act and should be in compliance with the specifications. 2.2 Where a recognized pharmacy (Schedule B of the Food and Drug Act) contains a specification for microbe content, which is included condition. 3. Appropriate specifications should be established for APIs in accordance with accepted standards consistent with the manufacturing process. Specifications should include a control of the impurities (e.g. organic impurities, inorganic impurities, and residual solvents). If the API contains a specification for microbiological purity, the appropriate action limitations for total microbe count and objectional organisms should be established and met. If the API contains a specifications for endotoxins, the appropriate action limitations should be established and satisfied. 4. Analytical methods should be validated unless the hiring method is included in the relevant pharmacopoeia or other recognized standard references. The proper use of all test methods used should however be verified under current conditions of use and documenting. 5. Methods should be validated to include consideration of features included in publications such as the ICH document entitled ICH Q3 (R1): Validation of Analytics Procedures: Text and Methodology. The analytical validation degree performed should reflect the purpose of the analysis and the scene in the API production process. 6. All tests are conducted according to approved specifications. These tests can be carried out in the canvas or by laboratory contract tests when a written contract specifies the responsibility of each party. 7. An inpiratory profile that describes identifying and identifying the impurities present in a typical batch generated by a specific controller production process should normally be established for each API. The impurity profile should include the identity or some designation analytical qualitative analytic (e.g. resentment time), the range of each observed inpiration, and the classification of each impurity identified (e.g. inorganic, organic, solvent). The impurity profile is normally depending on the production process and origin of the API. Inspiration profiles are normally not necessary for APIs from herbal or tissue animals. consideration of the biotechnology covered in ICH Q6B Guide. 8. The impurity profile should be compared to the appropriate interval against the impurities profile of the regulatory submission or compare against historical data in order to detect changes in API resulting from modification of raw materials, supply operating parameters, or the production process. 9. Information about the API's name including its proper class location, the batch number, and the date of release should be provided on the Certificate of Analysis (CoA). For APIs with an expiration date, they should provide the expiration date on the label and CoA. For APIs with an unused date, they should indicate the unused date should be indicated on the label and/or CoA. 10. Native Koas should be provided for each batch of API. 11. The CoA should list each test conducted in accordance with competent or customer requirements, including the acceptance limitations, and the numerical results obtained (if the test results are numerical). 12. Certificate analysis should be date and signed by authorized personnel of the quality and should show the name, address and phone number of the original fabric. Where the analysis was carried out in a repackager or reprodained, the CoA should display the name, address and phone number of repackager/reprocessor with a reference to the name of the original fabric. 13. If new certificates are issued at or on behalf of repackagers/reprocessorse, agents or brokers, these certificates should display the name, address and phone number of the lab that performs the analysis. They should also contain a reference to the name and address of the original canvas and of the original batch certificate, a copy that should be attached. 14. Any lot or batch of an API that does not comply with specifications should be quarantine pending final affinity, investigated and documented according to a procedure, and have not been made available for sale. Section C.02.019 A package / labeller of a drug, a distributor referred to in paragraph C.01A.003(b) and an import of a drug other than an active ingredient must test the product completion on a sample of the drug that takes either after receiving every lot or batch of the drug on the premises of Canada; or prior to receiving every lot or batch of the drug on premises in Canada if the following conditions are satisfied: the package/labeller, distributor or import have satisfaction proof of the Director demonstrates that drugs sold by the vendor in which many or batch are still manufactured in accordance with consistently complying with the specifications for these medications, and undertake comprehensive periodic testing, with a frequency satisfaction of the Principal, and the drug has not been transported or stored under conditions that can affect its compliance with the specifications for that drug. If the package/labeller, distributor or import receives a lot or bundles of a drug on premises in Canada the useful life of which is more than 30 days, the batch or batch will be tested for identities and the package/labeller will confirm the identity after many or batch is packaged/hell. Subsection (1) and (2) do not apply to a distributor if the drug is manufactured, package/marked and tested in Canada by someone holding an establishment license authorized that activity. Sources (1) and (2) do not apply to a distributor or import whether the drug is manufactured, package/marked and tested in an MRA country in a recognised building and both of the following conditions are met: the address of the building is laid out in their establishment license; and keep a copy of the batch certificate for every lot or batch of medications they receive. The Rationale C.02.019 design requirements and exemption such as when the product is complete (API) testing is to be done. Paragraph C.02.019(1)(b) condition description that must be met if the test ends perform before receiving premises in the drug. Interpretation 1. Positive identification of every lot or batch of a shipment in which the API should be carried out on a sample taken after wrapping. 2. Each lot should be accompanied by a native CoA or by a copy therein (an electronic copy and an electronic signature is acceptable). The CoA should expose actual numeric results and make references to the product specifications and test methods used; 3 Evidence should be available to demonstrate that every lot or batch receive has been transported and stored in a way that maintains the quality of the API. Further conditions are described in GUI-0069. Record Section C.02.020 Each fabric, package/labeller, distributor referred to in paragraph C.01A.003(b) and import will keep all these files on premises in Canada for each drug that they are fabric, package/ label, distributed or imported: Except in the case of an import of an active pharmaceutical ingredient, master production document for the drug; evidence that every lot or batch of the drug was manufactured, package/labelled, tested and stored in accordance with the procedures described in the master production documents; proof that the conditions under which the drug was manufactured, pack/marked, tested and stored are in compliance with the conditions of this Division; evidence that establishes the period during which the drug in the container in which it is sold or made available for further use of fabric will satisfy the specifications for that drug; and evidence that the product testing finished referred to in section C.02.018 was carried out, and the results of this test. Each distributor referred to in paragraph C.01A.003(b) and import will be made available to the Director, on request, the results of testing done on raw materials and packaging materials/labels for every lot or batch of drugs that he distributed or imported. Each manufacturer will hold on premises written for all raw materials and proper evidence of the testing of these materials before all corrections referred to in section C.02.009 and in the test results. Each person who packs a drug must be kept on premises written for all wrapping materials and adequate evidence of the test or testing these materials referred to in section C.02.016 and in any test result. Each fabricator, package/labeller and test must be kept on premises of plan Canada detailed with specifications of each building in Canada where to pack fabric/labels or test drugs with a description of design and construction of these buildings. Each manufacturer, packet/labeller and test must be kept on the premises of Personal Canada in respect of each person employing the fabric supervisor, packing/labelling and testing of drugs, including the person's title, responsibility, qualifications, experience and training. Section C.02.021 All with evidence on the fabric, wrapping/label, finished product test referred to in section C.02.018 and the deposit of a drug in the form of doses required to be maintained under this Division must be retained for one year after the drug's expiration date unless establishment licenses the person has specific other periods. Subject to subsection (4), all files and evidence in the fabric, Packaging/labelling, Testing product finished referred to in section C.02.018 and the storage of an active ingredient that is required to be kept under this Division must be kept in respect of each other or batch of active ingredients for after these periods unless the person maintains a specified facility license some other period: in the case of an active ingredient that has a remaining date, three years after the lot or bunch was fully distributed; and in any other case, a year after the expiration date of many or bundles. Subject to source (4), all records and evidence of material testing material are referred to in section C.02.009 and in the test of packaging material/labelling is required to be kept under this Say The slice will be retained for five years after the raw materials and packaging material/labels are used in the fabric or wrapping/labelling of a drug unless establishment licenses of the person in almost some other period. If a manufacturer is required to keep records and evidence of respecting the same active ingredient under Under Sections (2) and (3), they will be retained for longer periods that are applicable. Section C.022.022 All wholesaler, distributors referred to in C.01A.003 and imported into a drug in dose form will retain records of the sale of each or batch of the drug, allowing them to remember the lot or batch of the market, for one year after the expiration date of many or batch, unless establishment licenses are specific some other period. Each distributor of an active ingredient referred to in paragraph C.01A.003(A) and all engineers and import of an active ingredient will retain records of retail in every lot or batch of the active ingredient, allowing to remember the lot or batch from the market, for this period unless the person maintains and establishment licenses that specify some other period: in the case an active ingredient that has an unused date, three years after many or batch has fully distributed; or in any other case, a year after the expiration date of many or bundles. Section C.022.023 Upon receiving a complaint or any information that respects the quality of a drug or its deficit or danger, each fabric, package/labeller, institutional, distributor referred to in paragraph C.01A.003 and import of the drug must make a record of the complaint or information containing the following: the results of any investigations carried out by subsection C.02.015(2) and if applicable, actions taken; or name and address of the person's business in charge of the quality control department to whom the complaint or information was sent under subsection C.02.015 (2.1) and the date on which it was sent. Records referred to in subsection (1) must be retained for this period unless the person holds an establishment license specifying some other period: in the case of a drug in dose form, one year after the expiry date of the lot or batch of the drug; and in the case of an active ingredient, if the active ingredient has a stay date, three years after the lot or batch has fully distributed, or in any other case, one year after the expiration date of many or the batch of the active ingredient. Section C.02.024 Each fabric, package/labeller, distributor referred to in section C.01A.003, import and wholesaler will keep the files in the results of the self-inspection program required by section C.02.012 and in any action taken in connection with this program; and keep these records for at least three years. Each person's fabric or package/label a drug must keep files on the program operation sanitation required to apply under section C.02.007; and keep these records for at least three years. Section C.02.024.1 Each distributor of an active ingredient is referred to in paragraph C.01A.003(a) and each fabric, package/labeller, wholesaler and import of an active ingredient must add all of this information to the document that accompanied the active ingredient, immediately after any information such as which was added by another person: their establishment license number, or if none, their name, address, phone number, fax number and email address; an indication if they were manufactured, pack/bend, bulk, distributed or imported the active ingredient with the date that the activity was carried out; the expiration date; and the number a lot. Proper rationale documentation is an essential part of the quality assurance system and should therefore be applied to all aspects of GMP. Its objectives are to define the specifications for all materials and methods of fabric, packaging/labelling, and control; ensure that the quality control department has all the information necessary to make a decision as to whether a batch of an API should be released for sale; and providing a control trail that will allow for thorough investigations into the history of any batch suspected to be defective. Evidence that APIs have been manufactured, package/labelled, tested, and stored under prescribed conditions can be kept only after developing adequate file system. This evidence and related information should provide assurance that imported APIs are manufactured with packages/marked in a manner that is like those produced in Canada. Interpretation 1. Any documents that require evaluation Canada must be awarded in one of the official languages. 2. Fabricator, packages/labellers, tests, importers, distributors, and wholesalers are responsible for obtaining all types or regulatory information, as applicable, related to the production APIs of any part that provides services such as, but not limited to, agent, broker, distributor, repackages, or relabel. 3. For all sections of these Good Manufacturing Practice Guidelines for APIs, standard operating procedures (SOPs) should be established and kept for reference and inspection. These SOPs should be regularly reviewed and kept up to date by qualified personnel. The reasons for any review should be documented and a system should be in place to ensure that only current SOPs are in use. 3.1 The question, review, supervisor and retreat of all documents should be monitored and maintenance of review history. The 3.2 SOPs should be reviewed, approved, signed, and dated by the quality control department. 3.3 SOPs would not change without the approval of the quality control department. 3.4 The retention period of documents should be specified in applicable SOPs. For example, the types of documents that need retention are development history reports, scale-up reports, technical transfer reports, process validation reports, training files, output files, control files, and distribution files. 4. Specifications, instructions, procedures, and files can be kept either as original or as true copies such as photocopy, microphile, microfil, or other accurate reproduction of the original files. The above can also be maintained in electronic format provided that backup copies are also maintained and that the electronic files are easily retrieveables in a printed format. During the retention period, these files should be secured and easily available by the manufacturer, package/labeller, or imported within 48 hours of inspector's request. Files that can be promptly retrieved from another location by electronic or other average are acceptable. 4.1 Factory and laboratory files should be kept at the site where the activity occurs and must be easily available. 5. Where is an electronic system to create, modify or store records are required to keep under These Rules, the system should be qualified and tested for security, validity, and reliability, and records of such qualifications and tests should be retained. 5.1 An electronic signature is an acceptable alternative to a handwritten signature as long as it is authentic and secure. The validation of electronic identification systems should be documented. 6. A change in a document should be signed with date; the change should allow the reading of the original information. Where appropriate, the reason for the change should be recorded. 7. Fabricators and packages/labellers of APIs should keep proof that the conditions That the API was manufactured, pack/bedspread, tested, and stored should be in compliance with the requirements of Part C, Division 2 of the Food and Drug Regulations. All these records should be kept for (a) in the case of an API containing an unused date, three years after the lot or batch was fully distributed; and (B) in any other case, one year after the expiration date of the lot or batch. 7.1 Detailed plans and specifications in each building in Canada where fabric, wrapping/labelling or testing occurred, including a description of the design and construction of these buildings, should be maintained in the premises of the facility where the activity API occurred. These files should be retained for a period of at least one year past the expiration date of the API to which the files apply. 7.2 This evidence includes files produced under subsection C.02.012(2) and evidence that manufacturing and wrapping processes and analytical methods are validated.. 7.3 In case where the equipment works, the files of cleaning, calibration, maintenance, and use can be part of the batch or file kept separately. 7.4 Files of calibration equipment should be maintained on premises. 7.5 Record of respect of each employee to oversee the fabric, packaging/moon, and testing of APIs, including organization charts; each person, job description, responsibility, qualifications, experience, and training; and the name(s) of alternating each person's designated(s). 7.6 records should be kept detailed of the name, address, qualifications/experience of any consultant staff for GMP purposes, along with the services that each consultant provides. 7.7 Record on the operation of the sanitation program. 7.8 Batch output and lab control records at critical processing steps should be reviewed and approved by the Quality Unit(s) before a Batch API is released or distributed. Production and lab control records in non-critical processing steps may be reviewed by qualified production personnel or other units after these procedures are approved by the quality unit(s). 7.9 Record of the program self-inspection including the assessment, conclusion, and corrective measures applied. 7.10 Evidence establishes the period of time during which the API of the container in which it is sold or made available for further use of fabric should meet the specifications for that API. 7.10.1 The documentation should be maintained should include the written stability program, the data produced in accordance with this program, and the conclusions leading to the establishment of the period of time during which each API in the package in which it is sold compliant with the specifications so that API. 7.11 Record of storage conditions for material (e.g. controlling temperature and humidity when necessary). 8. Proof that every lot or batch of the API has been manufactured, package/marked, and stored in accordance with the procedures described in master production documents. This evidence should include the following: 8.1 Write procedures followed for the review and approval of batch production and laboratory control files, including wrapping and labels, determined compliance of the API and established specifications before a batch release or distribute. 8.2 Record Factory, wrapping files, test method, and test results for raw material, packaging material, and APIs. 8.3 When the API is manufactured or package outside of Canada / locates in the import, the files should be easily available by the import within 48 hours, on Canada's health request. 9. These documents should be retained by the manufacturer, package/labeller, wholesaler (agent, broker, traders and any other part provided services), distributors referred to in paragraph C.01A.003(a) and imported into an API as they relate to all operations in Canada. These records would be retained for a period, in case of an API containing an unused date, three years after the lot or batch was fully distributed or in any other case, one year after the expiration date of the lot or batch. 9.1 Distribution files of all sales in an API. 9.1.1 Record of all sales in every lot or batch of the API should be retained or kept easily accessible in a way that will allow a complete and quick reminder of any lot or batch of the API. 9.1.2 The records indicate that all customers who received a recalled API were notified. 9.1.3 Record of returned APIs should be maintained. For each return, the documents should include: the name and address of the design; API, many or batch numbers, and return quantity; reason to return; and use or disposition the API is returned. 9.2 File complaints or any information received orally or in writing the quality of an API or its deficiencies or hazards, and in subsequent investigation of complaints, including corrective actions taken. 9.2.1 The complaint files should include the following information: name and address of the complaint (if available); the name and phone number of the person submitting the complaint (if available); nature of the complaint (including the name and batch number of the API); the date of the complaint received; action is initially taken (including the date and identity of the person taking the action); actions taken, if any; the answer was provided for the complaint, where possible (including the date in which the response was sent); and the final decision on the batch API or many. 10. These documents should be maintained by the fabric and package/labeller on premises and maintain for a period of at least five years after the materials used in the fabric or wrapping/scaler of the API, unless the person's establishment license specifies some other period. 10.1 The Writing for the materials. 10.2 Adequate evidence of the receipt and source of each shipment of material for the manufacture of APIS. They should include the following information: the manufacturer's name, the date of receipt and the received number on receipt; identification and number of each shipment in each batch; the name of the provider; and the provider control number(s), whether known, or other identification numbers. 10.3 Evidence adequate to the test, or examination of such material as per section C.02.009 and C.02.016 and the results of this test. The following information should include: documentation of the examination and/or test of material for compliance with establishing specifications and conclusions from this; the final decision as to whether they accepted the baskets or were rejected; and trace files used in materials. 10.3.1 Lab Records should be maintained. 11. These documents should be maintained by the canvas, and/or package/labeller, in an API. All these records should be kept for (a) in the case of an API containing an unused date, three years after the lot or batch was fully distributed; and (B) in any other case, one year after the expiration date of the lot or batch. 11.1 Master output documentation per API. The master production documents should be signed and dated by a qualified person and then irrespectively checked, dated, and signed by someone in the quality unit. These documents should include the following information: the manufacturer's name API and an identifiable document reference code, if applicable; The list of raw materials is used and designated by names or specific sufficient codes to identify any special quality features; The correct amount and a unit of measure or report of each material before all editing is used. Where the quantity is not fixed, the calculation for each batch size or percentage of output should be included. Variations in quantity should include locations to justify; The location of production and greater production equipment is used; The detailed production instructions, including the tracking sequence, the process parameter chain to use, sample instructions and in-process control and their acceptance criteria, appropriate locations, time limits for completion of individual processing steps and/or the total process, appropriate location, and expected yield ranges in the appropriate phases of process or time; Where it's appropriate, any special notation and precautions are followed, or cross-reference to those, and the instructions for storage in the API ensure its suitable for use, including the clown and wrapping materials with special storage requirements and limit times, appropriate locations. 12. Packages/ labellers, importing, agents, brokers, traders, distributors, wholesalers should maintain complete traceability of the APIs that they distribute. Documents that should be retained and available include: 12.1 Identity Name original fabric with package / labeller; 12.2 Address of original fabric with package / labeller; 12.4 invoices to terminate (transportation document); 12.6 Name or designation of the API or intermediate; 12.7 The fabricator or package / labeller to number; 12.8 Transport and distribution files; 12.9 All Native Certificates of Analysis, including those of the original fabric; 12.10 Unused or expiration date. 13. The Manufacturer, package/labeller, wholesaler, distributors referred to paragraph C.01A.003(a), import of an API, including any part other than the original fabric that can trade and/or take possession, repackage, re-label, manipulation, or store an API, they should add the following information to the document that accompanied the API: 13.1 License Number Facility; if the facility does not have a license establishment, they should add their names, addresses, phone numbers, fax numbers and email addresses; 13.2 The activity including fabric, packaging/labeling, bulk, distribution or importation and the date that the activity occurred; 13.3 The expiration date and/or break date; and 13.4 quantity of the API. Sample SectionC.025 Each distributor referred to in paragraph C.01A.003(b) and imported into a drug form must be kept in Canada A sample in every lot or batch of the drug packet/marked for one year after the drug's expiration date unless establishment licenses are specific some other period. The source subject (4), the manufacturer of a drug in dose form will hold a sample of every lot or batch of raw material used in three years after the materials were last used in the fabric unless establishment licenses are specific some other period. Subject to source (4), the fabric of an active ingredient will hold a sample of every lot or batch of it for that period, unless license facilities specify some other period: in the case of an active ingredient that has a remaining date, three years after the lot or batch has been completely distributed; or in any other case, a year after the expiration date of many or bundles. If a manufacturer is required to hold samples of respect to the same active ingredient under Sub-section (2) and (3), they will be retained for longer periods that are applicable. Section C.02.026 Samples referred to in section C.02.025 must be of a sufficient amount to determine whether the drug or raw materials are corrected and their specifications for material or raw correction. These rational requirements help ensure that officials responsible in fabric, establishments and in Health Canada are ready for these samples that are essential for re-examination should a product quality concern arise. Interpretation 1. A sample of representatives must be taken for the purpose of performing a res.2. Wrapping there and keeping samples holding is for the of potential assessments of the quality of the batch of APIS and not for future stability reasons. 3. Appropriately identifying holding samples in each batch the API should be retained by the fabric of an API for one year after the expiration date of the batch, or for three years after distribution in the batch, regardless of the longer. For APIs and unused dates, similar hold samples should be retained for three years after the batch is fully distributed by the canvas. 3.1 Samples of resumption may be stored at another site published in a written agreement explicitly describes the responsibilities of each party. 4. The retention sample should be stored in the same wrapping system in which the API is stored or in one that is equivalent to or more protection than the branded wrapping system. Sufficient amounts should be maintained to perform at least two complete scans or, when there is no pharmacopoeial monography, two specific analyses complete. 5. The sample should be stored under the indicated conditions on the label. 6. Sample retention should be retained in accordance with a written procedure. Sample duties can be stored at another site that pursued a written agreement explicitly describes the responsibility of each party. Stability SectionC.02.027 Each distributor refers to paragraph C.01A.003(b) and import of a form drug will establish the period during which each drug in the package where it is sold will comply with the specifications for that drug. Each fabricator and import of an active ingredient will establish the period during which each drug in the package in which it is sold will comply with the specifications for that drug. Streamline program purpose of writing stability is to ascend against the expiration date or rest of an API, therefore to determine how long the APIs can be expected to remain in specifications under recommended storage requirements. The expiration date or rest for an API should be based on stability studies that are well-performed. The requirements for the stability studies are described in the Various Health Canadas, and ICH Guide. Interpretation 1. When an intermediary has the intermediary to be transferred outside the control of the fabricator's material management system with an expiration date or rest assigned, supporting stability information should be available (such as published data, test results). 2. An expiration API or rest of the dates should be based on an assessment of data from stability studies. Common practice is to use an unused date, not an expiration date. 3. Preliminary API expires or rest of the dates can be based on batch scale pilot if (1) batch are pilots employing a method of manufacture and procedure that simulates the final processing to be used on a commercial manufacturing scale; and (2) The quality of the API representing the material to be made on a commercial scale. 3.1 Accelerated stability data are considered preliminary Only. The accelerated data are supported by long-term tests. When the shelf-life is assigned based on accelerated data and extraordinary data long term, it should be verified by additional long term data as such data becomes available. 4. Stability samples should be stored in containers that simulate the market. For example, if the API is highlighted in bags of drum fiber, stability samples can pack in bags in the same bags and in smaller-scale drums of similar or identical material composition to the walking drum. 4.1 Stability justifies assigned expiration or unused dates should be performed if the API is repackage of a different type of container used by the fabrikator API. 5. Normally the first three commercial production plates should be placed on stability monitoring program to confirm the rest or expiration date. However, where data from previous studies showed that the API is expected to remain stable for at least two years, less than three batch can be used. 6. For imported products, stability studies from foreign sites are acceptable given that the data meets the requirements of various Canada and ICH guidelines regarding stability and which the site can demonstrate GMP compliance. 7. Where appropriate, the stability deposit requirements should be consistent with the ICH guidelines on stability. 8. Analytical test procedures used in stability assessments are validated in accordance with the Entitled ICH document, ICH Q2(R1): Validation of Analytical Procedures: Text and Methodology. The assay must be stability-indicating, (e.g., sufficiently specific to detect and quantify product degradation and distinguish between degraded and non-degraded materials). Limits for specifying individual, inspectors, and product total degradation are included. SectionC.02.028 Each distributor refers to paragraph C.01A.003(b) and imported into a form drug will be controlled, by means of an ongoing program, stability of the drug in the package in which it is sold. Each fabricator and import of an active ingredient will be controlled, by means of a continuing program, the stability of the drug in the package where it is sold. Streamline the program aims to write continuous stability is to control the validity of the API expiration or restoring date on an on-going basis. Interpretation 1. Stability samples should be stored in containers that simulate the market. For example, if the API is highlighted in bags of drum fiber, stability samples can pack in bags in the same bags and in smaller-scale drums of similar or identical material composition to the walking drum. 2. A documented, on-going test program should be designed to monitor the stability features of

APIs, and results should be used to confirm appropriate storage requirements and rest or expiration dates. 3. At least one batch per year in Manufacturing API (unless none products that year) should be added to the stability monitoring program and tested at least every year confirming the stability.4. For APIs and short-life shelves, tests should be done more frequently. For example, for those APIs that rack life in a year or less, stability samples should be found and should be tested monthly for the first three months and at three months intervals after that. When data exists that confirm that stability in the API is not compromised, elimination of specific test intervals (e.g. 9 months testing) can be considered.) 5 Appropriate places, stability deposit requirements should be consistent with the ICH guidelines on stability. 6. Any difference in the protocol for the program of continuous stability and the protocol for the formal stability studies should be scientifically justified. 7. Worst situations might be addressed by the ongoing stability program (e.g., inclusion of rework or reproduce a lot). 8. Any confirmed from specifications results or significant negative trends that may have an impact on the quality of the API should be evaluated and may require further stability studies. 9. For importing APIS, stability from foreign sites is acceptable, provided that the data meets the requirements of various Canada and ICH guidelines regarding stability and which the site can demonstrate GMP compliance. It should be the import responsibility obtained and kept up to date records associated with the ongoing stability program. Sterile Product SectionC.02.029 In addition to the other requirements in this Division, a drug intended to be sterile to be manufactured with packages/marked in separate and closed areas; under the supervision of trained personnel in microbiology; and not a scientifically proven method to ensure infertility. This guide applies to the inventory of sterile APIs only up to the point immediately before the API is rendered sterile. Sterilization and the aseptic process of sterile APIs are not covered by this council, but should be in accordance with Good Manufacturing Practice Guide, Edition 2009, Version 2 (GUI-0001). Medical Gas SectionC.02.030 This Guide does not apply to medical fuel. The guideline regarding the fabric, packaging, labeling, testing, distribution, and importation of medical gas is described in the Good Medical Manufacturing Guidelines for Medical Gas (GUI-0031). Appendix Acronyms AI Active Ingredients API Active Pharmaceutiical Din Drug Identification Number GMP Good Manifak Practising Products Health HPFB and Food Branch ICH International Conference on Harmonisation ICH Q7 Good Manufacturers Practice Guide Active Pharmaceutiical Ingredient Q7 MPD Master Production Document NoC Notice Compliance OOS from The Specification PIC/S Pharmaceutiical Inspection Cooperation/Scheme who appendix Appendix Blocks Glose of TheMes definitions apply to the terms used in these directions; they also apply to the terms used in their annex unless otherwise specified therein. Definition quoted two other documents are identified in parentheses at the end of definition. Accept criteria (criticize acceptance) – numerical limitations, ranges, or other appropriate measures to accept test results. (ICH Q7) Active Ingredient (active residues) – Means a drug that, when used as a raw material in the fabric of a drug form in doses, gives its intent effect. (Division 1A, Part C, Food and Drug Policy) Active Pharmaceutical Ingredient (active pharmaceutical reseller) – Means an active ingredient used in the fabric of a pharmaceutical. (Division 1A, Part C, Food and Drug Policy) Alternative Sample Resupply (ASR) Sites (alternative sites for draining sample profiles of drills) – An alternately specified site on a Drugs Standards License for storage of pursuant samples in section C.025(1) of the Food Regulations and Drug Regulations. (gui-0001) API Establishment License (license establishments poured less IPA) – A license to a person in Canada to license ac to a building has been inspected and assessed as being in compliance with Requirement 2 of the Food and Drug Regulations. API Starting Material (Produced from disappearance of empower IPA) – A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structure fragment in the structure of the API. A Materials API starts may be an item of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or in-house products. API Starts Materials are normally in defining chemical properties and structures. (ICH Q7) Batch (or Other) (your many fabrics) – A specific number of materials generated through a process or series of processing so that it is expected to be homogeneous to specified limitations. In the case of continuous output, a batch can match a fraction defined in the output. The batch size can be defined either by a fixed amount or by the amount generated at a fixed time interval. (ICH Q7) Batch number (number of fabrics) – A unique combination of numbers, letters, and/or symbols that identify a batch (or many) and from which the output and distribution history can be determined. (ICH Q7) Bioburden (Charge microbienne) – The level and type (as objection or not) of microorganisms that may be present in raw materials, API starts materials, intermediate or APIS. Bioburden should not be considered as contamination unless levels were exceeded or defined organisms objected to being detected. (ICH Q7) Biological drugs (biological drugs) – A drug listed in Schedule D of Food and Drugs Act. Bulk APIS (IPAs bulk vrac) - An API that is not in its final shipping configuration. Intermediate intermediate processes (product en vrac) – Means an active ingredient used in the fabric of either a drug of biological origin listed in Schedule C or a drug listed in Schedule D for the Law. (Division 1A, Part C, Food Regulation and Drug) Calibration (pace) – The demonstration that a particular instrument or device produces results of limitations specified by comparison with those produced by a reference or trackable standard on an appropriate set of measures. (ICH Q7) Campaign Production (consecutive production) – Sequential Processing of Materials, either more than a product of a multi-product facility or more than a lot of the same product in a dedicated facility, over a defined period of time. Campaign production could reach any point in a production process where common rooms/suite and/or equipment are reused for multiple/many products. (gui-0001) Certificate of Analysis (CoA) (d'analytical certificate) – A document containing the name and address of the laboratory to perform the test(s), name and specifications of the material(s), test(s) done, test method(s) used, actual numerical results, approval date(s), approved signature, and any other technical information deemed necessary for its appropriate use. (gui-0001) Manufactured Certificates (certificate of fabric) – A document provided by a vendor to a distributor or import manifest that a specific lot or batch of drugs generated in accordance with its master production documents. These certificates include a detailed summary of current batch documents, and references to respective dates of review, manufacture, and wrapping, and are signed and dated by the vendor type control department. Change control (controller two changes) – A written procedure describing the action to be taken if a proposed change (a) for the installations, materials, equipment, and/or processes used in the fabric, wrapping, and testing of drugs, or (b) that may affect the operation of the quality or support system. (gui-0001) Switch procedure (procedure of conversion) – A logical set of validated steps that ensure the proper cleaning of suites and equipment before the processing of a different product begins. (gui-0001) Computerized Systems (seystered computerized) – Consists of all components, including but not limited to hardware, software, personnel, and documentation, necessary to take, process, transfer, store, display, and manage information. (gui-0001) Concurrent validation (concomitant validation): A process where current output batch is used to monitor process parameters. It provides insurance to the present batch being studied, and offers limited coverage consistency of quality from batch to bundles. (gui-0029) Conflict (confirmation) – Total isolation of one or more steps of a manufacturing process to prevent cross-contamination of the product, or employees, from all other steps in the process. (gui-0001) Contamination (Contamination) The uninsured introduction of impurity into a chemical or microbiological nature, or of foreign issues, in or on a raw material, intermediate, or API during production, samples, samples or repair, storage or transport. (ICH Q7) Contractor (entrepreneur) - Legal entity carries out activities on behalf of a company that has pursued a written agreement. This includes other sites in the corporate restructuring structure. (gui-0001) Critical (critical) – Describes a step process, process requirement, test condition, or other relevant parameters or items that must be controlled through predetermined criteria to ensure that the API meets its specifications. (ICH Q7) Cross-Contamination (cruise contamination) – Contamination of a material or product with another material or product. (ICH Q7) Credential Design (DQ) (credential design) – Documented verification that proposes the design of the installations, equipment, or system is suitable for the intended purpose. (ICH Q7) Deviation (deviation) – Departure from an approved or established standard instruction. (ICH Q7) Director (director) - Assistant Deputy Minister, Health Products and Branch, at the Health Department. (A.01.010) Distributor (Distribute) or Manufacturer (FABRIC) – A person, including an association or an association, under their own name, or under a trade, design or brand, trade name or other name, word or mark controlled by them, selling a meal or drug. (A.01.010) Division 1A and 2 to apply for these distributors (C.01A.003): a distributor of an active ingredient or in a drug form in the form of doses listed in schedule C of the Act; and a drug distributor for which the distributor keeps the drug identification number. Dose form (posological form) - A drug product that is being treated to the point where it is currently in a form where it can be administered in human doses. (gui-0001) Drugs (drugs) – means a drug in the form of doses, or a drug that is an intermediate process that can be used in the preparation of a drug listed in schedule C's or the Schedule D for the Law that is of biological origin. It does not include a dilute drug pricing, a medication feed as defined in Section 2 of the Feeds Regulations, 1983, a drug used solely for the purposes of an experimental study in accordance with a certificate issued under Section C.08.015 or a drug listed in the Schedule H of the Law. : A license given by a person in Canada to perform licensed activities in a building has been inspected and assessed as being in compliance with the requirements of Division 2 4 of the Food and Drug Regulations. Drug Identification Number (drug identification): A Drug Identification Number (DIN) is a computer-generated eight digit number assigned by Canada Health to a drug product before being marked in Canada. He identify all drug products sold in a dose form in Canada and is located on the label of prescription and over-the-counter drug products that are evaluated and authorized for sale in Canada. A DIN uniquely identifies the following product features: manufacturer; product name; active ingredient(s); force(s) to active ingredient(s); pharmaceutiical forms; pathways administration. (gui-0001) Expiration date (or Expiration Date) (limit date d'utilisation) means in case of a drug in the form of doses, earlier to these dates, expressed at minimum as a year and month: the date up to and including which the drug maintains its marked potential, purity and physical characteristics, and the date after which the manufacturer recommends that the drug must not be used; and in the case of an active ingredient, regardless of the contents applicable date, expressed at minimum as a year and month: the rest date, or the date after which the manufacturer recommends that the active ingredient not be used. (date limited d'utilisation) (C.01.001(1)) Fabricate (manufacturers) – To prepare and preserve a drug for the purpose of selling. (C.01A.001) Filling (replissage) - Transfer an essential drug to its final container and lock it in the container. (GUI-0001) Import (importer) – Mean importing into Canada a drug for the purpose of selling at (C.01A.001) Impurity (impurities) – any component present at the intermediate or API that is not the desired entity. (ICH Q7) Impurity Profile (profil d'impurities) – A description of identifying and identifying the impurities present in an API. (ICH Q7) To control processing (controllers course of fabric): Checks performed during production in order to monitor and, if necessary, adjusts the process to ensure that the intermediary or API complies it to its specifications. The control of the production environment or equipment can also be regarded as part of in-process control. In-Process Testing (course analysis of fabric) – The Test or test of any material or mixture of materials during the manufacturing process. (gui-0001) Installation Credentials (IQ) (installation of the del qualifications) – Documenting verification that the equipment or system, as installed or modified, comply with the approved design, manufacturer's recommendation and/or user requirements. (ICH Q7) Intermediate (intermediate product) – A material generated during steps of the processing of an API that underwent more molecular change or purification before it becomes an API. Intermediate case or cannot be zoo. (ICH Q7) Label (etiquette) - Includes any legendary, word, or mark attached and, included in, belongs to, or accompany any food, drugs, cosmetics, devices, or packages (Section 2 of the Act). As described in packages/labels, the action of label refers to the posting inner or label outside of the drug. (C.01A.001) Other (many) - See the definition of batch. (ICH Q7) Many numbers (number numberings a lot) -. Any of milk, face, or both, where any food or drug can be drawn in manufactured and identified in distribution. (A.01.010) Factory (inventory) – All operations of receipts of materials, production, wrapping, repackaging, labelling, relabeling, quality control, release, storage, and distribution of APIs and related controls. (ICH Q7) Manufacturer (Fabric) or Distributor (Distribute) - See distributor definition. Marketing Authorization (Disappeared Authorization Highlights Maché) – A legal document made by Health Canada, authorizes the sale of a drug form in doses or a device based on the health and safety conditions of the Food and Drug Act and its associated regulations. Marketing authorization may be in the form of a compliance notice (NOC), Drug Identification Number (DIN), a device license for grade II, III and IV medical devices, or a natural product number (NPNN) or kayopatic DIN-HM). (gui-0001) Formula master (formule-type) – A document or set of documents specifying the raw materials and quantities and wrapping materials, along with detailed processing instructions, including the in-process controls and precautions required to produce a specific quantity of an API. Document Production Master (MPD) (document-type output) – Documents including specifications for raw materials, and for packaging materials; master formulas (including composition and instructions as described in the definition above), sample procedures, and other critical processes related to operating procedures (SOPs), whether these SOPs are specifically referenced in the master formula. Materials (fats) – A general term used to distort raw materials (start material, reactive, solvent), processing aid, intermediate, Apis and packaging materials. (ICH Q7) Medicine Ingredients (Medicinal Residue) - See the definition of active pharmaceutical ingredients. Mother Liquor (liquid-mere) - The residual liquid remaining after the crystallization processes or isolation. Mothers of the quorum can have materials that are not diarrhea, intermediate, API levels and/or impurities. It can be used for more processing. (ICH Q7) MRA Country (paid participants to ARM) - A country that participates in a mutual recognition agreement with Canada. (C.01A.001) Mutual Recognition Agreement (MRA) (Accord of Mutuelle Recognition (ARM) – An international agreement that provides for the mutual recognition of compliance certification for Proper Drug Manufacturing Practices. (C.01A.001) Operational Credentials (OQ) (oprational credentials) – Documented verification that the equipment or system, such as installing or modifying, is as intended in all chains to anticipate operating. (ICH Q7) Packet (shipped) – As described in package / label, the action of wrapping refers to put a drug into its immediate container. (C.01A.001) Package/ Label (wrapping/label) - To put a drug its immediate container or to post the interior or outdoor label of the drug. (C.01A.001). This includes the repackaging and relaxation of previously packaged and drugs containing laboratories. Batch File Packing (registering packaging of three fabrication) – Records demonstrate that the batch of a drug was packaged in accordance with the approved master production documents. (gui-0001) Packing matrial (matriel packing packing) - includes a label. (C.02.002) Note: For the following directive purposes, this definition also includes: Labels, printer wrapping materials, any material intended to protect the intermediate or API during storage and transport with the following elements of direct contact with the final API. Qualification performance (PQ) (request credentials) – Documented verification that supplies and ancillary systems, as connected together, can be done effectively and reproduction based on the approved processing method and specifications. (ICH Q7) Pharmaceutical (pharmaceutical products) – A drug other than a drug listed in Schedule C or D of the Act. (C.01A.001). Potential (digest) - The Activity or the amount of active moietire, or any form therein, indicates by label claims to be present. (gui-0001) Procedures (procedures) – A documented description of operations must be performed, precautions to be taken and measures must be applied directly or indirectly related to the manufacture of an intermediary or API. (ICH Q7) Process help (adjuvant de procédée) – Materials, excluding solvents, used as an aid in the manufacture of an intermediary or API that is not themselves involved in a chemical or biological reaction (e.g. filtered help, toggle carbon, etc.). (ICH Q7) Process Validation (PV) (firmware validation) – Documented evidence that the process, operating in establishing parameters, can be done effectively with reproduction to produce an intermediary or API meeting its predetermined specifications and quality attributes. (ICH Q7) Production (production) – All operations involved in the preparation of an API, from receiving to material, to processing and wrapping, completion of the final API, including storage. Batch File Output (worksheets from canvas) – Records demonstrate that the batch of a final API was manufactured in accordance with the approved master output documents. Purified Water (as defined) – As defined by any standard listed in Schedule B of the Food and Drug Act. (gui-0001) Purity (Purity) – The measure that a raw material or a final API is free of unrustable chemical or adultery, biological, or physical entity as defined by specifications. Qualifications (qualifications) – Actions of proven and documented which equipment or ancillary system are properly installed, work correctly, and actually lead to the expected results. Credentials are part of validation, but individual credential steps are alone by constituted validation processes. (ICH Q7) Quality Assurance (QA) (insurance) - The sum total of the organized arrangements was made with the object of ensuring that all APIS are of quality needed for use are intended and which quality systems are maintained. (ICH Q7) Quality control (QC) (controller of exalted) – Check or test which specifications are satisfied. (ICH Q7) Risk management type (gestion profiles the risk of exalted) – A systematic process for the assessment, control, communication and review of risk for the quality of the medicine product. It can be implemented both proactively and retrospectively (ICH Q9). Unit Type (dequalité unit) – An independent organizational unit of production that meets both Quality Assurance and Quality Control responsibilities. This can be in the form of separate QA and QC units or one person or group, depending on the size and structure of the organization. (ICH Q7) Quarantine (Quarantine) – Status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection. (ICH Q7) Raw materials (premiered fats) – A general term is used to discover starting, reactive materials, and solvents intended for use in intermediate production or APIS. (ICH Q7) Reconciliation (comparative billing) – A comparison, making allows for normal variations, between the amount of products or materials theoretically generated or used with the amount actually generated or used. (gui-0001) Recovery (resupply) – Introduction to all or part of the previous batch of the required quality of another batch in a defined stage of manufacture. (gui-0001) Standard Reference, Primary (talon de erefrence primaire) – A substance shown by an extensive range of analytic tests to be native material that should be of high purity. This standard can be: (1) found in an officially recognized source, or (2) prepared by independent synthesis, or (3) obtained from existing production materials of high purity, or (4) prepared by further purification of existing production material. (ICH Q7) Standard reference, Secondary (cotton of secondaire secondaire) – A substance that establishes quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis. (ICH Q7) Repackaging/Relabelling (remballer/eretiqueter) – Replacement of wrapping or labeling of previously packaged and branded products. (gui-0001) Reprocessing (retraitment) – Introducing an intermediary or API, including one that does not comply with standards or specifications, back to the process and repeat a crystallization step or other appropriate or physical manipulation steps (e.g., distillation, filtering, chromatography, fraising) that are part of the established manufacturing process. The continuation of a step process after an in-process control test showed that the incomplete step is considered part of the normal process, and not reprocessing. (ICH Q7) Rest date (date) ereanalyse) – The date when a material should be re-examined to ensure that it is always suitable for use. (ICH Q7) Reworked (revival) – Subject of an intermediary or non-compliant API with standards or specifications of one or more stage processes that are different from the established manufacturing process to obtain intermediate acceptable quality or API (e.g., recruited with a different solvent). (ICH Q7) Sell (vendor) – Offers for sale, exposure for sale, have in possession for sale, and distribute, regardless of whether the distribution is made for consideration. (Section 2 of the Food and Drug Act) Shelf Life (duration of conservation) - Interval of the time during which a drug is expected to remain within the approved specification provided that it is stored under the defined conditions on the label and in the proposed and closed containers. (gui-0001) Sign (signature) - Records of the person who performs a particular or reviewed action. This file can be initial, full written signature is written, personal seal, or authentic, and electronic signature security. (ICH Q7) Solvent (solvent) – An inorganic or organic liquid is used as a machine for the preparation of solution or suspension of the manufacturing of an intermediary or API. (ICH Q7) Specifications (specifications) – Mean a detailed description of a drug, the raw material used in a drug, or the packaging material for a drug and includes: a statement of all properties and types of the drug, material or wrapping material related to the manufacturing, Wrapping, and use of the drug, including identity, power, and purity of the drug, raw materials, or wrapping materials, a detailed description of the methods used for testing and examining the medication, raw materials, or by the wrapping materials, and a tolerance statement for the properties and drug types, previous materials, or wrapping materials. (C.02.002) Standard Operating Procedure (SOP) (proxy to normalized opratoire (PON)) – A written procedure containing instructions for performing operations not necessarily specific to a product or material but of a more general nature (e.g., equipment operation, maintenance and cleaning; validation; cleaning of local and control of the environment; sample and inspection). Certain SOPs can be used to boost product-specific meters and batch production documents. (gui-0001) System (Sistme) – A regular pattern of communicating activities and techniques that unite to form a whole organized. (gui-0001) Test (analyzes) – For testing, including any tests, assessments, and assessments, as specified in Division 2 of the Food and Drug Regulations. (gui-0001) Validation (validation) – A documented program that provides a high degree of assurance that a specific process, method, or system will always produce a pre-determined meeting results criteria. (ICH Q7) Vendor/Supplier (cathedron) - anyone or company that or stock supplies or services to another company. Also called providers. Veterinary drugs (veterinary dietary) – drugs that are administered to produce food and animal companions. (gui-0001) Wholesaler (crossing) - Means a non-distributor described in section C.01A.003 and is selling any of these drugs other than in Retail: A screenshot of drugs in dose form listed in Schedule C or D for Act or of Schedule F of Such Rules or a controlled drug as defined in G.01.001 source (1); or an active ingredient; or a narcotic as defined in Narcotic Control Regulations. (C.01A.001(1)) As for each new definition of wholesaler in Division 1A, Part C of Food and Drug Regulation, agents, brokers, traders are considered volumes. Yield, expected (forecasted yield) – The amount of material or the percentage of theoretical yield anticipates in any appropriate phase of production based on previous lab, pilot scale, or data manufacturer. (ICH Q7) Yield, Theatre (theatrical appointment) – The quantity that should be produced at any appropriate phase of production, based on the quantity of materials to be used, in the absence of any loss or error in the actual production. (ICH Q7) Appendix CCH Q7 Guidelines: Section 18 – Specific Guidelines for APIS Manufacturers by Telephone Culture/ Fermentation 18.1 Gen 18.10 Section 18 intended to address specific controls for APIS or intermediate manufacturers by cell culture or fermentation using natural or reconstructed or non-covered adequately in the previous sections. It is not intended to remain a stand-alone section. In general, the GMP principles in other sections of this document apply. Note that the principles of fermentation for classical processing processes for the production of small molecules and for processing using rebining and non-rebining organizations for production of proteins and/or polypeptides are the same, although the degree of control will differ. Where convenient, this section will address these differences. In general, the degree of control for biochemical processes used to produce proteins and polipeptides is greater than that for classic fermentation processes. 18.11 Term Biotechnology Processing (biotech) refers to the use of cells or organisms produced or modified by recommended ANA, hybridoma or other technologies to produce APIS. The apis produced by biotechnological processes normally consist of high molecular weight substances, such as proteins and polipeptides, for which specific advice is provided in this section. Certain APIS in low molecular weights, such as antibiotics, amino acids, vitamins, and carbohydrates, can also be produced by reconbining DNA technologies. Control levels for these types of APIs are similar to which are employed for classic shipment. 18.12 The classic fermentation term refers to processes that use existing microorganisms in nature and/or modified by methods (e.g. irradiation or chemical mutagenesis) to produce APIS. APis produced by classical eradication are normally low molecular weight products such as antibiotics, amino assistance, vitamins, and carbon. 18.13 Production of APIS or intermediates from cell culture or fermentation involves biological processes such as cultivation of cells or extraction and purification of materials from living organisms. Note that there may be additional process steps, such as physical modification, which are part of the manufacturing process. The raw materials used (media, suffering components) can provide the potential for growth of microbiological contaminants. Troubleshooting of 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. 18.14 Suitable control should be established at all stages of manufacturing to ensure intermediate and/or API quality. While this guide begins in the cell culture/eraser step, previous steps (e.g. cell bnking) should be performed under appropriate process control. This guide covers cell culture/eraseration from the point at which a vial of the cell bank recovering for use in manufacturing. 18.15 Proper equipment and environmental controls should be used to minimize the risk of contaminated soil. The acceptance criteria for quality of the environment and the monitoring frequency should depend on the stage of production and the production requirements (open, closed, or off-system). 18.16 In general, process controls should be taken into account: Maintenance of Bank of Phone Work (appropriate location); Good inokulation and expansion into the culture; Control of the critical operating parameters during eraser/cell culture; Monitoring of the process for cellular growth, viability (for most cell culture processes) and productivity where appropriate; Crop and purification procedures that remove cells, cell debris and media elements while protecting the intermediate or API from contamination (particularly in a microbiological nature) and from loss of quality; Monitoring of bioburden and, where necessary, endotoxin levels at the appropriate stages of production; Viral safety concerns as described in ICH Q5A Quality Guide to biotechnology products: Viral Safety Assessment of Biotechnology products from cell lines of Human Origin or Animal. 18.17 The proper location, removing components of media, host cell proteins, other process impurities related, impurities related to products and contaminates should be demonstrated. 18.2 Cell Maintenance Bank and Record Holding 18.20 Access to cell banks should be limited to authorized personnel. 18.21 Phone banks should be kept under deposit requirements designed to keep visible and prevent contamination. 18.22 Records of use of banks in the cell banks and deposits should be maintained. 18.23 Where appropriate, cell banks should periodically control the appropriate determination for use. 18.24 See ICH Guide Q5D Quality in biotechnology products: Derivation and characterization of cell phone substrate used for production biotechnology / biological products for a more comprehensive discussion about cell banks. 18.3 Cell Culture / Fermentation 18.30 Where aseptic addition to cell substrate, media, posting, and fuel needed, closing or containing system should be used where possible. If inoculation of the first container or subsequent transfer or add (media, sufferers) are performed in open vessels, there should be control and procedures in place to minimize the risk of contamination. 18.31 Where the quality of the API can be affected by microbe contamination, manipulations using open vessels should be made in a biosafety cabinet or similarly controlled environments. 18.32 Staffing should be appropriate to govern and take special precautions handling their culture. 18.33 Parameter operating critical (for example temperature, pH, hustle rate, addition to gas, pressure) should be monitored to ensure consistency with the established process. Cell growth, visibility (for most cell culture processes), and, where appropriate, productivity should also be controlled. Critical parameters will vary from one process to another, and for classic fraud, certain parameters (visible cells, for example) may not need to be controlled. 18.34 Cell culture equipment should be cleaned and sterilized after use. As appropriate equipment, fermentation equipment should be cleaned, and sanitize or sterilize. 18.35 Media Culture should be sterilized prior to use when appropriate to protect the quality of the API. 18.36 Should have the appropriate procedure in place to detect contamination and determine the course of action to be taken. This should include procedures to determine the contamination's impact on the product and decontaminate the equipment and return it to a requirement to be used in subsequent batch. Foreign organisms observed during erasure process should be identified as appropriate and the effect of their presence on product quality should be evaluated, if necessary. The results of these assessments should be taken into consideration in the disposition of the product material. 18.37 Record of contamination events should be maintained. 18.38 Shared (multi-product) equipment can guarantee additional testing after clearing between product campaigns, as appropriate, to minimize the risk of cross-contamination contamination. 18.4 Harvesting, Isolation and Purification 18.40 Harvesting stage, either to remove cellular or cell elements or collect cellular elements after disruption, should be made from equipment and areas designed to minimize the risk of contaminated soil. 18.41 Harvest and purification procedures that remove or inactive organisms produced, cellular debris and media (while minimizing degradation, contamination, and loss of quality) should be adequate to ensure that the intermediate or API is recovered with consistent quality. 18.42 All equipment should be cleaned and, as appropriate, sanitized after use. Multiple successful batch without cleaning can be used if intermediate or API quality is not compromised. 18.43 If open system is used, purification should be performed under environmental conditions appropriate for the preservation of product quality. 18.44 Other controls, such as the use of dedicated chromatography resins or additional testing, may be suitable if equipment is to be used for multiple products. Viral Removal 18.5 Inactivation step 18.50 See the ICH Q5A Quality Guide to Biotechnology ProDu Reality: Viral Safety Assessment of Biotechnology Products from Phone Lines of Humans or Animal Origins for more specific information. 18.51 Viral removal and viral inactivation steps are critical processing steps for some processes and should be performed within their validated parameters. 18.52 Proper precautions should be taken to prevent potential viral contamination from pre-viral to remove post-viral/inactivation steps. Therefore, opening processes should be performed in areas that are separated from other processing activities and have units handling the air separated. 18.53 The same equipment is not normally used for different purification stages. However, if the same equipment is to be used, the equipment would be suitable and sanitize before reuse. Appropriate precautions should be taken to prevent potential virus carry-on (e.g. via equipment or environment) from previous steps. Appendix DCH Q7 Q7 Guidelines: Section 19 – APIs for use in clinical trials 19.1 General 19.10 Not all the Control Read in the previous sections of this Guide are suitable for the manufacture of a new API for investigations used during its development. Section 19 provides specific advice unique in these circumstances. 19.11 Controls used in the manufacture of APIs for use in clinical trials should be consistent with the development stage of the drug product incorporating the API. Processes and testing procedures should be flexible to give for change as knowledge of the increased process and clinical testing of a drug progress generated from pre-clinical stage at clinical stage. Once drug development arrives at the scene where the API is generated for the use of drug products intended for clinical trials, manufacturers should ensure that APIS are manufactured at suitable facilities using appropriate production and control procedures to ensure the quality of the API. 19.2 Type 19.20 Suitable GMP Concepts should be applied to the production APIs for use in clinical trials and a suitable mechanism of approval in each batch. 19.21 A quality unit(s) independent of production should be established for the approval or rejection of each batch of API for use in the ordeal. 19.22 Some of the test functions commonly performed by the quality unit(s) can be performed in other organizational units. 19.23 Quality Measurements should include a system for testing of raw materials, packaging material, intermediate, and APIs. 19.24 Processing and quality problems should be evaluated. 19.25 Labelling for APIs intended for use in clinical trials should be appropriately monitored and should identify the material as being for investigational use. 19.3 Equipment and Facilities 19.30 Throughout the clinical development phase, including the use of small-scale or laboratory facilities are manufactured in APIS for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean and suitable for the use of its intentions. 19.31 Procedures for use in installations should ensure that the materials are handled in a way that minimizes the risk of contamination and cross contamination. 19.4 Control of Raw Material 19.40 Materials before all correction used in APIS production for use in clinical trials should be evaluated by testing, or receiving and analysis of a provider's and subject to identity testing. When a material is considered harmful, a supplier's analysis would be sufficient. 19.41 In some cases, the suitable of a material before use is based on acceptable in small-scale reactions (namely, test use) rather than on analytical tests alone. 19.5 Production of small-scale APIS production for use in clinical trials should be documented in laboratory notebooks, batch files, or by other appropriate means. These documents should include information on the use of production materials, equipment, processes, and scientific observations. 19.51 Output is expected to be more variable and less defined than expected yields used in commercial processing. Scrutiny of yield variations is not expected. 19.6 Validation Process 19.60 Validation Process for APIS production for use in clinical trials is usually not appropriate, where a single batch API is generated or where process changes during development API make batch replation difficult or inexplicable. The combination of control, calibration, and, appropriate location, equipment credentials ensures API quality during this development phase. 19.61 Validation Process should be performed in accordance with Section 12 when batch are generated for commercial use, even when these bundles are generated on a pilot or small scale. 19.7 Change 19.70 is expected during development, as knowledge is taken and the production is scaled up. Every change in the output, specifications, or testing procedures should be adequately recorded. 19.8 Lab Controller 19.80 While analytical methods designed to evaluate a batch of API for clinical trials cannot be validated, should be scientifically sound. 19.81 A system to hold samples reserved in all batch should be in place. This system must ensure that a sufficient in each reserved sample is retained for an appropriate length of time after approval, termination, or suspend an application. 19.82 Expiration and rest dated as defined in Section 11.6 apply to existing APIs used in clinical trials. For new APIS, Section 11.6 does not apply normally in early stages of clinical trials. 19.9 Documentation 19.90 A system should be in place to ensure that information was contained during the development and manufacture of APIs for use in documented and available clinical trials. 19.91 Development and implementation of the analytical methods used to support the release of a batch of API for use in clinical trials should be appropriate waivers. 19.92 A system for production and control records and documents should be used. This system should ensure that records and documents are kept for an appropriate length of time after the approval, termination, or stop of an application. Appendix E Annex in the current edition of the API Guide GMP Annexes is available on Canada's Health Website. Annex 1 of the current edition of Good Factory Practising Guide – Categories Select IV Monograph Drug (GUI-0066) Annex 2 of the current edition of Practical Manufacturing Good Practice Guide – Drug Scheduling, Biological Drugs (GUI-0027) Annex 3 of the current edition of Good Factory Practice Guide – Drug Schedule C (GUI-0026) Annex 4 In the current edition of Good Factory Practitioners Guide – Veterinary Drugs (GUI-0012) Annex 5 in the current edition of the Good Factory Practice Guide – Positron Emitting Radiopharmace PERs) (GUI-0071) PIC/S Annex 11: Computer System Annex 13 of the current edition of Pra of Manufacturing Good Articles Guide – Drugs used in clinical trials (GUI-0036) Annex 14 of the current edition In the Good Manufacturing Practices – Drug Scheduling, Human and Blood Components (GUI-0032) Annex 17 in the current edition of Good Manufacturing Practice Guidelines – Gu On Parameters Release (GUI-0046) Referrals Fairly Canada Law and Canada Rules are available on the Website of Justice Act. 2. Food and Drug Health Regulation Canada documents and Questions and Answers related to GMPs are available on Health Canada's 3 website. Good Practice Factory (GMP) Guide, Edition 2009, Version 2 (GUI-0001) 4. Proof tips demonstrate GMP drug compliance at foreign sites (GUI-0080) 5. Annex 3 of the current edition of Good Factory Practice Guide – Drug Scheduling (GUI-0026) 6. Annex 2 of the current edition of Good Factory Practicing Guide of Drug Scheduling (Biological Drugs) (GUI-0027) 7. Good Factory Practice Questions and Answers 8. Active Pharmaceutical Ingredient Questions and Answers 9. Risk Classification of GMP Observation (GUI-0023) 10. Temperature control guidelines of drug products during and Transportation (GUI-0069) 11. Product Reminder Procedure 12. Clean Validation Guide (GUI-0028) 13. Document Validation Requirements and Responsibilities for Drug Manufacturers, Packages/Labellers, Distributors and Importers (GUI-0042) 14. Process Validation Guide: Moist Heat Sterilization for Pharmaceuticals (GUI-0010) Sterilization Irradiation for Pharmaceutical (GUI-0 Gas Sterilization for Pharmaceutical (GUI-0007) Aseptic Process for Pharmaceutiicals (GUI-0006) 15. Questions and Exports and Answers 16. Alternative Sample Site Guide (GUI-0014) 17. Good Medical Gas Factory (GMP) For Medical Gas (GUI-0031) Documents Related to Stability available on Health Canada website in drug products section under Application and Submission. 18. Stability Testing of Existing Drug Substances and Products (TPD) Documents Director developed by the International Conference on Harmonisation (ICH) and adopted by Canada Health are available online in the Drug Products section under ICH (International Conference on Harmonisation). 19. Q1A ICH (R2): Stability Test of New Drug Substances and 20 Products. ICH Q1B: Stability Test: Photostability Test of New Drug Substances and 21 Products. ICH Q2(R1): Validation of Analytical Procedures: Text and Methodology 22. ICH Q7: Good Factory Practice Guide for Pharmaceutiical Ingredient Pharmaceutiical 23. ICH Q8: Pharmaceutiical Development 24. ICH Q9: Quality Risk Management 25. ICH Q10: Pharmaceutiical Quality Appendix F System