

Good Manufacturing Practices Questions and Answers

The Good Manufacturing Practices questions and answers (GMP Q&A) presented below have been updated following the issuance of the “Good Manufacturing Practices Guidelines, 2009 Edition (GUI-0001)”. Some Q&As have been deleted because they have been incorporated in GUI-0001. Some Q&As have been modified as a result of the revision of GUI-0001. Also, the majority of the Q&As have been renumbered.

This Q&A list will be updated on a regular basis.

Premises - C.02.004 **(Updated)**

Equipment - C.02.005

Personnel - C.02.006 **(Updated)**

Sanitation - C.02.007 & C.02.008 **(Updated)**

Raw Material Testing - C.02.009 & C.02.010 **(Updated) (New)**

Manufacturing Control - C.02.011 & C.02.012 **(Updated)**

Quality Control Department - C.02.013, C.02.014 & C.02.015

Packaging Material Testing - C.02.016 & C.02.017

Finished Product Testing - C.02.018 & C.02.019 **(Updated)**

Records - C.02.020, C.02.021, C.02.022, C.02.023 & C.02.024 **(Updated)**

Samples - C.02.025 & C.02.026 **(Updated)**

Stability - C.02.027 & C.02.028 **(Updated)**

Sterile Products - C.02.029 **(Updated)**

Premises - C.02.004 (Updated)

Q. 1 Are firms required to use high-efficiency particulate air (HEPA) filters for air supply in areas used for the manufacture of non-sterile dosage forms? (Updated)

A.1 Division 2, Good Manufacturing Practices (GMP), of the *Food and Drug Regulations* does not specifically require manufacturing facilities for non-sterile drugs to maintain HEPA filtered air.

The Regulations do require the use of equipment for adequate control over air pressure, microorganisms, dust, humidity and temperature, when appropriate. In addition, this section calls for use of air filtration systems, including prefilters and particulate matter air filters on air supplies to production areas, as appropriate. These provisions speak to measures to prevent cross contamination, and the key phrase is “when appropriate”.

Despite the lack of an explicit GMP requirement, some firms may elect to use HEPA filtered air systems as part of their dust control procedures. For example, firms may perform dust containment assessments and decide that such filters are warranted to prevent cross contamination of highly potent drugs that, even in small quantities, could pose a significant health hazard when carried over into other products.

Q.2 Is there an acceptable substitute for dioctyl phthalate (DOP) to integrity testing of high-efficiency particulate air (HEPA) filters?

A.2 Yes. Dioctyl phthalate aerosols also called Di (2-ethylhexyl) phthalate, di-sec octyl phthalate, DOP, or DEHP, have long been used to test the integrity of HEPA filters but concern about the potential health effects to people working with DOP test aerosols has led to a search for a safer equivalent replacement.

The product of choice from US Army testing with assistance from various private companies was a Henkel Corporation (Emery Group) product called Emery 3004 PAO. This product is a polyalphaolefin (POA) in the 4 centistoke (4 cSt) viscosity grade, used primarily as a lubricant base stock for oils, lubricants, and electrical/hydraulic fluids.

Emery 3004 (POA) can replace DOP in HEPA integrity testing.

Q.3 What is the acceptable limit for dew point of the compressed air used in pneumatic equipment and to dry the manufacturing tanks after cleaning?

A.3 Under the “[Good Manufacturing Practices Guidelines, 2009 Edition \(GUI-0001\)](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php)” (<http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php>), there is no limit for the relative humidity % of the air used for pneumatic equipment and to dry manufacturing tanks. From a general perspective, based on Interpretation 4 under Section C.02.004 Premises, the humidity must be controlled where required to safeguard sensitive materials. Consequently, it is the fabricator, packager/labeller’s responsibility to establish the pertinence of such control. If the humidity % of the compressed air used at the last step of drying of a reservoir is too high, micro-droplets of water could be generated on the internal surfaces by condensation, hence contributing to the possibility of microbial growth following storage. Similarly, it is important to make sure that residual water has been completely eliminated from hard to reach surfaces of the equipment after cleaning operations.

Q.4 What are the requirements applicable to Quality Control (QC) and engineering personnel who travel many times daily between self-contained facilities and the regular facilities?

A.4 Movement of personnel between self-contained and other facilities must be subject to procedures that will prevent cross-contamination. This may include but is not limited to decontamination procedures such as showering and change of clothes.

Q.5 What should be the standard of compressed air used in the manufacture of a drug?

A.5 Air that comes into direct contact with primary contact surfaces and/or the product should be monitored to control the level of particulates, microbial contamination, and the absence of hydrocarbons. Limits used should take into consideration the stage of manufacture, product, etc. Additional tests might be required due to the nature of the product. Gas used in aseptic processes must be sterile and filters checked for integrity.

Q.6 Does the concept of self-contained facilities apply equally to research and development laboratories (susceptible to contain highly sensitizing, highly potent or potentially pathogenic material in the analytical scale) that may be in the same building as the manufacturing facilities, or is this concept limited to actual manufacturing operations?

A.6 It is the responsibility of the manufacturer to ensure that their premises and operations have been designed in such a manner that the risk of contamination between products is minimized. This would include research and development areas within facilities where marketed drug products are fabricated and packaged. Further guidance can be found under Interpretation 11, Section C.02.004 Premises of the “[Good Manufacturing Practices Guidelines, 2009 Edition \(GUI-0001\)](#)” (<http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php>).

Equipment - C.02.005

Q. 1 Should equipment be labelled with calibration dates?

A.1 Major equipment should be identified with a distinctive number or code that is recorded in batch records. This identification requirement is intended to help document which pieces of equipment were used to make which batches of drug product.

Division 2, Good Manufacturing Practices (GMP), of the *Food and Drug Regulations* does not require that each piece of equipment bear status labelling as to its state of calibration or maintenance. However, equipment must be calibrated and/or maintained according to an established schedule, and records must be kept documenting such activities.

The regulations do not distinguish critical from non-critical equipment for calibration and maintenance purposes. However, the need for calibrating a given piece of equipment depends on its function. In general, equipment that measure materials warrant calibration. Equipment not requiring calibration/maintenance need not be tracked or included in the firm’s calibration/maintenance program, but the firm must be able to support its decision to exclude a particular piece of equipment from the calibration/maintenance program.

During an inspection a firm should be able to document when a specific piece of equipment was last calibrated/maintained, the results or action, and when its next calibration/maintenance is scheduled. The absence of such documentation is considered a GMP deviation. While the absence of a calibration/maintenance tag is not objectionable, the presence of a calibration/maintenance tag alone should not be assumed to satisfy regulatory demands, and the supporting documentation should be audited. The firm should also be able to support its decision to not include a particular piece of equipment in the calibration/maintenance program.

Personnel - C.02.006 (Updated)

Q.1 Is a company required to notify the Inspectorate of a change in key personnel, such as the person in charge of Quality Control (QC) or manufacturing department?

A.1 No. However, it is the company’s responsibility to make sure that the new person meets the

requirements of Interpretation 1, 2, 3, or 4 under C.02.006 Personnel, depending on the activities performed.

Sanitation - C.02.007 & C.02.008 (Updated)

Q.1 Is fumigation a requirement under sanitation?

A.1 The written sanitation program should include procedures for pest control as well as precautions required to prevent contamination of a drug when fumigating agents are used.

Fumigation is not a requirement per se. Infestation should be monitored and controlled. Where fumigation is used, appropriate precautions should be taken.

Methods of sanitary control that satisfy the requirements of Sections 8 and 11 of the *Food and Drugs Act* would be considered to be acceptable.

Q.2 What limits are acceptable on product residues regarding sanitation? (Updated)

A.2 Guidance for the establishment of limits can be obtained from the "[Cleaning Validation Guidelines \(GUI-0028\)](#)".

(http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/validation/gui-0028_cleaning-nettoyage_ltr-doc-eng.php).

Q.3 Are gowning rooms required even in pilot plant operations?

A.3 Even in a pilot plant consisting of a small laminar flow area where the apparatus for filter sterilization of solutions are set up, it is an unacceptable practice to gown in there. A change room should be available besides their sterile pilot plant production area.

Based on the assumption that the pilot plant will produce drugs for sale - including clinical studies - then the same principles and considerations that apply to full scale production operations must also be utilized in pilot plant facilities.

Q.4 What are considered as being acceptable limits for cross-contamination when performing cleaning validation? (Updated)

A.4 Guidance for the establishment of limits can be obtained from the "[Cleaning Validation Guidelines \(GUI-0028\)](#)".

(http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/validation/gui-0028_cleaning-nettoyage_ltr-doc-eng.php).

Q.5 In terms of cleaning, what would be the frequency and type of cleaning for equipment and premises for successive manufacturing of batches of the same product? And for different strengths of the same product? (Updated)

A.5 Interpretation 3.5 under Section C.02.007 Sanitation specifies that “a cleaning procedure requiring complete product removal may not be necessary between batches of the same drug”. The frequency and type of cleaning for equipment and premises must address the length of time between consecutive lots with the ultimate goal that a particular lot won’t be contaminated by the previous lot or the environment. It must also ensure that residual quantities of the previous lot won’t impact on the quality of the following lot. Thus, a partial cleaning would be required between two lots of the same product, especially for forms such as liquids or suspensions, in order to prevent a few units at the beginning of a new lot from being filled with residual quantities from the previous lot that may be located in equipment such as hoses or pumps. A procedure should be established to ensure adequate removal of residual quantities from the previous lot and validation available for the maximum period of time between two successive lots in order to avoid problems such as microbial contamination, accumulation of residue, or degradation of product. The number of lots of the same product which could be manufactured before a complete/full cleaning should be determined.

Q.6 Clothing: Is it acceptable to have two levels of clothing in the non-sterile manufacturing areas, i.e., one level for operators with full gowning and coveralls and another level for QA auditors and visitors? What environmental monitoring data is required?

A.6 Yes. There are basic clothing requirements for any person entering the manufacturing areas, such as hair, mustache and beard covering, as well as protective garments. However, a firm may decide to apply more stringent requirements for operators, such as dedicated shoes and garments providing a higher level of protection. There are no specific environmental monitoring requirements for clothing worn in the non-sterile manufacturing areas.

Q.7 Can the sampling for the microbial monitoring of air in non-sterile areas where susceptible products are produced be conducted when there are no manufacturing packaging activities?

A.7 The sampling should occur during actual manufacturing or packaging in order to reflect the conditions to which the products being produced are really exposed. Monitoring between production runs is also advisable in order to detect potential problems before they arise.

Q.8 Must written procedures be available to prevent objectionable microorganisms in drug products not required to be sterile?

A.8 Yes. Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, should be established and followed. This means that even though a drug product is not sterile, a firm must follow written procedures that pro-actively prevent contamination and proliferation of microorganisms that are objectionable.

Raw Material Testing - C.02.009 & C.02.010 (Updated) (New)

Q.1 What are requirements of maintaining an impurity profile?

A.1 The United States Pharmacopoeia (USP) defines an impurity profile as “a description of the impurities present in a typical lot of drug substance produced by a given manufacturing process.” (ref. USP <1086>). Each commercial lot should be comparable in purity to this standard release profile which is developed early on and maintained for each pharmaceutical chemical. We can also call this profile a “Reference Profile”

because the quality control unit refers to it (1) when assessing the purity of each batch of active pharmaceutical ingredient (API), and (2) when evaluating the viability of proposed process changes.

For further information regarding the control of impurities, please consult [Impurities in New Drug Substances - ICH Q3A \(R\)](#)

([http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q3a\(r\)-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q3a(r)-eng.php)) & [Impurities in New Drug Products - ICH Q3B \(R\)](#)

([http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q3b\(r\)-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q3b(r)-eng.php)).

Q.2 Does every individual container of a raw material need to be sampled for identification (ID) purposes regardless of the number of containers of the same lot available or are composite samples acceptable provided they are obtained from a maximum of 10 containers? (Updated)

Q.2 For human drugs, according to Interpretation 6.1 under C.02.009 Raw Material Testing, each container of a lot of a raw material must be tested for the identity of its contents. Therefore, each container of all raw materials, including excipients and active pharmaceutical ingredients (API), must be opened and sampled. Then, 2 options are available:

- 1) To test every sample for ID using a discriminating method (it is not mandatory to perform all ID tests in the specifications, for example United States Pharmacopoeia (USP), but the test must be specific).
- 2) If the raw material can be tested for potency, the other option is to mix and pool individual samples taken from each containers in a composite sample but without exceeding 10 individual samples in a composite. A specific ID test is then performed on each composite **and**, in addition, a potency test is performed to assure the mass balance of the composite. (In such cases, an equal quantity of each individual sample in the composite must be weighed to ensure that the mass balance is representative.)

As an example, say 72 containers of the same lot of a raw material are received. Each and all containers must be opened and a sample taken from each container. After that, the first option is to test each sample for ID (which implies 72 ID tests). The second option is to combine equal quantities of those individual samples in a way that the number of samples in any composite does not exceed 10 and test those composites for ID and potency. In this case, the easiest way to combine those samples would be 8 composites of 9 individual samples. For a given composite, a potency result of 88.8 % or so would indicate that one of the containers does not contain the right material as each individual sample contributes 1/9 or 11.11% of the total mass of the composite (similarly a result of 77,7 % would indicate 2 containers with the wrong material). In such case, each container selected for this particular composite would have to be tested for ID to pinpoint the one (or more) containers with the wrong material.

However, the use of a composite sample to establish the ID of a raw material cannot be used when the potency limits are too wide or, similarly, when the precision of the assay method is not sufficient to properly establish the mass balance.

Q.3a An active pharmaceutical ingredient (API) can be used after the retest date assigned by the API fabricator if a re-analysis done immediately before use shows that it still meets its specifications. Can the new data generated be used by the drug fabricator to assign a longer retest date to future lots of this API obtained from the same fabricator?

A.3a No. The extension of the retest date originally assigned to the API should be supported by data generated through a formal stability protocol. This may require the filing of a notifiable change submission. Please refer to the appropriate review Directorate.

Q.3b What about inactive ingredients? (Updated)

A.3b Normally, any inactive raw material should bear an expiry date. When an inactive raw material is received without an expiry date, the fabricator should assign either an expiry date or a re-test date based on stability data or other documented evidence that this raw material is not subject to chemical / physical modifications or is not susceptible to microbial contamination.

Q.4 With respect to the re-test date of the drug substances, we have the stability data of a drug substance for up to 24 months at real time stability condition. The re-test period is assigned up to 24 months. According to the “Evaluation of Stability Data - ICH Q1E”, 2.4.1.1(the proposed retest period or shelf life can be up to twice, but should not be more than 12 months beyond, the period covered by long-term data), the retest period can be assigned up to 36 months. Can we assign the retest period up to 36 months? If yes, does it require retesting of the active pharmaceutical ingredient (API) at 24 months?

A.4 Retest period and expiry date for APIs should be based on stability data. If an expiry date has been assigned to an API then its batches cannot be used after the expiry period. However, if a retest period has been assigned to the API, then after the retest period is over the API batch can be tested and used immediately (e.g., within one month of the testing). In the scenario presented above extrapolation of expiry date beyond 24 months should be based on stability data both at long-term and accelerated storage conditions. If the test results are satisfactory the retest period can be extended to a period not exceeding 36 months. Once the retest period of the API has been extended to 36 months, testing batches at the 24 months time point would be part of the ongoing stability protocol (it will not be considered *retest*). For further guidance on retest period and expiry period please consult [Stability Testing of New Drug Substances - ICH Q1 A \(R2\)](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ich/qual/q1a(r2)-eng.php) ([http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ich/qual/q1a\(r2\)-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ich/qual/q1a(r2)-eng.php)) & [Evaluation of Stability Data - ICH Q1E](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ich/qual/q1e-eng.php) (<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ich/qual/q1e-eng.php>).

Q.5 We are a subsidiary of a United States (US) corporation. This US corporation supplies us with active pharmaceutical ingredients (APIs) that are fully tested after receipt on its premises. Can the US site be certified for the purpose of testing exemptions for the Canadian site? (Updated)

A.5 The US parent company cannot be considered the vendor. To be certified, the vendor must be the original source of the API. In this instance, the US company would be acting as a contract laboratory and should meet the requirements under Interpretation 6.10, Section C.02.015 Quality Control Department. When received by the Canadian site, a specific identity test must be performed and if for an API, the testing must be as per Interpretation 6.1, Section C.02.009 Raw Material Testing (i.e., each container sampled and tested). The above mentioned would be acceptable based on the fact that no repackaging is done by the US site (i.e., the materials must be supplied in their original containers with the original labels and Certificate of Analysis (C of A) as received from the vendor).

Q.6 What documentation does a laboratory have to have in place to be considered qualified to run a test method for raw materials (drug substances and excipients) in order to satisfy Health Canada Regulations? (Updated)

A.6 Documentation should include a summary of the analytical method validation, an assessment of the results and comparison to the acceptance criteria, and a conclusion as to the acceptability of the data as they relate to the ability of the laboratory analysts to successfully perform the procedure in the particular laboratory.

Q.7 Is the sampling plan based on the ($\sqrt{n+1}$) acceptable for identifying the number of containers of raw material to be sampled?

A.7 Sampling plans and procedures must be statistically valid and should be based on scientifically sound sampling practices taking into account the risk associated with the acceptance of the defective product based on predetermined classification of defects, criticality of the material, and past quality history of the vendor. In some circumstances, such as for large number of containers, a sampling plan based on ($\sqrt{n+1}$) may be acceptable. However, a sampling plan based on ($\sqrt{n+1}$) may present a significant risk of accepting defective goods in certain circumstances, such as the sampling of a small number of containers. As with all sampling plans, documented justification must be available.

Q8. If we already test each batch of our finished product for the absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa*, is it required to test it also for the purified water? (New)

A8. Yes, you are required to test the purified water for the absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa*. It is the general expectation that raw material testing support finished product testing.

Manufacturing Control - C.02.011 & C.02.012 (Updated)

Q.1 Can a single lot number be assigned to two or more co-mingled lots of bulk finished drug products packaged during the same run? (Updated)

A.1 The “[Good Manufacturing Practices Guidelines, 2009 Edition \(GUI-0001\)](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php)” (<http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php>) require that each batch must be identified by an individually numbered manufacturing batch document, each lot or batch of the finished product shall be fully tested against the specification and retained samples for each lot or batch shall be kept. Packaging of multiple lots of bulk finished drug product in a single packaging run with one lot number should be done only in exceptional circumstances and should be well documented with appropriate justification. The shortest expiry date of all the lots packaged must be indicated on the label. In case of a product recall, the company must recall the entire lot comprising all the sub-lots.

Q.2 What is the acceptable deviation in physical counts of finished product stock?

A.2 The allowable deviation between physical counts versus counts as per records (including computer records) should be zero. All finished product stock must be fully accounted for and records of distribution

and disposition must be maintained. Any deviations from physical counts versus expected counts as per the records, should be investigated and the results of such investigations should be documented.

Q.3 When are independent checks by another operator necessary?

A.3 The “[Good Manufacturing Practices Guidelines, 2009 Edition \(GUI-0001\)](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php)” (<http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php>) indicate that a number of measures be taken to maintain the integrity of a drug product from the moment the various relevant raw materials enter the plant to the time the finished dosage form is released for sale. These measures seek to eliminate as many sources of error as possible so that only those drugs which have met established specifications are distributed.

One of the approaches proposed to achieve this goal is to have written procedures that ensure that each ingredient added to a batch is subjected to one or more checks for identity and quantity by qualified personnel.

If by its design, construction, operations and security features the procedure is such that the company assures that it is impossible to make an error, an independent check by another operator may not be considered necessary.

Checks for identity and quantity of dispensed materials also require independent checks by a second individual.

However, independent checks that materials have been added to the batch have traditionally been assumed to take place at the time of actual addition of the materials.

Other means of verifying the addition of materials may be considered. One alternative involves checking staged materials in the immediate compounding area prior to starting processing and then afterwards, verifying the empty containers before clearing the compounding area. This would be in conjunction with the use of individual processing rooms, otherwise we would need to be satisfied that there was very good separation of compounding operations.

Q.4 What are the expectations on label accountability? (Updated)

A.4 It is expected that sufficient controls are in place to ensure that correct labels are applied during a labelling operation and that printed packaging materials are accounted for.

One acceptable means of meeting this requirement is to issue an accurately counted number of labels. That number should be reconciled with the number of labels used, damaged and returned to stock.

In theory, the target set in your procedure should be “0” deviation for labels and other printed packaging materials. Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units packaged is investigated and satisfactorily accounted for before release.

Q.5 Is verification of empty containers an acceptable check for addition of ingredients?

A.5 Yes. It is acceptable to check staged materials prior to and after processing as a method of checks for addition through verification of empty containers.

The preferred method for conducting addition checks is by direct observation by the verifier. The verification of empty containers is an acceptable alternative, but only where stringent controls exist regarding the handling of dispensed raw materials.

Such controls include:

- assurance that a dispensed raw material does not end up in the wrong batch; locked portable cages are being used by some firms and only pertinent cages are permitted in the room at the same time.
- adequate operator awareness, training and motivation; the operator has to assure that additions are performed in the proper sequence; any spillage of raw materials must be promptly reported.
- pre and post checking should be performed by qualified personnel and whenever possible should be the same person.
- the post processing check must be performed prior to removal of any material from the area.

Q.6 Are quarantine and release stickers required on all containers of raw materials and packaging materials?

A.6 Quarantine and release stickers are required on all containers of raw materials and packaging components to identify status when a physical quarantine/release system is used.

However, such stickers are not required when a validated electronic quarantine system which effectively prevents the possibility of inadvertent use of unreleased material is in place.

When fully computerized storage systems are used, backup systems should be available in case of system failure.

Q.7 Is an answering machine acceptable for recall activation outside normal working hours?

A.7 A telephone answering machine may be used as part of the provisions for off-hours product recall activation. It should provide information on who to contact, their phone numbers, etc. Its use, functions and monitoring requirements should be included in the written procedures.

Q.8 Is it necessary to document quantities by lot numbers of finished stock destroyed?

A.8 For products returned to the distributor's facility for destruction due to reasons such as damaged or expired product, it may not be mandatory to document the quantities destroyed by lot number.

For products returned following a recall, it is mandatory to document the returns by lot number as it is a requirement to perform a final reconciliation.

If an establishment recall procedures depend on dates of first and last sale of a given lot, records of destruction by lot numbers may provide necessary information pertaining to accountability per lot.

Q.9 Is there a standard on what should be stated in a recall procedure? (Updated)

A.9 Section C.02.012(1)(a) of the *Food and Drug Regulations* requires that every fabricator, packager/labeller, distributor, importer, and wholesaler of a drug maintains a system of control that permits complete and rapid recall of any lot of batch of the drug that is on the market. Such a system must be tailored to an individual organization and operation.

A written recall system should be in place to ensure compliance with Section C.01.051 of the *Food and Drug Regulations* and should include the requirements outlined in Interpretations 1.1 to 1.11 under Section C.02.012 Manufacturing Control of the “[Good Manufacturing Practices Guidelines, 2009 Edition \(GUI-0001\)](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php)” (<http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php>). Additional information is available in the “[Recall Policy \(POL-0016\)](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/drugs-drogues/pol_0016_recall_policy-politique_retrait_ltr-doc-eng.php)” (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/drugs-drogues/pol_0016_recall_policy-politique_retrait_ltr-doc-eng.php) and the document entitled “[Product Recall Procedures](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/recall-retrait/recall_proc-marche_retrait-eng.php)” (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/recall-retrait/recall_proc-marche_retrait-eng.php).

Q.10 Under what circumstances must one initiate a recall? (Updated)

A.10 Please refer to the “[Recall Policy \(POL-0016\)](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/drugs-drogues/pol_0016_recall_policy-politique_retrait_ltr-doc-eng.php)” (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/drugs-drogues/pol_0016_recall_policy-politique_retrait_ltr-doc-eng.php) and the document entitled “[Product Recall Procedures](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/recall-retrait/recall_proc-marche_retrait-eng.php)” (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/recall-retrait/recall_proc-marche_retrait-eng.php).

Q.11 May firms omit second person component weight check if scales are connected to a computer system?

A.11 No, for an automated system that do not include checks on component quality control release status and proper identification of containers.

Yes, for a validated automated system with bar code reader that registers the raw materials identification, lot number and expiry date and that is integrated with the recorded accurate weight data.

Q.12 For a contract fabricator, is it a requirement to test the raw materials offered by customers? (Updated)

A.12 Testing of raw materials (RM) is a responsibility of the fabricator. Therefore, an observation will be made to a fabricator for not testing a particular RM (even when this RM is provided by the client) if he is not excluded by his client according to a contract. Interpretation 3.2 under Section C.02.012 Manufacturing Control covers the written agreements with regard to the fabrication, and packaging/labelling among the parties involved, and Interpretation 6.10 under Section C.02.015 Quality Control Department covers the written agreements with regard to the testing among the parties involved. If no such agreement is in place, the observation will be made against the party responsible according to the Good Manufacturing Practices.

Q.13 If the customer asks a contract fabricator not to test a finished product, is it necessary for the contract fabricator to test the product?

A.13 Interpretation 3.2 under Section C.02.012 Manufacturing Control covers the written agreements with regard to the fabrication, and packaging/labelling among the parties involved, and Interpretation 6.10 under

Section C.02.015 Quality Control Department covers the written agreements with regard to the testing among the parties involved. If no such agreement is in place, the observation will be made against the party responsible according to the Good Manufacturing Practices.

Q.14 Is a contract fabricator or packager responsible for qualification of utilities and systems and cleaning validation or is it the responsibility of the distributor? And what about the validation of the manufacturing/packaging process and test methods?

A.14 The contract fabricator is responsible for the qualification of utilities and systems and cleaning validation as those requirements are not product specific.

For process validation and test method validation, the main responsibility rests with the distributor, according to Section C.02.003 of the *Food and Drug Regulations*. The contract fabricator, packager or tester retains responsibility in terms of process or test methods validation unless a written agreement is signed by both parties that excludes the responsibility of the contract fabricator, packager or tester to perform validation activities.

Q.15 How long in advance can the raw materials be weighed? (Updated)

A.15 It is acceptable to weigh the raw material (RM) in advance of the scheduled date of production. However, the firm should be able to demonstrate that the materials and design of the containers in which the RM are weighed and kept will not alter their quality, the characteristics of the RM must also be taken into consideration. Interpretation 2 of Section C.02.026 Samples may provide guidance to this effect. Pre-weighed material should be appropriately labelled to ensure traceability. A system should be in place to ensure that the material is still suitable for use on the date of manufacturing.

Q.16 If a licensed packager/labeller is packaging a drug for a foreign establishment which is not intended to be sold in Canada as described under Section 1.0 of "[Conditions for Provision of Packaging/Labelling Services for Drugs under Foreign Ownership \(GUI-0067\)](#)" (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui_67-eng.php), should this foreign site be listed on the licence of the packager/labeller?

A.16 No. Since this drug would not be sold by the packager/labeller, this establishment would not be considered as an importer under Division 1A of the *Food and Drug Regulations* and thus, this site would not have to be listed on the licence of the packager/labeller. However, the packager/labeller would still need to fulfil all the requirements outlined under Section 4.0 of GUI-0067 that is: obtaining evidence of GMP compliance of the foreign site and supplying the proper information to Health Canada within the prescribed time frame.

Quality Control Department - C.02.013, C.02.014 & C.02.015

Q.1 If a product fails its particulate matter specifications, can it be released for sale?

A.1 No. The particulate matter requirement is treated in the same way as any other specification: failure would constitute non-compliance with the labelled standard.

Q.2 Are the United States Pharmacopoeia (USP) general notices enforceable?

A.2 Yes. The USP General Notices provide in summary form the basic guidelines for interpreting and applying the standards, tests, assays, and other specifications of the USP so that these general statements do not need to be repeated in the various monographs and chapters throughout the book. Where exceptions to the General Notices exist, the wording in an individual monograph or general test chapter takes precedence.

This concept is further emphasized in the introduction to the General Information chapters which states, "The official requirements for Pharmacopoeial articles are set forth in the General Notices, the individual monographs, and the General Tests and Assays chapters of this Pharmacopoeia." The General Tests and Assays chapters are those numbered lower than 1000.

Q.3 If a lot meets United States Pharmacopoeia (USP) specifications but fails the firm's internal specifications, can it be released?

A.3 If a lot does not meet its declared release specifications, then the lot should not be released. Where more stringent internal specifications act as an alert limit and not as the basis for release, then the lot may be released after investigation and justification provided it meets its release specifications.

Q.4 Is it acceptable for firms to export expired drugs for charity?

A.4 No. While it is recognized the dire need for drugs in distressed parts of the world, once the expiration date has passed there is no assurance that the drugs have the safety, identity, strength, quality and purity characteristics they purport or represent to possess. As such, expired drugs are considered adulterated and their introduction or delivery for introduction into commerce is prohibited.

Q.5 Explain the United States Pharmacopoeia (USP) measurement uncertainty (MU) requirement for balances.

A.5 USP General Chapter <41> Weights and Balance states a weighing device providing accurate weighing for assay and test is to have MU of less than 0.1% of the reading and gives an example of $50 \text{ mg} \pm 50 \text{ } \mu\text{g}$ as acceptable. To qualify MU of a balance, an appropriate National Institute of Standards & Technology (NIST) traceable weight within the weighing range of the balance is weighed 10 times or more. The resulting weights are calculated so that three times the calculated standard deviation divided by the amount weighed should be less than 0.001.

For different balance class designations and detailed information on weights and balance, the USP General Chapter <41> is to be consulted.

Q.6 Can an older version of an official method be used or must the most updated version always be used?

A.6 In resolving issues of conformance to an "official standard", the most up to date version of the analytical method is the method that must be used to determine compliance.

Q.7 What is the Inspectorate's position on the use of secondary reference standards (RS) and what are

the conditions for the use of secondary reference standards?

A.7 While the Inspectorate recommends the use of the official standards for the analysis of compendia articles, the use of a secondary RS is acceptable if each lot's suitability is determined prior to use by comparison against the current official reference standard and each lot is requalified periodically in accordance with a written protocol. The protocol should clearly address the receipt, storage, handling and use of primary reference standards, the purification of secondary standards, and their qualification against official reference standards.

Q.8 Is it acceptable to use a third party lab's available pharmacopeial reference standard to qualify an establishment's secondary standard?

A.8 This practice is acceptable providing the contract testing lab has an Establishment Licence (EL) and has been audited by the client to demonstrate its capability to qualify the secondary standard (i.e., the official standard and the proper equipment is available on the tester's premises, the method used has been validated, etc.). Transfer of the standard between the sites should be under controlled conditions.

Q.9 What is the Inspectorate's position on the use of loose work sheets as opposed to bound notebooks for the purpose of recording laboratory data?

A.9 The recommended method of recording laboratory data is a bound book but the use of loose work sheets would be acceptable as long as it is controlled by a system or a procedure to ensure that all raw data are true and accurate, properly recorded and captured, adequately maintained and easily retrievable. The system should also provide accountability and traceability of work sheets.

Q.10 It is generally accepted in the industry to perform process validation on three consecutive lots. How does the Inspectorate view validation when reworking is required (i.e., three consecutive incidents will never happen)?

A.10 Reworking of a batch should be a very rare occurrence. As such, validation of reworking is not considered mandatory as it is not generally feasible. The reworking should be carried out in accordance with a defined procedure approved by Quality Control (QC) and with the conditions described in Interpretation 6 of Section C.02.014 Quality Control Department. This procedure should include supplementary measures and testing during the reworking operations to ensure that the quality of the final product is not compromised.

It is mandatory that rework proposals and reworked product also be fully investigated with respect to impact on release characteristics and potential impact on bio-availability. Changes in formulation due to reworks including the incorporation of additional lubricant or dissolution aid or additional critical processes may require comparative bio-availability studies. Furthermore concomitant stability studies must be undertaken on reworked batches to ensure that critical characteristics are not compromised with time due to the rework.

Q.11 Is it mandatory for the approval of a procedure to sign each page or is it acceptable to only sign the first page?

A.11 It is not mandatory for the approvers to sign each page of the procedure. It would also be acceptable to only sign the last page.

Packaging Material Testing - C.02.016 & C.02.017

Q.1 What is the Inspectorate's position on 2-mercaptobenzothiazole (MBT) in rubber closures?

A.1 MBT is sometimes used in the manufacture of rubber stoppers used as closures for vials or as components of syringes. Due to the concerns about the potential toxicity of MBT, its use in the manufacture of packaging materials that are in direct contact with injectable drugs is not permitted.

Q.2 Is it necessary to include a chemical identification test in a specification for a packaging component (such as a plastic bottle)? Must this chemical identification (ID) be conducted for each lot received? Would vendor certification be considered an acceptable substitution for testing upon receipt?

A.2 If the type of material is described on the Certificate of Analysis (C of A) and if a specific test has been performed by the fabricator of the packaging materials confirming the identity of the starting polymer used to manufacture a specific lot, it is not necessary to repeat the chemical ID (such as Infra-Red). But each lot of packaging materials should be visually examined to confirm the identity.

Q.3 Can industrial grade nitrogen be used as a blanketing agent during the manufacture of a drug product?

A.3 No. Any gas used as a blanketing agent should be of compendial standard.

Finished Product Testing - C.02.018 & C.02.019 (Updated)

Q.1 Do bacteriostasis and fungistasis testing have to be performed for each lot of product in reference to the United States Pharmacopoeia (USP) sterility test?

A.1 No. This needs to be established only once for a specific formulation to determine the suitable level of inoculate for that product. If the formulation has not changed for a number of years, periodic verification can be done as microorganisms become resistant to preservatives in a formulation.

Q.2 Does the Inspectorate encourage the use of environmental isolates for preservative effectiveness testing?

A.2 While the use of environmental isolates in addition to the specified compendia cultures is acceptable, the use of environmental isolates alone is not acceptable.

Q.3 What are the Inspectorate's expectations for process parametric release for foreign and Canadian manufacturers? (Updated)

A.3 Further information is available in the document entitled "[Annex 17 of the Current Edition of the Good Manufacturing Practices Guidelines - Guidance on Parametric Release \(GUI-0046\)](#)"

(http://www.hc-sc.gc.ca/dhp-mps/compli-conform/int/part/gui_0046_tc-tm-eng.php). Please note that requests will be considered only for terminally sterilized drugs in their immediate containers and following

submission and approval of evidence acceptable according to this guidance.

Q.4 Should an inspector observe and question a technician's analytical work?

A.4 An inspector may verify if the laboratory staff is qualified to carry out the work they undertake. This could occasionally include the observation of what the laboratory technicians are performing and question their actual analytical work in conjunction with standard operating procedures (SOP), methods or equipment used.

Also, inspectors will frequently examine testing data from the laboratory for format, accuracy, completeness, and adherence to written procedures. These matters would usually be regarded as requirements under Section C.02.015 Quality Control Department. The general requirements are outlined in Interpretation 6. Laboratory supervisors must sign off subordinates work as per Interpretation 6.3.

Q.5 Does the official method DO-25 apply to tablets labelled as being professed or as manufacturer's standard?

A.5 Section C.01.015 of the *Food and Drug Regulations* specifies requirements relating to tablet disintegration times. These regulations require that all drugs in tablet form, intended to be swallowed whole, disintegrate in not more than 60 minutes when tested by the official method.

The regulations also prescribe a specific disintegration requirement and test for tablets which are enteric coated. Subsection (2) specifies conditions where subsection (1) requirements for DO-25 are not required, i.e., (e) drug demonstrated by an acceptable method to be available to the body, and (f) tablets which are for example extended release. Refer to C.01.011 and C.01.012.

The Inspectorate has no objection to the use of an alternate disintegration or dissolution method to demonstrate compliance with the prescribed release requirements provided that the method had been properly validated. It is understood the DO-25 is not generally used for new drugs.

Q.6 Do tests for impurities have to be repeated for finished products if they have been done on the raw materials?

A.6 The sponsor may have evidence that a related impurity present in the drug product is a previously identified/qualified synthetic impurity. In this case, no further qualification for that impurity is required at the drug product stage. The concentration reported for the established synthetic impurity may be excluded from the calculation of the total degradation products in the drug product, and should be clearly indicated as such in the drug product specifications. Evidence should be provided in the submission demonstrating the related impurity is indeed a synthetic impurity (e.g., by showing constant levels during accelerated and/or shelf-life stability studies and confirmation by providing chromatograms of spiked samples). In cases where the methodology applied to the drug substance and drug product differs, the claim should be confirmed by appropriate studies and the results submitted (e.g., using actual reference standards for that compound).

For further information regarding the control of impurities, please consult [Impurities in New Drug Substances - ICH Q3A \(R\)](#) ([http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q3a\(r\)-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q3a(r)-eng.php)) and

[Impurities in New Drug Products - ICH Q3B \(R\)](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q3b(r)-eng.php)

([http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q3b\(r\)-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q3b(r)-eng.php)).

Q.7 What are the minimum testing requirements for solid dosage drugs?

A.7 The testing requirements for solid dosage form products include description, identification, purity, and potency and other applicable quality tests depending on the dosage form (e.g., dissolution/disintegration/drug release, uniformity of dosage units, etc.).

For new drugs, the minimum testing requirements have to be approved by the review Directorates.

Q.8 What are the standards other than the United States Pharmacopoeia (USP) that have official status in Canada? (Updated)

A.8 The acceptable standards are described in Schedule B of the *Food and Drugs Act*;

- European Pharmacopoeia (Ph.Eur.)
- Pharmacopée française (Ph.F.)
- Pharmacopoeia Internationalis (Ph.I.)
- The British Pharmacopoeia (B.P.)
- The Canadian Formulary (C.F.)
- The National Formulary (N.F.)
- The Pharmaceutical Codex: Principles and Practices of Pharmaceuticals
- The United States Pharmacopoeia (U.S.P.)

Trade standards are also acceptable under certain conditions.

Q.9 Should compendial test methods be validated?

A.9 Since compendial methods cannot encompass all possible formulations of a drug product, the applicability of a compendial method to a company's particular formulation of a drug product must be demonstrated. It must be determined that there is nothing in the product that causes an interference with the compendial method or affects the performance of the method. It must also be established that the impurities that would be expected from the route of synthesis or formulation are controlled by the compendial method.

The main objective of validation of an analytical procedure is to demonstrate that the procedure is suitable for its intended purpose.

For guidance on validation of analytical procedures, please refer to [Text on Validation of Analytical Procedures - ICH Q2A](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q2a-eng.php)

(<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q2a-eng.php>) and [Validation of Analytical Procedures - ICH Q2B](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q2b-eng.php)

(<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q2b-eng.php>).

Q.10 Must all identification tests stated in a compendial monograph be performed?

A.10 Yes, all tests stated in the monograph must be performed.

Q.11 Are solid dosage drugs exempted from dissolution testing if sold under a manufacturer's standard?

A.11 No, solid dosage drugs should include a routine test for monitoring release characteristics (e.g., dissolution).

Q.12 Do products labelled as United States Pharmacopoeia (USP) have to be tested as per the USP test methods?

A.12 No. An alternate method can be used, but the distributor must demonstrate that USP drugs comply with USP specifications when tested by USP methods. If an alternate method is used, it must be fully validated and results from a correlation study should be available.

Q.13 What should be the calibration frequency for a dissolution apparatus used with both baskets & paddles?

A.13 The "[Good Manufacturing Practices Guidelines, 2009 Edition \(GUI-0001\)](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php)" (<http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php>) call for equipment calibration at suitable intervals. Although specific time periods are not given, equipment should be calibrated at a frequency necessary to ensure reliable and reproducible results and covered in the firm's standard operating procedures (SOP). The firm may consult the apparatus manufacturer's manual for guidance. Historical or validation data may also be used by the firm to support an appropriate calibration frequency.

In case of any event that might change operating characteristics of equipment, such as maintenance or moving it, it should be calibrated as required.

Q.14 In performing system suitability as per United States Pharmacopoeia (USP) <621>, do all replicate injections have to be completed before any analyte sample injections are made?

A.14 No.

Q.15 Is routine product pH testing required for endotoxin (*limulus amoebocyte lysate* - LAL) testing?

A.15 No, provided that the method is validated and the firm has not committed to such testing in a new drug submission.

Q.16 Is the use of recycled solvents for high performance liquid chromatography (HPLC) columns acceptable?

A.16 Yes, provided that appropriate validation studies have been performed.

Q.17 If one lot of a product made in a Mutual Recognition Agreement (MRA) country is split into two separate shipments, is it mandatory for the importer to obtain separate manufacturer's batch certificate for each shipment?

A.17 No. However, the importer should demonstrate that the conditions of transportation and storage applicable to this product have been met for each shipment.

Q.18 Is it acceptable to perform the testing, including the potency, before packaging or is it mandatory to perform this testing after packaging?

A.18 Other than the Identity testing which must be performed after packaging, as per Interpretation 1 under C.02.019 Finished Product Testing, there is no specific requirement to perform the other tests after packaging including potency. In such cases, the manufacturing process must be validated to demonstrate that the packaging / filling operation does not alter the quality of the product (including potency). These validation data must also demonstrate that the homogeneity of a product is maintained by appropriate means throughout the entire filling process for dosage forms such as lotion, creams or other suspensions. For parenteral, ophthalmic, and other sterile products, at least identity and sterility testing must be performed on the product in the immediate final container.

For the requirement to perform the identity testing after packaging, the unique identifier principle can be used as long as the chemical / biological identity test has been performed after the unique identifier is applied to the product.

Q.19 A product is manufactured in a non-Mutual Recognition Agreement (non-MRA) country, then shipped in bulk in a MRA country where it is packaged and tested before being released and exported to Canada. Would the testing exemption provided by Interpretation 4 under C.02.019 Finished Product Testing apply?

A.19 No.

Records - C.02.020, C.02.021, C.02.022, C.02.023 & C.02.024 (Updated)

Q.1 Must standard operating procedures (SOP) referenced in master production documents (MPD) be available at the importer's premises?

A.1 Procedures related to critical processes must be available, whether or not they are referenced in the MPD.

Q.2 Can chromatograms be stored on disc instead of retaining the hard copy? (Updated)

A.2 Yes, refer to the Interpretation under Section C.02.020 to C.02.024 Records.

Q.3 Does the person in charge of quality control have to sign Quality Control (QC) data and documents? (Updated)

A.3 QC data and documents must be signed by the person in charge of QC or by a designated alternate as per Interpretation 1.4 of Section C.02.006 Personnel, or Interpretation 2.2 in the case of a wholesaler. The person in charge remains accountable for the tasks delegated and retains the necessary authority.

Q.4 According to Section C.02.020 Records, documents to be kept by the fabricator, packager/labeller, distributor and importer must be stored on their premises in Canada. In the case of a distributor or importer particularly, these documents are sometimes kept only on the premises of a consultant hired to provide Quality Control (QC) services, therefore they are not available on the premises of the distributor or importer at the time of the inspection. Is this practice acceptable?

A.4 No. All documents required under Division 2 of the *Food and Drug Regulations* must be available on the premises of the distributor or importer. Exceptionally, the consultant may bring a file home for a short time to review it but if at the time of the inspection, required documentation are not available on the premises of the distributor or importer, an observation to this effect will be made in the report. In some cases, this could also lead to a non-compliant rating.

Q.5 If electronic signature is not validated, must the signed paper copy be available?

A.5 Yes. The signed paper copy should be available if the electronic signature system has not been validated.

Samples - C.02.025 & C.02.026 (Updated)

Q.1 What is considered an adequate sample when tank loads of a raw material is received?

A.1 As per Interpretation 3 under Section C.02.025-C.02.026 Samples, the retained sample should represent at least twice the amount necessary to complete all required tests. For bulk materials received in tankers, the retained sample should be taken before being mixed-up with the unused quantities still present in the storage tank.

Q.2 A pressurized tanker of hydrocarbon raw materials (isobutan, propane, etc.) is normally sampled and approved before pumping. What is the current Inspectorate policy for sample retention given the inherent risks generated by these flammable gases under pressure?

A.2 The intent of regulation C.02.030 is applied to these cases. Samples of pressurized raw materials are not expected to be retained by manufacturers.

Q.3 If a product is fabricated in Canada and exported outside of Canada (the product is not sold on the Canadian market), are samples of this finished product to be retained in Canada? (Updated)

A.3 No. This Canadian site is a contract fabricator and not a distributor. Subsection C.02.025 (1) of the *Food and Drug Regulations* (FDR) requires that a sample of each lot of the packaged/labelled drug be kept by the distributor and the importer (not the fabricator). This is also applicable if the Canadian fabricator manufactures a product for a Canadian distributor (Drug Identification Number (DIN) owner). While subsection C.02.025(2) of the FDR for retained samples of raw materials, the requirement applies to the fabricator (the person that transforms the raw material into a finished product), not the distributor. Subsection C.02.025(2) of the FDR for retained samples of raw materials, applies to the fabricator (the person that transforms the raw material into a finished product), not the distributor.

Q.4 If a product is fabricated in Canada, and contract packaged by another company in Canada and then exported outside of Canada (the product is not sold on the Canadian market), who is responsible

for retaining samples of the finished products?

A.4 The Canadian fabricator and the Canadian packager/labeller are not responsible for retaining samples of the finished product. Subsection C.02.025 (1) of the *Food and Drug Regulations* (FDR) requires that a sample of each lot of the packaged/labelled drug be kept by the distributor and the importer (not the fabricator). This is also applicable if the Canadian fabricator manufactures a product for a Canadian distributor (Drug Identification Number (DIN) owner). This could vary according to the requirement of each health authority. On the other hand, both parties (Canadian fabricator or packager/labeller) could negotiate a written contract or agreement with the foreign client (the distributor/owner of the product) in order to clearly mention who will be responsible to keep the retained samples of the finished product, as long as this is acceptable to the health authority of that country. Each country could have their own regulatory requirement.

Stability - C.02.027 & C.02.028 (Updated)

Q.1 Do batches have to be tested for preservatives at initial release and then in the continuing stability program? (Updated)

A.1 Finished products where antimicrobial agents are added to preparations such as multiple dose injections, topical creams, and oral liquids, an assay with limits should be included in the specifications.

An antimicrobial preservative effectiveness testing is performed during the development phase of the product to establish the minimal effective level of preservatives that will be available up to the stated expiry date, and for which a single regular production batch of the drug is to be tested for antimicrobial preservative effectiveness at the end of the proposed shelf life. Once the minimal effective preservative level has been determined, all lots of any preservative containing dosage form included in the stability program must be tested at least once at the expiry date for preservative content. For sterile drugs, the declaration of preservatives on the label is mandatory and those should be treated as for active ingredients (i.e., tested for preservative content at pre-established control points for those batches enrolled in of the continuing stability program). Where the lower limit of the preservative is less than 90 percent of label claim, the challenge test should be performed on samples at or below the lower limit. The challenge test need not be included in the specifications, provided that an assay for the preservative is included.

Q.2 Can it be assumed that United States Pharmacopoeia (USP) chromatographic assay methods are stability indicating?

A.2 No.

Q.3 Is it acceptable to place an expiry date on a bottle cap instead of on the bottle label?

A.3 No. Please refer to Section C.01.004(c)(v) of the *Food and Drug Regulations*. The expiration date must appear on any panel of the inner and outer label.

Q.4 When the labelled expiration date states only the month and year does it mean the end of the month?

A.4 Yes. The product should meet approved specifications up to the last day of the specified month.

Q.5 Can accelerated stability data of less than three months be used?

A.5 Accelerated stability studies of any length are considered as preliminary information only and should be supported by long term testing.

The assignment of expiry dates should be based on long term testing.

Q.6 Should drugs packaged into kits and subsequently sterilized, be tested for stability?

A.6 Yes. These operations are part of manufacturing. For drugs that are packaged into trays or kits and the resulting package is sterilized prior to being marketed, data should be available to demonstrate that the sterilization process does not adversely affect the physical and chemical properties of the drug. The testing should be sensitive enough to detect any potential chemical reactions and/or degradation, and the test results should be compared with test values obtained prior to sterilization.

Sterile Products - C.02.029 (Updated)

Q.1 Does the supervisor of a sterile product manufacturing facility need to have a degree in microbiology?

A.1 Section C.02.029(b) of Division 2 of the *Food and Drug Regulations* requires that "...a drug that is intended to be sterile shall be produced under the supervision of personnel trained in microbiology...". The expression "trained in microbiology" does not mean that this person must have a University degree in microbiology. However, the person must have taken university courses in microbiology.

Q.2 If water that has already been used in compounding is later found to contain endotoxins, what actions need to be taken? (Updated)

A.2 Water can be used for production prior to obtaining microbiological testing results but the results of these tests must be available prior to final release of the product. Good Manufacturing Practices permit release only after raw material and finished product testing is completed and results demonstrate compliance of the product with its specifications.

The appropriate action would include an investigation into:

- (i) the potential sources of endotoxins;
- (ii) the sanitation and maintenance of the water system.

Q.3 Are sterile products in amber glass and plastic ampoules exempt from 100% visual inspection? (Updated)

A.3 No. Each final container of injections must be subjected to a visual inspection. The 100% visual inspection test does not limit itself to particulate matter but includes sealing defects, charring, glass defects, underfills and overfills, missing print, etc. Please refer to Interpretation 84 under Section C.02.029 Sterile

Products. For parenterals, there are additional requirements for packaging (i.e., the immediate container shall be of such material and construction that visual or electronic inspection of the drug is possible). Please refer to Section C.01.069 of the *Food and Drug Regulations*.

Q.4 What are the requirements in terms of monitoring/testing for the release of sterile gowns to be used in a controlled environment (Grades A or B) when those are obtained from a supplier?

A.4 There is no specific requirements in the “[Good Manufacturing Practices Guidelines, 2009 Edition \(GUI-0001\)](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php)” (<http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php>) for the sterility testing of the protective garments to be worn in Grades A and B areas. However, the sterility cycle used by an outside supplier to sterilize these garments should have been validated according to scientifically sound procedures. Among other aspects, validation should address penetration/distribution studies of the sterilizing medium (gas, radiation, heat, etc.), load patterns of the sterilizers, determination of the Sterility Assurance Level with Bio indicators, etc. Also, the integrity of the outside wrapping in order to maintain sterility should be demonstrated.

Q.5 What are the room classification requirements for the preparation of containers and other packaging materials to be used in the fabrication of sterile products?

A.5 The preparation (cleaning, washing, etc.) of containers and packaging materials is normally performed in a “clean” room (Grades C or D). After these operations, the containers and materials used for drugs sterilized by filtration (and not further subjected to terminal sterilization in their final containers) must be depyrogenated and sterilized before being introduced in the aseptic rooms by the use of double-ended sterilizers or any other validated method. The depyrogenation step can be done using pyrogen-free water for injection (WFI) for the last rinse prior sterilization or by performing the depyrogenation and sterilization in one operation using a dry heat oven. Filling of these products normally takes place in a Grade A with a Grade B background.

For products submitted to terminal sterilization, it is not mandatory to use containers and packaging materials that are sterile but those that are in direct contact with the product should be free of pyrogen. This is usually achieved by using pyrogen-free WFI for the last rinse of these materials unless they are subsequently depyrogenated by another method (e.g., dry heat oven).

In addition, the initial bioburden of these materials should meet pre-established limits (that are based on sound science) and the risk of contamination during their introduction in the filling areas should be kept to a minimum.

Q.6 For the validation of moist heat sterilization cycles, will the new standards include the use of prions as the organism of choice instead of *Bacillus stearothermophilus*? (Updated)

A.6 At the present time, it is recognized in the scientific and pharmaceutical community that the spores of *Bacillus stearothermophilus* are the organisms of choice for the validation of moist heat sterilization cycles. Validation of such cycles is based on biological indicators containing a known count of organisms in order to determine a lethality factor for a given cycle. Those studies are based on parameters such as the “D” value of certain organisms and also imply a microbiological testing of these indicators at the end of the cycle in order to establish a survival rate. The use of prions (infectious proteins) could be inadequate in that their detection

and quantification, which is based on animal models, is very difficult. Moreover, these proteins are very difficult to destroy and could present a danger should they accidentally be spread in a plant.

Q.7 According to the monograph on parenteral products (0520) of the 4th edition (2002) of the European Pharmacopeia (Ph. Eur.), injections for veterinary use with a volume dose of less than 15 mL are exempted from bacterial endotoxins/pyrogen testing by the European Union (EU). Is this interpretation correct? If so, would this EU exemption be applicable in Canada?

A.7 Yes, this interpretation is correct but this exemption is not applicable in Canada.

As per Section C.01.067(1) of the *Food and Drug Regulations*, it is required that each lot of a drug for parenteral use be tested for the presence of pyrogens using an acceptable method and be found to be non-pyrogenic. The Bacterial Endotoxins and Pyrogen test methods described in the United States Pharmacopoeia (USP) and Ph. Eur. are considered acceptable methods for that purpose. For all parenteral drug products, the Bacterial Endotoxins test should be preferred over the Pyrogen test unless the latter is demonstrated to be justified (more appropriate) or has been approved by a review Directorate. Therefore, the specification of all drug products for parenteral use intended for the Canadian market should include a test for Bacterial Endotoxins or Pyrogens and the EU current "15 mL exemption" is not applicable in Canada.

The only acceptable exemptions are those provided by Section C.01.067(2) (i.e., for parenteral drug products inherently pyrogenic or those which cannot be tested for the presence of pyrogens by either test methods). In other words, not testing a parenteral drug product for the presence of pyrogens would be considered acceptable only if documentation is available demonstrating that the parenteral drug product is inherently pyrogenic or that it cannot be tested by any of the methods.

Q.8 For radiopharmaceuticals, can it be acceptable to verify the integrity of the sterilizing filter only after use and to not perform the pre-filtration integrity testing?

A.8 As per Interpretation 4.7 under Section C.02.029 Sterile Products, the integrity of the sterilizing filter must be verified before and after use. However, the pre-filtration integrity testing for that type of products could lead to radioactive contamination as a result of the venting process of the filter assembly that must be performed before the start of product filtration. This would pose an unacceptable health risk for the operators and could result in disruption of production until the facility is decontaminated. It is therefore acceptable to use two filters of a minimum filter rating of 0.22 micron and to verify the integrity of the sterilizing filters after use only for these products. However, data should be available from the filter manufacturer that the filters are supplied pre-assembled and individually integrity tested by the filter manufacturer.

Q.9 What is the Inspectorate's position on pooling of samples within the same batch (e.g., 7 samples in one pool) for testing for sterility? The European Pharmacopoeia (Ph. Eur.) does not mention explicitly a pooling of samples for testing for sterility.

A.9 It is acceptable if companies pool samples for sterility testing with the membrane filtration method. However, it is not acceptable to pool samples when the direct inoculation method is used. Exceptions can be tolerated, when the volume of the sample-pool does not exceed 10% of the culture medium volume.