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To: Associations

I am pleased to inform you that the final version of the guidance document entitled “GMP Interpretation Decision Record” is now available on the Therapeutic Products Programme (TPP) website at:

www.hc-sc.gc.ca/hpb-dgps/therapeut

For any further information regarding this document, please contact Ms. France Dansereau, Bureau of Compliance and Enforcement by telephone at (613) 957-1492, by fax at (613) 952-9805 or by e-mail at france_dansereau@hc-sc.gc.ca.

Original signed by

Dann M. Michols
Director General

Therapeutic Products Programme

OUR MISSION: To ensure that the drugs, medical devices, and other therapeutic products available in Canada are safe, effective and of high quality and that narcotic and restricted substances are controlled in an effective and efficient manner.

Programme des produits thérapeutiques

NOTRE MISSION: Faire en sorte que les médicaments, les matériels médicaux et les autres produits thérapeutiques disponibles au Canada soient sûrs, efficaces et de haute qualité et que les stupéfiants et les drogues d'usage restreint soient contrôlées de façon efficace et efficiente.

Bureau of Compliance & Enforcement
Therapeutic Products Programme
"GUIDE"

GMP INTERPRETATION DECISION RECORD

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GMP INTERPRETATION DECISION RECORD

INTRODUCTION

1.1 PURPOSE

The purpose of this record is to provide the inspectors / evaluator and industry with a reference to decisions made regarding GMP interpretations and to establish a standardized procedure for obtaining such interpretations.

This document will be updated to coincide with the revisions to the GMP Guidelines and other applicable guidance documents on Quality (e.g. ICH) and will be available on the web site and in print, in both official languages.

Alternate approaches to the situations described in this document may be acceptable provided they are supported by adequate scientific justification.

1.2 BACKGROUND

Enquiries may be received from industry by different approaches, such as during an inspector's visit at the premises of the firm or through the firm's contact with the Region's inspection/ investigation unit heads, or through contact with TPP head office, or through trade associations.

In most instances the responses to such enquiries will have already been established and will have been addressed in the GMP Guideline, or through the compilation of existing GMP Interpretation Decision Records, based on previous responses to industry and trade associations.

However, when an exceptional situation arises, and for which there is no established interpretation already available in writing, the response to the situation may result in setting a precedent.

1.3 SCOPE

The scope of this guide is limited to the resolution of issues pertaining to Part C, Division 2, Good Manufacturing Practices (GMP's). An attempt has been made to keep the issues of GMP current in this document. Due to the time required to collect all relevant questions and answers and the necessary editing, the information may require updating periodically.

The scope of this guide does not include any other parts of the Food and Drug Act and Regulations.

1.4 PROCEDURE

Enquiries may be submitted by stakeholders or associations either by writing to the regional offices of the TPP or at OCPC in Ottawa. The enquiries should be sent to the respective Head of the GMP unit or program manager of the region or the Head, GMP Unit in OCPC. The addresses of the regional offices of the TPP and OCPC are listed in Appendix 1. Enquiries may be submitted by mail (regular or electronic) or by Fax.

All enquiries will be proceeded as described in the SOP-0053.

2.0 GMP QUESTIONS & ANSWERS
(Grouped by Section of Division 2 Regulations)

2.1 PREMISES - C.02.004

2.1.1 ARE FIRMS REQUIRED TO USE HEPA FILTERS IN THE MANUFACTURE OF TABLETS AND CAPSULES ?

The GMP regulations do not specifically require tablet and capsule manufacturing facilities to maintain high-efficiency particulate air (HEPA) filtered air.

The Regulations do require use of equipment for adequate control over air pressure, microorganism, 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 "as 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.

2.1.2 IS THERE AN ACCEPTABLE SUBSTITUTE FOR DOP TO INTEGRITY TESTING OF HEPA FILTERS ?

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 high efficiency particulate air (HEPA) filters. Concern about the potential health effects to people working with DOP test aerosols has led to a search for a safer equivalent replacement.

The prime candidate from U.S. Army testing with assistance from various private companies was a Henkel Corporation (Emery Group) product called Emery 3004 PAO. This product is a polyalphaoefin (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.

2.1.3 OUR FIRM USES A DEDICATED SUITE FOR THE MANUFACTURING OF ANTINEOPLASTICS WHICH IS UNDER NEGATIVE PRESSURE TO THE REST OF THE FACILITY AND HAS THE AIR VENTED TO THE OUTSIDE; THE EQUIPMENT, HOWEVER IS NOT DEDICATED. IS THIS ARRANGEMENT ACCEPTABLE TO TPP?

According to our 1998 Edition GMP Guidelines under Premises C.02.004 Interpretation #11, certain biologic and cytotoxic drugs are required to be fabricated and packaged in separated facility with adequate containment. For specific facility requirements, the firm is to ask the respective review bureau. Equipment that is to be shared with other products must have cleaning validation with appropriate product residue limits that will satisfy the safety aspects of product cross-contamination.

2.2 EQUIPMENT - C.02.005

2.2.1 SHOULD EQUIPMENT BE LABELED WITH CALIBRATION DATES ?

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.

The GMP regulations do not require that each piece of equipment bear status labeling 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 noncritical equipment for calibration and maintenance purposes. However, the need for calibrating a given piece of equipment depends on its function. In general, things that measure materials warrant calibration. Equipment not requiring calibration/ maintenance need not be tracked or included in the firm's 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 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.

2.2.2 WHAT IS THE EXTENT OF CALIBRATION REQUIRED FOR VACUUM GAUGES?

Vacuum gauges are used during the essential evacuation of residual from high pressure cylinders, and therefore, need adequate calibration.

Vacuum gauges should undergo two types of calibrations. The first calibration is performed on a daily basis. The vacuum gauge should be checked with no vacuum present to ensure that the needle on the gauge returns to the "zero." This check could be recorded on the batch production record or on a separate vacuum gauge log.

The second and more significant calibration requires the vacuum gauge to be calibrated to standards established by the National Institute of Standards and Technology. The frequency of calibration could be what the gauge manufacturer recommends, or a firm could establish its own.

2.3 PERSONNEL - C.02.006

2.3.1 DOES THE SUPERVISOR OF A STERILE PRODUCT MANUFACTURING NEED TO HAVE A DEGREE IN MICROBIOLOGY ?

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..." TPP does not however interpret "trained in microbiology" to mean that the person supervising must have a University degree in microbiology. However, the person must have taken university courses in microbiology.

2.4 SANITATION - C.02.007 & C.02.008

2.4.1 IS FUMIGATION A TPP REQUIREMENT UNDER SANITATION ?

TPP expects that written sanitation programs include procedures for pest control as well as precaution 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.

2.4.2 WHAT IS TPP’s ACCEPTABLE LIMITS ON PRODUCT RESIDUES REGARDING SANITATION ?

Guidance for the establishment of limits can be obtained from the TPP's draft Cleaning Validation Guideline available on the TPP website.

2.4.3 SHOULD INDIVIDUALS WHO ARE KNOWN CARRIERS OF COMMUNICABLE DISEASES BE ALLOWED TO WORK IN PRODUCTION AREAS ?

The GMP regulations, Section C.02.008 deal with diseases which are in a communicable form. As long as Good Manufacturing Practices are followed, what might otherwise pose a small theoretical risk for transmission of Hepatitis B virus or HIV infection becomes negligible. Discriminatory action to restrict known carriers would almost certainly have no impact on product safety and might confer a sense of false security.

Nothing less than assuming every employee is a source of potential microbial contamination, is acceptable. This assumption serves to emphasize the continuing need to apply production and quality control standards meticulously.

Notwithstanding the above comments, it would appear to be appropriate to re-assign employees to alternate work should they volunteer information regarding their sero-positive status and request such reassignment.

2.4.4 ARE GOWNING ROOMS REQUIRED EVEN IN PILOT PLANT OPERATIONS ?

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 un-acceptable practice to gown in there. One should have a change room besides their sterile pilot plant production area.

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

2.4.5 WHAT ARE CONSIDERED AS BEING ACCEPTABLE LIMITS FOR CROSS-CONTAMINATION WHEN PERFORMING CLEANING VALIDATION ?

Contamination may include not only carry over from a previous product or residual cleaning solvents, but also detergents and surfactant.

No established standard acceptance limits for cleaning validation exist. Due to the wide variation in both equipment and products produced, it would be unrealistic for a regulatory body to determine a specific limit.

However, firms need to establish limits that reflect the practical capability of their cleaning processes, as well as the specificity of the analytical test method.

When determining the acceptance limit, relevant factors generally include: (1) Evaluation of the therapeutic dose carryover; (2) toxicity of the potential contaminant; (3) concentration of the contaminant in the rinses; (4) limit of detection of the analytical test method; and, (5) visual examination.

Guidance for the establishment of limits can be obtained from the TPP's draft Cleaning Validation Guideline available on the TPP website.

2.5 RAW MATERIAL TESTING - C.02.009 & C.02.010

2.5.1 WHAT IF WATER THAT HAS ALREADY BEEN USED IN COMPOUNDING IS LATER FOUND TO CONTAIN ENDOTOXINS, WHAT ACTIONS NEED BE TAKEN ?

Water can be used for production prior to obtaining microbiological result but one must have testing results prior to release of the product. GMP's require release only after testing is completed.

A product should be recalled if there is either a violation of the Act or Regulations or if it was beyond your direct control.

Since sterilization would not remove endotoxins, the product as an injectable sold with a potential for the presence of endotoxins in the product would be a violation and the hazard to health associated with the use of a violative product must be determined.

The appropriate action would include an investigation into:
(i) the potential sources of endotoxins;
(ii) the sanitation and maintenance of the water system;
(iii)the GMP deficiency that allows injectable products to be released prior to receiving test results. Procedures should be revised to prevent further occurrences.

2.5.2 WHAT ARE ACCEPTABLE MICROBIAL LIMITS FOR PURIFIED WATER ?

Firms should set and justify their own microbial limits for purified water (PW) based on at least two factors in production. First is the microbial specification of the finished product or the equipment surfaces which contact the water. The microbial limit for the water as a component should be more stringent than the limit set for the end product. For example, where a finished product has a microbial limit of not more than 100 cfu/ml, the corresponding limit for water as an ingredient in that product should be less than 100 cfu/ml.

The second factor is the validated water system's operational data. Properly controlled and well designed Purified Water systems should be capable of producing validated water quality in the range of 30-50 cfu/ml. Such operational data would not justify establishing a less stringent specification of "not more than 100 cfu/ml."

2.5.3 WHAT ARE THE CHANGES TO THE USP MONOGRAPHS FOR WATER ?

Please refer to the last edition of the USP and its supplements.

2.5.4 WHAT ARE THE REQUIREMENTS OF MAINTAINING AN IMPURITY PROFILE ?

The 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 24 <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, refer to:

TPP guidance *Identification, Qualification, and Control of Related Impurities in New Drugs*;
TPP guidance *Identification, Qualification, and Control of Related Impurities in Existing Drugs*;
ICH/TPP guideline *Impurities in New Drug Substances*;
ICH/TPP guideline *Impurities in New Drug Products*.

2.6 MANUFACTURING CONTROL - C.02.011 & C.02.012

2.6.1 IS COMPUTERIZED QUARANTINE ACCEPTABLE TO TPP ?

TPP has seen an increased use of computers in Manufacturing and Quality Control over the past few years. Computers are now used for material control, process controls, processing, packaging and release.

With this increased used of computer control it is not necessary to physically segregate and identify the status of a material after the material is assigned a unique incoming number that is used through the manufacturing process.

2.6.2 WHAT IS THE ACCEPTABLE DEVIATION IN PHYSICAL COUNTS OF FINISHED PRODUCT STOCK ?

The allowable deviation between physical counts v. counts as per the computer record should be zero. If product has been removed or disposed of for other than distribution purposes, a record should be maintained.

2.6.3 WHAT IS TPP's POSITION ON SOFTWARE VERIFICATION ?

Software is regarded as an adjunct to manufacturing procedures and controls and subject to the Good Manufacturing Practices Regulations (C.02.005 and C.02.011). Verification of software is a manufacturer's responsibility.

No specific guidelines have been issued to inspection staff for the review of computerized systems. Inspectors will review a company's procedures and systems, including computer systems, to determine that the requirements of the Good Manufacturing Practices Regulations (GMP) are being met. It is

possible that the company will be asked how they know a computer system in place is functioning as it should.

It is important to note that where the expression "written" is used in the GMP, the maintenance of hard copy records and data is required. Where "written" does not appear in the GMP, maintenance of information in electronic form is acceptable. It must, however, be emphasized that in cases where information is stored in electronic form, the information must be available on site at all times.

2.6.4 WHAT IS TPP's POSITION ON A PAPERLESS SYSTEM ?

Keeping in mind that we have yet to see a paperless system in place in the industry, we have the following comments:

The requirements under Records C.02.020 apply regardless of the system being paperless.

In design, the issues to be considered especially regarding validation would be based on the extent of the use of computerization and how is it built into the system. For example, in dispensing, will it be interfaced with the scale to have built-in verification of weights based on the input of a particular formulation?

Other possible considerations:

- who creates manufacturing masters and what is the assurance of current documents being used;
- how will all manufacturing information be reported; will it be restrictive or will there be allowance for deviations to be reported on the documents;
- will each operator have a code known only to them or will anyone have the ability to use others signatures;
- qualification validation - will the system work, especially regarding the control on issuance of work orders, release and approval of the batch at various stages of a process;
- will it be run against the paper system for a sufficient period of time as part of validation;
- will back-ups be made at appropriate intervals in case of system failure;

2.6.5 WHEN ARE INDEPENDENT CHECKS BY ANOTHER OPERATOR NECESSARY ?

Regulations requires 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 alternatives proposed by TPP 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 persons having the qualifications outlined.

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 will 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.

TPP has considered other means of verifying the addition of materials. 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.

2.6.6 WHAT ARE TPP's EXPECTATIONS ON LABEL ACCOUNTABILITY ?

Regarding label accountability, TPP expects 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.

Machine vision systems are available in different make models, feature and sensitivity.

Compatibility with variation in line speed, quality of print, container positioning, container size must be evaluated. The system should be validated. A routine calibration/sensitivity check must be implemented.

The common approach by industry is to have both systems in place simultaneously and then reduce the extent of label accountability checks once adequate confidence is gained using the specific model of machine vision for a specific set of variables of a labelling operation.

2.6.7 IS VERIFICATION OF EMPTY CONTAINERS AN ACCEPTABLE CHECK FOR ADDITION OF INGREDIENTS ?

Yes; it is acceptable to check staged materials prior to and after processing as a method of addition checks through verification of empty containers.

The preferred method for conducting addition checks is by direct observation by the verifier, however TPP has accepted the practice in question, 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.

- the individual doing pre and post checking should be the same.

- the post processing check must be performed prior to removal of any material from the area.

2.6.8 ARE THERE GUIDELINES FOR IN-HOUSE COMPUTER SYSTEMS ?

No specific guidelines have been issued to inspection staff for the review of computerized systems and for the type of documentation required regarding the validation of in-house computer systems.

Inspector will review company's procedures and systems, including computer systems to determine that the requirements of the GMP regulations are being met. If it is possible, that company will be asked how they know a computer system in place is functioning as it should, e.g. systems and procedures used to take into account for inventory of the printed materials.

2.6.9 WHAT ARE TPP's EXPECTATIONS OF SOFTWARE VALIDATIONS PERTAINING TO PRODUCT RELEASE SYSTEMS ?

There are currently no requirements under the GMP Regulations related specifically to the validation of computer software.

Manufacturers are responsible to develop and maintain evidence demonstrating that software and equipment are operating as designed and expected as being part of an over all process validation.

Though no specific guidelines have been issued to inspection staff for the review of computer systems, companies may be asked how they know their system(s) is operating as it should.

2.6.10 ARE QUARANTINE AND RELEASE STICKERS REQUIRED ON ALL CONTAINERS OF RAW MATERIALS AND PACKAGING MATERIALS ?

No, quarantine and release stickers are not required on all containers of raw materials and packaging components to identify status unless a physical quarantine/release system is used.

The interpretation of Section C.02.011 of the Good Manufacturing Practices Regulations states that raw materials and packaging materials should be held in quarantine and so identified until released by the Quality Control Department. The method of such identification is not specified. Any system, such as an electronic quarantine system, which effectively prevents the possibility of inadvertent use of unreleased material would be considered adequate with adherence to specified standard operating procedures.

2.6.11 IS AN ANSWERING MACHINE ACCEPTABLE FOR RECALL ACTIVATION OUTSIDE NORMAL WORKING HOURS ?

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

2.6.12 IS IT NECESSARY TO DOCUMENT QUANTITIES BY LOT NUMBERS OF FINISHED STOCK DESTROYED ?

Returned goods are received at the distributor's facility for destruction due to such reasons as damage or expired product. This is then sent to a disposal facility for incineration. It may be necessary to document the quantities destroyed by lot number.

TPP's position is that depending on the recall procedures of a company it is necessary to document the quantities of drugs destroyed by lot number where product distribution traceability is based on a lot number. Such records are felt to be necessary in order to facilitate an appropriate recall.

2.6.13 WHAT ARE ACCEPTABLE LIMITS ON PRODUCT ACCOUNTABILITY IN A DRUG PRODUCT RECALL ?

TPP considers a recall procedure to be satisfactory if it is effective in a worst case scenario (Class I Recall) - that is, the firm is able to contact 100% of its customers in a timely manner by the most efficient way. In all instances TPP expects that a firm will have in place the necessary procedures to reconcile what has been shipped and what has been returned to stock. The class of the recall will govern TPP's expectations as to the degree of customer response; the recovery of stock and the speed with which the recall is accomplished.

2.6.14 DO TPP STANDARDS EXIST ON WHAT SHOULD BE STATED IN A RECALL PROCEDURE ?

Regulations C.02.012 requires that every manufacturer and importer 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.

Considerations for design of an effective recall system are provided in the GMP Guidelines. Other guidance is available in Information Letter Number 661 and its attachment entitled Product Recall Procedures. This provides such information as useful definitions, recall strategies and general guidance which will aid in developing a good recall system.

Such a system must be tailored to an individual organization and operation.

The inspection process along with GMP's should not be viewed as static but one which is continuously evolving to best meet the identified concerns in a changing industry.

2.6.15 UNDER WHAT CIRCUMSTANCES MUST ONE INITIATE A RECALL ?

TPP does not have the legislative mandate under the Foods and Drugs Act to order the recall of defective drugs in the marketplace. As a result, recalls are usually carried out voluntarily by the distributor/ legal agent of the drug.

Assuming that a company discovers that one of its drugs is defective and decides to recall it: once the company has made this decision it must then comply with Regulation C.01.051. This regulations legally imposes an onus on the recalling firm to inform TPP "forthwith" of its decision to recall and it must also provide the data specified in the Regulation.

In these instances, the recalling company takes full responsibility for the recall and necessary effectiveness checks. TPP's role is to monitor the effectiveness of the recall and to provide scientific, technical and operational advice. The initial contact should be directed to the nearest Regional Office. TPP requires the company to provide a list of the affected lot number(s) of the recall product.

Each Region has product category "recall coordinators" in place. Contact after hours is also possible through cell phones.

Each Region has a person on stand-by after hours seven days a week.

In other instances TPP may inform a company of findings that one of its drugs is defective and recommends that a voluntary recall be initiated. Usually the company complies. If it does not, TPP may, depending on the seriousness of the situation, seize product in the marketplace and elsewhere and it may also through the Minister, issue an alert to the general public in which they would be advised of the health risk and warned against consuming the defective lot or lots of the drug in questions.

Information Letter 661 contains detailed information about TPP's procedures (for copies, please contact HPB Communications, Building #7, Tunney's Pasture, Ottawa, Ontario K1A 0L2 Phone: (613) 957-0629).

2.6.16 WHAT ARE TPP's EXPECTATIONS OF A FIRM'S SELF-INSPECTION PROGRAM?

There has been no change to TPP's approach to the evaluation of compliance with the requirements of Section C.02.012 of the Good Manufacturing Practices Regulations.

Acceptable elements of a self-inspection program are described in the current edition of the GMP Guidelines.

2.6.17 MAY FIRMS OMIT SECOND PERSON COMPONENT WEIGHT CHECK IF SCALES ARE AUTOMATICALLY RECORDED TO A COMPUTER SYSTEM ?

Normally, automatically recording weight alone would not meet the specific intent if the automated system did not include checks on component quality control release status and proper identification of containers.

However, 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 would be an acceptable alternative to a second person for weight check

2.6.18 MUST A BATCH BE FORMULATED TO PROVIDE NOT LESS THAN 100% OF THE ACTIVE PHARMACEUTICAL INGREDIENTS ?

Master formulae must be written to provide not less than 100% of the active pharmaceutical ingredients. When manufacturing a batch, the present interpretation 27.4 in C.02.011 requires to adjust the quantity of each Raw Material, where necessary, according to assay results. Literally, this means that the quantity of each raw material should be adjusted even when the assay results are just slightly below 100%. However, because of the increased possibilities of calculation errors, it is considered acceptable to adjust the quantity of active Raw Material only when the assay value is less than 99.0% calculated on “as is” basis.
The next edition of the GMP guidelines will be revised accordingly.

2.6.19 MUST WRITTEN PROCEDURES BE AVAILABLE TO PREVENT OBJECTIONABLE MICROORGANISMS IN DRUG PRODUCTS NOT REQUIRED TO BE STERILE ?

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.

The meaning of "objectionable" has several facets that need to be evaluated on a case by case basis by each drug manufacturer. The primary meaning relates to microbial contaminants that, based on microbial species, numbers of organisms, dosage form, intended use, patient population, and route of administration, would adversely affect product safety. OF course, most objectionable would be organisms that pose a threat of patient infection or mortality.

Microorganisms may be "objectionable" by virtue of other problems. For example, microbial content that adversely affects product stability, would be objectionable. Likewise, microorganisms that react with, or potentially damage the integrity of, the container closure system (fermentation creating gaseous pressures that explode a container would be an extreme, though legitimate, example), would be objectionable. Similarly, microbial content that interferes with analytical methods, or active ingredient bioavailability, would be objectionable.

For new drugs, the above considerations will likely have been addressed during the new drug review process and may result in microbial specifications for the end product.

Establishing production time limits is an example of a control to prevent objectionable microorganisms. When appropriate, time limits for the completion of each phase of production must be established and followed. Where a firm finds it necessary to hold a bulk topical or liquid product for several months until it is filled, the firm should establish a holding time limit to prevent microbial build up that would be objectionable. Validation and control over microbial content of purified water systems used in certain topical products are also examples of such procedures.

2.7 QUALITY CONTROL DEPARTMENT - C.02.013, C.02.014 & C.02.015

2.7.1 IF A PRODUCT FAILS USP PARTICULATE MATTER SPECIFICATIONS CAN IT BE RELEASED FOR SALE ?

The particulate matter requirement in the USP is treated in the same way as any other compendia requirement: failure would constitute non-compliance with the labelled standard.

Action by TPP would be appropriate to the hazard involved. This may involve anything from a stop sale on current stock to a recall in a more hazardous situation. Where failures occur, TPP would expect that the distributor investigate the situation and take appropriate corrective measures to prevent future recurrences of the problem.

This requirement is also applicable to products official in the USP but marketed as a manufacturer's standard by virtue of section C.01.011.

A distributor may employ alternative methods of analysis on a routine basis - providing that the alternative method is shown to produce equivalent results.

With regard to New Drugs, the particulate matter requirement is part of the new drug submission review and approval process which is administered by the TPP.

2.7.2 ARE VETERINARY STERILE PRODUCTS AND HUMAN STERILE PRODUCTS IN AMBER GLASS AND PLASTIC AMPOULES EXEMPT FROM 100% VISUAL INSPECTION ?

USP General Requirements for Injections states that Good Pharmaceutical practice requires each final container of Injections be subject individually to a physical inspection, whenever the nature of the container permits and that every container whose contents show evidence of contamination with visible foreign material be rejected.

Veterinary products are not exempt form this compendium requirement neither are they exempt from the GMP Regulations-- particulate are of GMP concern and may at times be of stability concern depending upon the causes; the 100% visual inspection test does not limit itself to particulate matter but includes sealing defects, charring, glass defects, underfill and overfills, missing print, etc.

2.7.3 DOES TPP INTEND TO PROHIBIT THE USE OF CHLORO FLUOROCARBON IN DRUGS ?

The regulation of CFC's, (as far as its effect on the ozone layer is concerned), is within the jurisdiction of Environment Canada. Current requirements under legislation administered by Environment Canada prohibit the use of CFC's in hair sprays, deodorants and anti-perspirants. Information on additional restrictions over the use of CFC's being considered may be obtained by contacting Environment Canada directly.

2.7.4 ARE THE USP GENERAL NOTICES ENFORCEABLE ?

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. Here it states, "The official requirements for Pharmacopeial articles are set forth in the General Notices, the individual monographs, and the General Tests and Assays chapters of this Pharmacopeia." The General Tests and Assays chapters are those numbered lower than 1000.

2.7.5 IF A LOT MEETS USP SPECIFICATIONS BUT FAILS THE FIRM'S INTERNAL SPECIFICATIONS, CAN IT BE RELEASED ?

Determine how the firm intends to apply the internal specification. If the more stringent specification functions as an alert limit, and not a hard and fast lot release criterion, then the lot may be released. These limits should be based on appropriate validation studies.

On the other hand, if the firm has committed itself (e.g., in a new drug submission, or otherwise) to the specification as a lot release condition, then the lot should not be released, because as a matter of GMP's, the firm did not adhere to its established release specifications. The lot should be rejected, if it fails the hard and fast release specification.

In addition to the appropriateness of lot release, you should also consider whether or not the firm investigated the failure of the lot to meet either the alert or release specifications. Failure to meet specifications must be thoroughly investigated, and the investigation must include conclusions and follow up.

2.7.6 IS IT ACCEPTABLE FOR FIRMS TO EXPORT EXPIRED DRUGS FOR CHARITY ?

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 adulterated which as such prohibits the introduction or delivery for introduction into commerce any drug that is adulterated.

2.7.7 CAN A SINGLE LOT NUMBER BE ASSIGNED TO TWO OR MORE CO-MINGLED LOTS OF BULK FINISHED DRUG PRODUCTS REPACKAGED DURING THE SAME RUN ?

GMP guidelines require each batch must be identified by an individually numbered manufacturing order, 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. If these requirements are met, a company can decide to package under one lot number from 2 or more manufacturing batches of bulk finished drug products. The shortest expiry date of all the lots packaged must be indicated on the label.

However, should a company plan to go ahead with this, it must consider that in case of a product recall, the company must recall the entire lot comprising all the sub-lots. Until such scientific evidence proves beyond doubt that a particular isolated sub-lot is identified as the cause of recall, all the co-mingled lots would also have to be recall from the finished product supplier.

2.7.8 CAN THE SAME LOT NUMBER BE ASSIGNED TO A RE-PACKAGING OPERATION WHEN THE PRODUCTS ARE FROM THE SAME ORIGINAL MANUFACTURER'S LOT ?

Yes. Drug products should be identified with a lot or control number that permits determination of the history of the manufacture and control of the batch. The fact that the repackager receives the single manufacturer's lot as separate shipments does not make each shipment a separate lot itself. However, the repackager may, at its own discretion, want to further identify each packaging run with a unique number.

Repackager should be performing an identity test on a representative sample of each lot in each incoming shipment of drug products, regardless of whether identity testing was performed previously on samples from the same lot received during an earlier shipment.

2.7.9 CAN INDUSTRIAL GRADE NITROGEN BE USED AS A BLANKETING AGENT DURING THE MANUFACTURE OF A DRUG PRODUCT:

No, unless the manufacturing process of the industrial grade is known, and its potential contaminants that may be a resultant of the process is evaluated, and the nitrogen is analyzed for all possible impurities and contaminants, it would be unacceptable to use industrial grade products in the manufacturing of pharmaceutical drugs.

The filling of medical and industrial grade nitrogen whether it be gaseous or liquid is quite unique. The problems are usually not only with the product itself, but also with the container closure system, i.e., the high pressure cylinder and hazardous substances to which they have been exposed.

Industrial cylinders are widely distributed throughout all types of industry, and are routinely exposed to hazardous substances, some of which are extremely toxic, i.e., hydrocarbons, arsenic compounds, chlorine, etc. Therefore, it would be nearly impossible to determine what a specific cylinder had been exposed to and to analyze for that specific contaminant.

On the other hand, medical gas cylinders are prepared under carefully controlled conditions to ensure that the drug product meets the requirements of both GMPs and the USP, and are not exposed to contamination from industrial sources.

Each high pressure cylinder undergoes rigorous pre-qualifying inspections and examinations with one of the most significant being the vacuum evacuation step, prior to filling a product.

According to USP 23, the General Notices, Tests and Assays, Foreign Substances and Impurities, it is impossible to include in each monograph a test for every impurity, contaminant, or adulterant that might be present. Tests suitable for detecting such occurrences should be employed in addition to the tests provided in the individual monograph.

2.7.10 WHAT ARE THE CURRENT USP REQUIREMENTS FOR PRODUCT TITLES FOR INJECTABLE PRODUCTS ?

For established names of injectable products, the following USP classification system should be used in determining the product's title:

LIQUIDS

Title for liquid preparations that are drug substances or solutions thereof:
[DRUG] INJECTION

Title for liquid preparations of solids suspended in a suitable liquid medium:
[DRUG] INJECTABLE SUSPENSION

Title for liquid preparations of drug substances dissolved or dispersed in suitable emulsion medium:
[DRUG] INJECTABLE EMULSION SOLIDS

Title for dry solids that, upon the addition of suitable vehicles, yield solutions conforming in all respects to the requirements for Injections:
[DRUG] FOR INJECTION

Title for dry solids that, upon the addition of suitable vehicles, yield preparations conforming in all respects to the requirements for Injectable Suspensions:
[DRUG] FOR INJECTABLE SUSPENSION

2.7.11 KINDLY EXPLAIN THE USP MEASUREMENT UNCERTAINTY (MU) REQUIREMENT FOR BALANCES:

USP 23 General Chapter <14> 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 mg ± 50 µg as acceptable. To qualify MU of a balance, an appropriate NIST traceable weigh 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, USP 23 General Chapter <14> is to be consulted.

2.7.12 CAN AN OLDER VERSION OF AN OFFICIAL METHOD BE USED OR MUST THE MOST UPDATED VERSION ALWAYS BE USED ?

In resolving issues of conformance to an "official standard" , the current version of the analytical method is the method that will be used to determine compliance.

From a compliance point of view, all compendia products must meet, at any point in their shelf lives, the standards set forth in the revision of the compendia that was current at the time the drugs were manufactured.

Monographs published in the current revision of the compendia supersede all earlier revisions.

2.7.13 IS THE YEAR 2000 A POTENTIAL GMP COMPLIANCE PROBLEM. IF SO WHY ?

Much has been written about the year 2000 (y2k) problem regarding how some software performs date related computations. Be aware of potential y2k problems firms may face in the context of GMP records and computations. Here's why.

When mainframe computers were in the majority and computer memory was at a premium, software frequently represented dates in formats (such as DDMMYY) that used only two digits to represent the year. Date related computations were calculated reliably using this format. For example, if you were born in 1960 the software might calculate your age by subtracting the last two digits of your birth year from the last two digits of the current year (for example, 96-60=36). However, using this method when the current year is 2000 would yield a negative number (00-60=-60), with unpredictable consequences. Date sorting, too, can be erroneous. The years 1965, 1905 and 1966 would, for example, correctly sort in ascending order as 05, 65 and 66, but adding 2015 would incorrectly yield 05, 15, 65, and 66.

Some firmware may also have difficulty with y2k. Basic Input and Output Systems (BIOSes) may, by ignoring the century indicating bit, not accurately read or set some older real-time clock chips. In addition, some firmware reportedly "wraps" back to 1994 from 1999.

To test your machine, set its clock to 11:58 p.m., December 31, 1999. Turn off your computer and, after waiting a few minutes, turn it back on and see if the date and time crossed the millennium correctly.

Drug establishments should know how their software calculates dates and, in particular, if their systems are susceptible to the y2k problem. Although we don't expect many such systems to exist in what is essentially a very progressive industry, you may nonetheless encounter some older systems, or newer GMP related software, that use two digits to represent the year. Vulnerable programs will likely need to be changed to retain the accuracy of such GMP computations as determining: expiration dates, equipment calibration and maintenance dates, records and reserve sample retention intervals, and trends to assess the need for manufacturing changes.

2.7.14 WHAT IS TPP's POSITION ON THE USE OF SECONDARY REFERENCE STANDARDS AND WHAT ARE THE CONDITIONS FOR THE USE OF SECONDARY REFERENCE STANDARDS ?

As outlined in TPP's guideline *Acceptable Methods* (section 2.3.2), a House or Working Standard may be used if it is properly validated against the official standard. Data that would be considered acceptable for the use of a Secondary Reference Standard would include: (i) copies of its IR and UV spectra together with the spectra of the official standard, run concomitantly, (ii) a copy of the certificate of analysis, and (iii) a description of any additional purification steps used for the standard.

2.7.15 IS IT ACCEPTABLE TO USE A THIRD PARTY LAB'S AVAILABLE USP REFERENCE STANDARD TO QUALIFY AN ESTABLISHMENT'S SECONDARY STANDARD?

This practice is fully acceptable providing the contract testing lab has an EL and has been audited by the client to demonstrate its capability to qualify the secondary standard (ie. the official standard and the proper equipment is indeed available on the tester's premises, the method used has been validated...). TPP recommends that the client to obtain from the contract lab copies of all raw data such as log books, chromatogram, etc... as part of the record for the secondary standard.

2.8 PACKAGING MATERIAL TESTING - C.02.016 & C.02.017

2.8.1 IS LABEL DISCLOSURE OF NON-MEDICINAL INGREDIENTS BEING ENCOURAGED BY TPP ?

Sponsors are encouraged to declare qualitatively all non-medicinal ingredients in the Composition section of the Product Monograph. and on product labels. For injectable products, the active ingredients and the preservatives used shall be quantitatively declared on the container labels as described in the Food and Drugs Regulations section C.01.004 (2).

2.8.2 WHAT IS TPP'S POSITION ON 2-MERCAPTOBENZOTHIAZOLE IN RUBBER CLOSURES ?

MBT is sometimes used in the manufacture of rubber stoppers used as closures for vials or as components of syringes. Due to the concerns of the potential toxicity of MBT, its use is not permitted.

2.8.3 IS THERE A LIMIT TO THE NUMBER OF WITHDRAWALS THAT MAY BE MADE FROM AN INJECTABLE MULTI-DOSE CONTAINER ?

USP contains the following requirements: Unless specified in the individual monograph , no multiple-dose containers contain a volume of Injection more than sufficient to permit the withdrawal of 30 mL. The total number of withdrawals is based on the volume of the container and the dose to be administered. For Injections in multiple-dose containers labelled to yield a specific number of doses of a stated volume, the volume is such that each syringes delivers not less than the stated dose.

2.9 FINISHED PRODUCT TESTING - C.02.018 & C.02.019

2.9.1 DOES THE VENDOR/ FABRICATOR HAVE TO PERFORM FINISHED PRODUCT TESTING ?

Section C.02.019 (1) requires that the packager/labeller, distributor referred in C. 01A.003(b) or importer test each lot of drug after receipt or alternatively qualify and periodically confirm the adequacy of testing performed by the supplier (or the custom lab employed by the supplier). The responsibility for carrying out testing under Section C.02.019 (1), rests with the aforementioned, not the vendor. Consequently, each lot of drug need be adequately tested only once.

The vendor has the option of not doing finished product testing, and instead can ship the product under quarantine to the aforementioned who would then do complete testing on each lot.

If the vendor opts to test (or have tested) each product lot before releasing it, this does not relieve the aforementioned of the responsibility under the Regulation to either retest each product lot after receipt or qualify and periodically confirm the adequacy of the vendor's test results.

Where the packager/labeller, or distributor in Canada has a corporate association with the supplier and can show that this relationship is truly in effect ie. labelled as to both fabricator and distributor, then finished Product Testing need not be performed. As of the GMP 1998, if requirements of Interpretation 2.1 are met, then 2.1.3 ie. One lot per dosage form applies.

When confirmatory testing is performed by the distributor it is preferable that a laboratory other than the one that initially performed the testing, do the confirmatory testing; however if Interpretation 2.1 is met, then the suppliers laboratory may do the confirmatory reduced testing. Interpretation 2.1.2 applies regarding Authentic Certificate of Analysis.

2.9.2 DO BACTERIOSTASIS AND FUNGI STASIS TESTING HAVE TO BE PERFORMED FOR EACH LOT OF PRODUCT IN REFERENCE TO THE USP STERILITY TEST ?

No. This needs only to be established once for a specific formulation to determine the suitable level of inoculant for that product. However , the laboratory must incorporate applicable preparation into the Sterility test method when the article is shown to have bacteriostatic / fungi static properties. It is advisable to carry out bacteriostatic / fungi static testing with typical pathogenic and environmental organisms. Also, if the formulation has not changed for a number of years one may periodically verify as microorganisms become resistant to preservatives in a formulation.

2.9.3 DOES TPP ENCOURAGE THE USE OF ENVIRONMENTAL ISOLATES FOR PRESERVATIVE EFFECTIVENESS TESTING ?

Both the BP/Ph.Eur. and USP reference preservative effectiveness testing in their respective pharmacopoeia; both pharmacopoeia reference specific test organisms to be used.

Other microorganisms in addition to those listed, may be included in the test on an optional basis especially if it appears likely that such microorganisms may represent contaminants likely to be introduced during the use of the drug.

Environmental isolates in place of the specified cultures is not an acceptable alternative.

As for item 2.9.2 above, because microorganisms may become resistant to ingredients in a formulation, one may periodically verify, if the formulation has not changed.

2.9.4 DO COMPENDIA/ NON-COMPENDIA BIOLOGICAL ASSAY METHODS HAVE TO BE VALIDATED ?

Yes. Refer to TPP's guideline *Acceptable Methods* or ICH/TPP guidelines *Text on Validation of Analytical Procedures* and *Validation of Analytical Procedures: Methodology* for acceptable approaches to the validation of analytical methods. For compendial methods, Table 3-4 of the *Acceptable Methods* guideline outlines the criteria necessary to validate compendial methods.

2.9.5 WHAT ARE TPP'S EXPECTATIONS FOR PROCESS PARAMETRIC RELEASE FOR FOREIGN AND CANADIAN MANUFACTURERS ?

Both Canadian and foreign manufacturers may submit evidence to establish that processing controls ensure the sterility of a drug in its final container. Where the submitted evidence has been found satisfactory, sterility testing of the drug in its final container is not required. During GMP inspections and other in-plant activities, inspectors will review documentation/practices to determine that the submitted processing controls have been followed during production. PPR is considered acceptable, but the procedure should receive approval prior to its implementation.

For additional information, refer to the ICH guideline *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Products: Chemical Substances and Products*.

2.9.6 DOES TPP ACCEPT ATP BIOLUMINESCENCE TECHNOLOGY AS AN ALTERNATE FOR TRADITIONAL MICROBIOLOGY; IF SO TO WHAT EXTENT IS VALIDATION REQUIRED ?

Yes, TPP is aware that the ATP Bioluminescence technology has been studied as an alternate for the traditional standard plate count analysis in certain products.

This method was developed to detect the presence of bacteria through their ATP content determined by enzymatic reactions producing light (bioluminescence meaning intensity of light emitted is proportional to ATP concentration).

The technique was studied mainly in the food sector (fish, meat, milk). So far, the procedures described are only tentative and useful only under tightly defined circumstances. The ATP method seems to provide a fast indication of the total count of microorganisms.

It is important to validate the technique for each raw material analysed because of the possibility of false positive as a result of non-microbial ATP or false negative produced by degradation of ATP or interference by the raw material itself.

2.9.7 SHOULD AN INSPECTOR OBSERVE AND QUESTION A TECHNICIANS ANALYTICAL WORK ?

An inspector may verify is 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 SOP's, 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 Quality Control Dept. C.02.015. The general requirements are outlined in Interpretation para 6, in particular 6.3 laboratory supervisors must sign off subordinates work as per 6.3.

2.9.8 DOES THE OFFICIAL METHOD DO-25 APPLY TO TABLETS LABELLED AS BEING PROFESSED OR AS A MANUFACTURER'S STANDARD ?

Sections 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) ie requirements for DO-25 are not required. ie. (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.

TPP 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.

2.9.9 FOR MULTI VITAMIN TABLETS DOES THE IMPORTER HAVE TO PERFORM COMPLETE CHEMICAL IDENTITY ?

Physical identity, after receipt on the premises, is only permissible in instances where the full chemical identity has previously been performed by the fabricator on a container/closure system that is unique for that product i.e. the fabricator must meet all of the requirements of the TPP policy on unique identifiers.

Refer to TPP compliance guideline: *Unique Identifier Principles for Positive Identification of Drug Products*.

2.9.10 DO TESTS FOR IMPURITIES HAVE TO BE REPEATED FOR FINISHED PRODUCTS IF THEY HAVE BEEN DONE ON THE RAW MATERIALS ?

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, refer to:

TPP guidance *Identification, Qualification, and Control of Related Impurities in New Drugs*;
TPP guidance *Identification, Qualification, and Control of Related Impurities in Existing Drugs*;
ICH/TPP guideline *Impurities in New Drug Substances*;
ICH/TPP guideline *Impurities in New Drug Products*.

2.9.11 WHAT IS THE MINIMUM TESTING REQUIREMENTS FOR SOLID DOSAGE DRUGS ?

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 additional information, refer to the ICH guideline *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Products: Chemical Substances and Products*.

2.9.12 WHAT ARE THE STANDARDS OTHER THAN THE USP THAT HAVE OFFICIAL STATUS IN CANADA ?

Section 10 of the Food and Drugs Act sets out requirements `Where Standard Prescribed for Drug', ie. Division 6 Canadian Standard Drugs , `Trade Standards' ie. Schedule B of the Food and Drugs Act , and `Where No Prescribed or Trade Standard'. Other accepted pharmacopoeia include the British Pharmacopoeia (BP) and the European Pharmacopoeia (Ph.Eur.).

2.9.13 SHOULD COMPENDIA TEST METHODS BE VALIDATED ?

Yes. For compendial methods, Table 3-4 of TPP's guideline *Acceptable Methods* outlines the criteria necessary to validate compendial methods.

2.9.14 MUST ALL IDENTIFICATION TESTS STATED IN THE COMPENDIA MONOGRAPH BE PERFORMED ?

All tests as stated in the monograph should be performed. In the case of Identification tests, the BP/Ph.Eur. may state that optional tests could be performed (e.g., perform tests A, B, and E or perform tests C and D).

2.9.15 ARE SOLID DOSAGE DRUGS EXEMPT FROM DISSOLUTION TESTING IF THE DISTRIBUTOR CLAIMS IT AS BEING A MANUFACTURER'S STANDARD ?

It is TPP's position that solid dosage form should include a routine test for monitoring release characteristics (e.g., dissolution). If there is a change to a Manufacturer's standard, the minimum requirements of the compendial or professed standard at the time of registration should be met.

2.9.16 DOES A PRODUCT LABELLED AS BP HAVE TO MEET USP SPECIFICATIONS ?

If a product is labelled and tested according to BP, which is a Schedule B standard, it does not have to be tested for compliance to USP even if the limits and/or test methods differ.

2.9.17 DO PRODUCTS LABELLED AS USP HAVE TO BE TESTED AS PER THE USP TEST METHODS ?

Though products labelled USP need not be routinely tested by USP methods, the distributor must demonstrate that such products can be properly tested by USP methods and found to comply with USP specifications when so tested. If a House analytical method is used in place of a compendial method, it must be fully validated and results from a correlation study should be available.

2.9.18 WHY DOES TPP PUT BLIND ACCEPTANCE ON USP TEST METHODS ?

TPP does not blindly accept the USP test methods. While it is an official publication, through its inclusion in Schedule B, difficulties are sometimes noted in the published information. Sponsors are encourage to contact the USP if these situations are encountered.

2.9.19 WHAT SHOULD THE FREQUENCY OF CALIBRATION BE FOR A DISSOLUTION APPARATUS USED WITH BOTH: BASKETS & PADDLES ?

The GMP regulations call for apparatus calibration at suitable intervals. Although specific time periods are not given, apparatuses should be calibrated to a frequency necessary to ensure reliable and reproducible results and covered in the firm's SOP. The firm may consult the apparatus manufacturer's manual for guidance. This calibration requires testing with both baskets and paddles at both 50 and 100 rpm with both USP Calibrator Tablets, Prednisone Tablets and Salicylic Acid Tablets. The only exception is if a company uses either baskets or paddles exclusively. In those rare instances, the firm only needs to calibrate with both Calibrator Tablets at both speeds and the single stirring element that it uses.

In case of any event that might change operating characteristics of an apparatus, such as construction or moving it, it should be calibrated as described above prior to use.

The USP Calibrator Tablets that presently have official status are Prednisone Tablets and Salicylic Acid Tablets The current lots numbers are published in the Pharmacopoeial forum. All previous lots have expired. Both official lots are labeled to "Keep container tightly closed. Store in a desiccator or in a dry place at room temperature; humidity is the primary cause of instability of both calibrator tablets.

2.9.20 WHAT SHOULD BE THE INCUBATION TIME/ TEMPERATURE FOR MEDIA- FILLS IN THE VALIDATION OF AN ASEPTIC PROCESS ?

Refer to the TPP guideline *Process Validation: Aseptic Processes for Pharmaceuticals*.

It is recommended that data be collected to support any incubation cycle vs microorganisms to be detected eg. yeasts and molds. Official sources do not state a specific cycle ie. Temperature or combination of temperatures for incubation.

2.9.21 IS THE USE OF A HOKE BOMB ACCEPTABLE FOR SAMPLING GASES FROM A STORAGE TANK ?

Yes, provided the firm has validated the process. A hoke bomb is a stainless steel cylinder with a valve on each end which allows a gaseous product to flow through. The most significant step in the validation process is the time required to fully purge the cylinder which provides assurance that complete evacuation of the cylinder has been accomplished.

2.9.22 IN PERFORMING SYSTEM SUITABILITY, AS PER USP 23 <621> DO ALL REPLICATE INJECTIONS HAVE TO BE COMPLETED BEFORE ANY ANALYTE SAMPLE INJECTIONS ARE MADE ?

As the splitting of injections for the SST is considered to represent a more challenging test than if performed prior to the analyses of sample, there would not be objections to this proposal.

2.9.23 IS ROUTINE PRODUCT pH TESTING REQUIRED FOR ENDOTOXIN (LAL) TESTING ?

No, not unless a firm has committed to such testing in a new drug application. Measurements of pH on routine endotoxin samples each time a specimen is tested are not required for a validated method. The positive product control on routine testing, which must be included during each test, will fail if the specimen pH is out of control.

The firm's endotoxin validation and should be compared with the finished product release pH range to make sure the validation lots covered the upper and lower limits used to release product. If the validation lots covered only a narrow range this would be a valid concern, rather than the lack of pH testing of each test specimen.

2.9.24 ARE THE USE OF RECYCLED SOLVENTS FOR HPLC COLUMNS ACCEPTABLE?

There is no specific policy on recycled HPLC solvents above and beyond the USP and GMP requirements regarding suitability of laboratory equipment and analytical methods. Therefore, it would be acceptable to

use recycled solvents which do not interfere with analytical results or equipment operation provided the appropriate validation studies have been performed.

2.9.25 WHAT IS TPP'S POSITION ON PRE-SHIPMENT SAMPLES ?

Pre-shipment sampling has been used by some firms on bulky packaging components and finished products; acceptability of such a system would depend on the level of confidence one gains with respect to the supplier over time. Such a sampling plan would require supplier re-qualification once a problem is observed on-line when using the component.

Regulations call for sampling after receipt on the premises of the legal agent, unless the provisions of C.02.019 are met. Even if section C.02.019(1)(b) is used, the periodic complete confirmatory testing should be on a sample taken by the legal agent since this is an audit function.

2.9.26 CAN TTP CLARIFY THE REQUIREMENTS FOR UNIQUE IDENTIFIERS? OUR FIRM HAS A NUMBER OF IMPORTED FINISHED PRODUCTS WHICH WE BELIEVE THEY BELONG TO THIS CLASS OF PRODUCTS. FOR EXAMPLE:
(1) TABLET PRODUCT IS IDENTIFIED BY A LETTER ENGRAVED ON ONE SIDE AND SCORED ON THE OTHER SIDE. IT IS THE ONLY TABLET PRODUCED AT THE PLANT WHICH BEARS THESE MARKINGS.
(2) A SCHEDULE D DRUG IN AMPULES IS UNIQUELY IDENTIFIED BY THE ETCHED SERIGRAPHY OF THE NAME AND STRENGTH OF THE PRODUCT ONTO THE AMPULES WHICH ARE ISSUED TO THE FILLING LINE.
(3) A SCHEDULED D DRUG IN VIALS WHICH BEAR TWO LARGE COLOUR DOTS, SPECIFIC TO THE PRODUCT AND STRENGTH. IN ADDITION, THE VIALS HAVE A COLOURED CAP UNIQUE TO THIS PRODUCT AND STRENGTH.
(4) A DRUG WHERE ALL AMPULES ARE UNIQUELY IDENTIFIED BY TWO COLOUR CODED RINGS, A COLOUR RING SPECIFIC TO THE PRODUCT AND A COLOUR RING SPECIFIC TO THE STRENGTH ON THE AMPULES. THE AMPULES ARE ISSUED TO THE FILLING WHEN MANUFACTURED.
(5) A SCHEDULED D DRUG IN A PRE-FILLED SYRINGE FORM - THE PRE-FILLED SYRINGE FORMAT IS THE ONLY PRODUCT THAT USED THIS EXACT TYPE/SIZE OF PRE-FILLED SYRINGES ON THAT FILLING LINE. CLEAR LABELS ARE APPLIED TO THE SYRINGES AFTER FILLING, IN DIFFERENT COLOURS FOR TWO DOSAGES.

Insofar as unique identifiers are concerned, they are not limited to the drug itself and as stated in the Interpretive Document there are other options such as identification on caps of injectables, colour closure systems, coloured vials, dedicated facilities and preprinted vials or ampules. The examples you quote would fall within the stated options.

The importer has the responsibility to have evidence from the fabricator that the identifier is indeed unique to satisfy the requirements of C.02.019. The analysis at the fabricator site should be done after packaging is completed and the certificate of analysis should describe the unique characteristic of the packaging component. Also, the uniqueness should be confirmed every year by the fabricator and that confirmation should be available for review at the time of the inspection.

2.9.27 AS AN IMPORTER, OUR FOREIGN MANUFACTURER IS FULLY COMPLIANCE WITH GMP, DO WE REQUIRE TO SUBMIT A REQUEST FOR REDUCED TESTING IN WRITING TO THE BCE WHILE FULL RE-TESTING IS IN PLACE? IS THERE A NEED FOR CONDUCTING FULL CONFIRMATORY TESTING ON THE FIRST 3 CONSECUTIVE BATCHES EACH YEAR?

Requirement for reduced testing are fully described in the GMP Guideline, 1998 edition and there is no mention about providing an application. Again, the compliance to the requirements will be evaluated at the time of the inspection.

Insofar as complete confirmatory testing on the first three consecutive batches is concerned , the GMP Guidelines only require periodic complete confirmatory testing of at least one lot per year per dosage form, per vendor, selected on a rotational basis, provided that adequate evidence of GMP compliance is available. We would suggest that such testing be conducted on the first lot received.

For additional information, refer to the ICH guideline *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Products: Chemical Substances and Products*.

2.9.28 DO THE STERILITY AND GENERAL SAFETY TESTS NEED TO BE PERFORMED AS PART OF THE PERIODIC CONFIRMATORY TESTING OF ONE LOT / YEAR / VENDOR?

No. But the COA received with each lot must provide evidence that:
1) for terminally sterilized products, the sterility test has been performed on each sterilizer load
2) for products that have been aseptically filled, that the samples include containers filled at the beginning and end of the filling and / or after any significant interruption of work.
3) that the fabricator has conducted a General Safety Test and provided the results, if it is a requirement in the product specifications.

2.10 RECORDS - C.02.020, C.02.021, C.02.022, C.02.023 & C.02.024

2.10.1 CAN DOCUMENTS MADE AVAILABLE IN CANADA BE IN A FOREIGN LANGUAGE ?

The proficiency of company personnel in a foreign language and their willingness to assist inspectors at the time of inspection are taken into consideration. When documents in a foreign language are encountered by inspectors, the following situation would be considered acceptable:

-The certificate of analysis and the batch documentation made available by the exporter to the importer is in a standard format.

-There is an English or French translation of the standard format on the premises of the importer.

-The exporter undertakes in writing to advise the importer each time a change occurs in the standard form.

-The batch documentation and certificate of analysis are "product specific", with numerical figures being the only variable from one batch to another.

2.10.2 MUST SOP'S REFERENCED IN MASTER PRODUCTION DOCUMENTS BE AVAILABLE AT THE IMPORTER'S PREMISES ?

One of the fundamental principles upon which the development of the Good Manufacturing Practices Regulations (GMP) was based was that importers/ distributors should be knowledgeable about the formulation of the products they were selling; how the products are made, and have evidence that each lot of drug was produced in accordance with those procedures and requirements. This principle led to the development of Sections C.02.020(1)(a) and (b) of the GMP which require every importer/ distributor to maintain Master Production Documents (MPD) on his premises in Canada for each drug sold and have evidence that each lot has been produced in accordance with the requirements and procedures of the MPD.

With respect to procedures, processing procedures should be available when they contain any information that is covered by the definition of "master production document" or "master formula" found in the guide "Good Manufacturing Practices for Drug Manufacturers and Importers". Where a procedure relates to the processing of a drug, that procedure should form part of the MPD. With respect to Sterile Products, procedures relating to the sterilization aspects of processing should form part of the MPD.

The availability of either a plant or drug master file with TPP does not absolve manufacturers and importers from complying with their responsibilities under the Good Manufacturing Practices Regulations. Trade secrets or confidential information may be filed with an independent third party.

With respect to procedures, processing procedures should be available when they contain any information that is covered by the definition of "master production document" or "master formula" found in the guide "Good Manufacturing Practices for Drug Manufacturers and Importers".

Where a procedure relates to the processing of a drug, the procedure should form part of the MPD. With respect to Sterile Products, procedures relating to the sterilization aspects of processing should form part of the MPD.

The information described under the definition of Master Formula contained in the guide "Good Manufacturing Practices for Drug Manufacturers and Importers" must be maintained in Canada. The use of an independent third party, for that information considered to be trade secret or confidential may be considered.

Examples of what should be included in the master production documents:
Final QS for addition of sterile water; pressure testing of filter cartridge (both sterile and non-sterile); sterilization procedures for "sterile" production equipment; sampling requirements for in-process weight variation; set-up (i.e. operating criteria/parameters) of film coating equipment.

Trade secrets or confidential information may be filed with an independent third party.

2.10.3 ARE ELECTRONIC DOCUMENTS ACCEPTABLE WHERE IT IS STATED “WRITTEN” IN THE GMP REGULATIONS ?

There are two different types of "Records" to be maintained as per the GMP’S, i.e. documents and evidence; keeping of this information on a computer would satisfy the requirements of C.02.020(1). Failure to produce a printout should the computer be down or defective the manufacturer is technically in violation at that time.

The word "written" as it appears in the GMP’S was intended to convey a different meaning than the word evidence.

"Written" includes printed, typewritten, painted, engraved, lithographed or photographed in a usable form.

Therefore, electronic documents do not become "written" until the computer prints out the document. The printout satisfies the work "written" as stated in the GMP regulations.

The Branch has accepted that procedures, policies, data and records can be stored electronically and that signatures can be generated electronically, provided that, there are appropriate controls to ensure that such entries, revisions and signatures can only be made by the authorized individuals in question.

2.10.4 WHAT IS INDUSTRIES LEVEL OF COMPLIANCE WITH RESPECT TO MASTER PRODUCTION DOCUMENTS ?

There is a high rate of compliance for distributors who obtain products from a corporate affiliate. The only area where compliance is less than satisfactory is for the importers or distributors of products obtained from non-related firms. In the latter case the problem is the unwillingness of the fabricator to divulge proprietary manufacturing information.

In such cases, TPP’s position is unchanged: distributors have to make the MPD information available for inspection. This can be accomplished by using a legal counsel as an independent to keep any proprietary manufacturing information from the distributors but available to TPP inspectors.

2.10.5 WHAT TYPE OF DOCUMENTATION IS REQUIRED IN-LIEU OF TESTING IN THE EXAMPLE GIVEN BELOW ?

In the general test for organic Volatile Impurities in the USP the following statement was made:"Unnecessary testing may be avoided where a manufacturer has assurance, based on knowledge of the manufacturing process and controlled handling and storage of an article, that there is no potential for specific toxic solvents to be present and that the material, if tested, will comply with established standards".

Documentation would be required to back up the position that testing is not required, indicating that due to the nature of the manufacturing process and the handling procedures, a particular impurity will not be present. Such a document should be from the vendor (fabricator) of the raw material, and should make reference to the master manufacturing process by number and/or date of issue and should provide

assurance that the given process cannot contribute to the presence of organic volatile impurities and sufficient testing has been performed by the raw material manufacturer establishing the same.

The drug manufacturer must have knowledge of the raw material process and the potential for presence of organic volatile impurities in the raw material. This document must be regularly updated. The test for "organic volatile impurities" must be performed periodically as per the requirements of Section C.02.010 (1)(b) if the manufacturing process uses organic solvent. On the other hand, if there is evidence to the drug manufacturer that the vendor of the raw material does not use organic solvent in the process, the retest of this parameter by the manufacturer is useless.

2.10.6 CAN CHROMATOGRAMS BE STORED ON DISC INSTEAD OF RETAINING THE HARD COPY ?

Where the expression "written" is used in the Good Manufacturing Practices Regulations (GMP) the maintenance of hard copy records and data is required. Where "written" does not appear in the GMP, maintenance of information in electronic form is acceptable.

It must however be emphasized that in cases where information is stored in electronic form, the information must be available on site at all times.

If a chromatogram is produced for the analytical determination, the chromatogram is required to be maintained as a record under Section C.02.020 of the GMP; if no chromatogram is produced for the analytical determination, disc storage of the data is acceptable and a chromatogram need not be produced to comply with the GMP.

Records such as electronic transfer of data between instruments and spread sheets used for calculations are evidence that should be available to demonstrate that systems and equipment are operating as designed and expected. Though no specific guidelines have been issued to inspection staff for the review of "computerized" or electronic data handling systems, it is possible that a company will be asked to demonstrate that their system is operating as it should.

2.10.7 DOES THE PERSON IN CHARGE OF QUALITY CONTROL HAVE TO SIGN QC DATA AND DOCUMENTS ?

As per sections C.02.009, C.02.015(1), C.02.016 and C.02.018 of the Regulations, a company must have evidence that all production and transportation procedures and specifications have been approved by the head of the quality control department or his/her designated alternate.

Evidence must be available as per Section C.02.014 of the Regulations that all pertinent data has been reviewed and concurred with by the head of the quality control department or her/his designated alternate.

It is expected that the individuals who have summarized and evaluated the stability data be identified by the records. It is also expected that the person in charge of quality control, or the designated alternate, be cognizant of the conclusions and has attested in writing to concurrence with the findings.

TPP has accepted that data and procedure can be stored electronically and that signature can be generated electronically provided that there are appropriate controls to ensure that such signatures can only be entered by the individual in question.

2.11 SAMPLES - C.02.025 & C.02.026

2.11.1 WHAT IS CONSIDERED AN ADEQUATE SAMPLE WHEN TANK LOADS OF A RAW MATERIAL IS RECEIVED ?

The amount of a sample of the raw material taken at the time of receipt, before it is combined, which is sufficient for re-testing by in-house QC as well as for independent analysis is what we consider satisfactory.

2.12 STABILITY - C.02.027 & C.02.028

2.12.1 DOES TPP AGREE WITH FDA's ACCELERATED STABILITY STUDY CRITERIA ?

Not necessarily. The TPP follows the internationally accepted stability criteria as outlined in the following documents:

ICH/TPP guideline Stability Testing of New Drug Substances and Products
ICH/TPP guideline Stability Testing: Photostability Testing of New Drug Substances and Products
ICH/TPP guideline Stability Testing: Requirements for New Dosage Forms
TPP guidance *Stability Testing of Existing Drug Substances and Products*

2.12.2 WHAT IS CONSIDERED TO BE ADEQUATE STABILITY TESTING FOR EACH TYPE OF PACKAGING MATERIALS ?

The GMP Regulations (1998 edition) require that every distributor establish the period of time during which each drug in the package in which it is sold will comply with its specifications; and that each distributor monitor, by means of continuing stability program, the stability of the drug in the package in which it is sold.

The stability of the drug is determined prior to marketing and prior to the adoption of significant changes in formulation, manufacturing procedures or packaging materials that may affect the shelf-life of the drug.

For further information regarding the stability testing of packaged dosage form, refer to:

ICH/TPP guideline *Stability Testing of New Drug Substances and Products*,
TPP guidance *Stability Testing of Existing Drug Substances and Products*
TPP Policy on *Extension of Expiration Dates*

2.12.3 WHAT IS TPP'S DEFINITION OF 'DATE OF MANUFACTURE' FOR CALCULATING THE EXPIRY DATE ?

The date of manufacture should be the date of the beginning of the actual dispensing of raw materials for manufacturing operations.

2.12.4 DO BATCHES HAVE TO BE TESTED FOR PRESERVATIVES DURING RELEASE AND STABILITY TESTING ?

Finished products have to be tested against their specifications. For preservatives, two types of analysis are generally performed. Initially, firms perform analysis to establish the lowest level of efficacy that will cover the expiry date. Once that level has been determined, firms may decide to include or not this test in their finished product specifications. If it is included, they will have to meet the limit for the initial release for sale. However, for a parenteral product, it is mandatory to include this test in the finished product specifications and set adequate limits given that it is a requirement to indicate the quantitative list of preservatives on the label. The product shall meet its specifications to be released. With regard to stability, the analysis of preservatives is not mandatory for non-sterile drugs that are not regulated under Division 8 of the Food and Drugs Regulations but a microbial test shall be done to cover the expiry date. For sterile products, the analysis of preservatives is mandatory and the firm should demonstrate that the product meets its limit for the lowest level of efficacy during its entire shelf-life.

2.12.5 CAN IT BE ASSUMED THAT USP CHROMATOGRAPHIC ASSAY METHODS ARE STABILITY INDICATING?

No.

2.12.6 IS IT ACCEPTABLE TO PLACE AN EXPIRY DATE ON A BOTTLE CAP INSTEAD OF ON THE BOTTLE LABEL ?

No. The expiration date must appear on the immediate container (except when single-dose containers are in individual cartons, in which case the expiration date may be placed on the individual carton instead of the immediate product container). A bottle cap is part of the immediate container closure system, but is not the immediate container itself.

If the expiration date were to be placed on the bottle cap, there would be a greater chance of mix-up at the end user (or pharmacy dispensing) level because many bottle caps fit either bottles of different lots of the same product, or different products.

2.12.7 WHEN THE LABELLED EXPIRATION DATE STATES ONLY THE MONTH AND YEAR DOES IT MEAN THE END OF THE MONTH ?

Yes; the product should meet approved specifications through the last day of the specified month. Manufacturers should take this into consideration when assigning the expiry to a new lot of drug product. Many firms assign the expiry period for a new lot starting with the date of QC release. Generally, this is acceptable if the date of release is not longer than approximately 30 days from the start of manufacturing. The start of manufacturing is the date that the first active ingredient, preservative or antioxidant is initially introduced into the lot.

For products that are labelled with the month and year of expiry, when a lot is released at the beginning of the month, that entire first month should be included in the expiry period. For example, a lot which has a supportable 2 year expiry period that is released on February 10, 1998, should be assigned an expiry date of no later than January 2000.

2.12.8 CAN AN ACCELERATION STUDY PERIOD OF LESS THAN THREE MONTHS BE USED ?

Accelerated stability studies of less than three months are questionable.

2.12.9 SHOULD DRUGS PACKAGED INTO KITS AND SUBSEQUENTLY STERILIZED, BE TESTED FOR STABILITY ?

Yes. These operations, are by definition, part of manufacturing. Drugs that are packaged into trays or kits and the resulting package is sterilized prior to being marketed, data should be available demonstrating 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. Additionally, if the kits are sterilized with ETO (ethylene oxide) gas, ETO residues in the drug need to be controlled at safe levels.

2.13 STERILE PRODUCTS - C.02.029

2.13.1 WHAT ARE THE REQUIREMENTS FOR STERILE FILTRATION VALIDATION ?

Refer to the TPP guideline *Process Validation: Aseptic Processes for Pharmaceuticals*.

2.13.2 WHAT IS THE MICROBIOLOGICAL SPECIFICATION FOR CRITICAL SURFACES IN ASEPTIC AREAS:

Product, container, and closure contact surfaces are known as "critical surfaces." Microbiological monitoring of critical surfaces should yield zero colony forming units (CFUs). Firms often express this action limit as <1 CFU per 4 cm. sq.. FDA's 1987 "Guideline on Sterile Products Produced by Aseptic Processing" states:

> "Equipment surfaces which contact sterilized drug product or sterilized container/closure surfaces should, of course, be sterile. It is just as important in aseptic processing to properly validate sterilization processes applied to these equipment surfaces as it is to validate such processes for the drug product and container/closures."

This standard can also be found in international publications such as the European Union's "Manufacture of Sterile Medicinal Products" (Annex I to the European Union Guide to Good Manufacturing Practice); FDA Technical Report # 13 `Fundamentals of Microbiological Environmental Monitoring Program' and the USP 23 Chapter <1116> `Microbiological Evaluation of Cleanrooms and other Controlled Environments' in the 8th supplement.

The last includes a glossary amongst which are : Product Contact Areas which are areas and surfaces in direct contact with products, containers, or closures; and Sterile Field ... space...where the potential for microbial contamination is highest.

The USP limit is less than 0.1 cfu per cubic foot of air. The FDA document is the same.

2.13.3 AS AN IMPORTER OF STERILE PRODUCTS , I HAVE THE FOLLOWING QUESTIONS: A) IS IT NECESSARY TO REPEAT THE STERILITY TESTING? B) IS IT POSSIBLE TO RETURN THE SAMPLE TO THE ORIGINAL LABORATORY FOR RETESTING PURPOSE?

a) Under the current GMP guidelines (1998 Edition) in the section Finished Product Testing C.02.019 (1)(b), an importer can choose to rely on the original manufacturer's test results in the form of authentic Certificate of Analysis (COA) as the confirmatory test for sterility for the imported product. The COA should include actual numerical results, product specifications, validated test methods used and their test limits specific to the sterilizer load. Considering that the value of the sterility test is limited as compared to validation processes, the cost of additional sterility testing could be prohibitive considering the number of units required. In the guidelines, there is already an exemption to keep retained sample for sterility (interpretation 4, C.02.026) , we therefore consider that retesting for sterility is not required.

b) The Therapeutic Products Programme (TPP) accepts the original COA provided that the importer has evidence the manufacturer is GMP compliance with the validated sterilization process. Such information is in the form of summary of protocol, pre-evaluation studies, process qualification on the type of sterilization and its loading specifications and expert evaluation. If the importer so chooses, a sample may be returned to the manufacturer for the remaining annual confirmatory tests.

2.14 MEDICAL GASES - C.02.030

2.14.1 SHOULD MEDICAL AIR U.S.P. BE EXEMPT FROM THE ANALYSIS FOR WATER/OIL, CARBON DIOXIDE, NITRIC OXIDE/NITROGEN DIOXIDE AND SULPHUR DIOXIDE WHEN PRODUCED SYNTHETICALLY FROM RAW MATERIALS MEETING OXYGEN U.S.P. AND NITROGEN N.F. SPECIFICATIONS?

It is agreed that the contaminants listed in the U.S.P. monograph for Medical Air are most likely to occur in the air produced by either water or oil lubricated compressors. However, it is recommended that the finished product specifications state the rationale for not having to conduct these tests, and the process should be validated to assure that none of the above-mentioned impurities show up, for whatever reason, in the finished product. It is understood that the two component gases, that is, oxygen U.S.P. and nitrogen NF, are fully tested and meet the U.S.P. specifications, e.g., oxygen should contain N.M.T. 0.03% of CO_2 and N.M.T. 0.001% of CO.

2.14.2 IS THE FULL SCOPE OF GMP APPLIED TO ALL MEDICAL PACKAGING, WITH THE EXCEPTION OF THE DISPENSING OF LIQUID OXYGEN FROM THE LIQUID CONTAINER TO PATIENT HOME CARE UNITS?

It is the policy of the Programme that the full scope of GMP applies to all stages except dispensing the liquid oxygen from the liquid container (by the supplier).

2.14.3. WHAT IS THE STATUS OF 93% OXYGEN AND THE INSPECTION OF HOSPITAL BASED OXYGEN CONCENTRATORS?

As far as the classification of Oxygen Concentrators, they would be considered as devices if they are used for the purpose of directly delivering oxygen to patients as a treatment. They would not be considered as devices if they are not part of a delivered system.

2.14.4 WHAT ARE THE REQUIRED PROCEDURES FOR VISUAL INSPECTIONS OF NEW AND USED MEDICAL GAS CYLINDERS?

Regulation C.02.016(1) requires that each lot or batch of packaging material shall, prior to its use in the packaging of a drug, be examined or tested against the specifications for that packaging material. The regulations also provide a definition for the term specifications. Procedures established to comply with Transport Canada regulations would provide evidence of compliance with Regulation C.02.016.

2.14.5 A PRESSURIZED TANKER OF HYDROCARBON RAW MATERIALS (ISOBUTANE, PROPANE, ETC.) IS NORMALLY SAMPLED AND APPROVED BEFORE PUMPING. HOWEVER, GIVEN THAT IT IS DIFFICULT TO RETAIN SOME OF THESE MATERIALS BECAUSE OF DANGEROUSLY HIGH PRESSURES, WHAT IS THE CURRENT TPP POLICY FOR SUCH MATERIALS?

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.

2.14.6 WHAT SAMPLE OR SAMPLES SHOULD BE RETAINED WITH RESPECT TO BULK CHEMICALS WHERE A TANK LOAD IS RECEIVED, TESTED AND THEN COMBINED WITH THE PREVIOUS LOT IN BULK STORAGE?

A sample of the raw material taken at the time of receipt, before it is combined, is what we consider satisfactory.

2.14.7 WHAT REQUIREMENTS EXIST FOR EQUIVALENCY OF TEST METHODS WITH RESPECT TO MEDICAL GASES?

The requirements indicate that the specifications for a medical gas are of pharmacopoeial or equivalent status and that, where test methods are not of pharmacopoeial or equivalent status, the accuracy and precision of such methods are established and documented. Where a manufacturer or importer wishes to use a non-pharmacopoeial method, the method of choice should be carried out parallel with the pharmacopoeial method. Sufficient data must be obtained to establish the equivalency (precision and accuracy) of the method of choice when compared to data obtained when the pharmacopoeial method is used on samples of the same lot of product. Where there is no pharmacopoeial method for a particular test, the test method adopted is validated (precision and accuracy) in its own right.

2.14.8 WHAT IS THE CURRENT POLICY ON TESTING THE BALANCE GAS IN MEDICAL MIXTURES QUALITATIVELY AND QUANTITATIVELY?

For medical gas mixtures, an identity test can be made on a lot basis for the balance gases, and the life supporting component could be analysed on an individual cylinder basis. Industry practice does allow for the quantitative determination of the balance gas by subtracting the analytical values of the minor components from the balance gas. For this situation, it is understood that a lot is considered to be the individual cylinder in the case of mixtures of two or more life supporting components; single gases are sampled and tested upon the completion of each rack (lot); where, for example, oxygen is the balance gas, it is tested for identity upon the completion of each rack prior to the addition of the second gas. This life supporting component is then tested on each cylinder.

2.14.9 IN A SMALL FILLING STATION FOR MEDICAL GASES CAN ONE PERSON BE RESPONSIBLE FOR Q. A. AND PRODUCTION ?

Due consideration is given to situations where:

a) it is impossible to have distinct organizational units on site.
b) chances of error are eliminated.
c) reporting relationship is different while the employee performs quality control functions and production activities.
d) the employee is fully aware of his dual role, understands clearly responsibilities and line authority and acts accordingly.

It is conceivable that a small filling location, one person be designated as being responsible for quality control functions as well as other production activities.

2.14.10 WHEN IS OXYGEN EXEMPT FROM BEING TESTED FOR CARBON DIOXIDE ?

The USP exempts Oxygen with purity of no less than 99% from the requirements of the tests for carbon dioxide and carbon monoxide when the oxygen has been produced by the air liquefaction method.

In such cases, the person receiving Oxygen USP should have documentation available from the supplier which states that a specific lot(s) of oxygen have been produced by the air liquefaction process.

2.14.11 WHAT ARE THE REQUIREMENTS FOR MODIFYING THE ZERO STEP OF THE CALIBRATION PROCEDURE FOR SERVOMEX (R) OXYGEN ANALYZERS ?

The Servomex (R) Oxygen Analyzer instruction manual states that the analyzer zero step (zeroing) is to be checked once a week, after transportation, or if the instrument has undergone a temperature change of $10^{o}C/18^{o}F$ or more.

These instruments are usually placed in a room that is well ventilated, and in many instances open to the outside environment when filling operations are underway.

Thus, the analyzer would be expected to be exposed to temperature fluctuations of 10°C/18°F or more during a 24 hour period.

Calibration of the analyzer zero step at weekly intervals may be appropriate if a manufacturer can document that the instrument had not been moved and that the temperature of the area where the analyzer is kept did not fluctuate more than 10°C/18°F. The use and retention of 24 hour temperature recording charts would be acceptable documentation.

If a manufacturer is unable to supply such documentation, the analyzer should be calibrated daily, or more often, when cylinders of Oxygen USP are being filled.

Additionally, before considering accepting monthly calibration of the analyzer zero step, validation data should support a firm's contention that monthly calibration is appropriate. Such data should include 24 hour temperature charts and daily zero step calibration checks for at least one (1) year.

Each individual facility would be required to perform its own oxygen analyzer validation study.

2.14.12 CAN MIXTURES OF MEDICAL GASES BE LABELLED ONLY AS BEING A 'USP MIXTURE' ?

No, mixtures of medical gases which individually meet USP requirements cannot be labelled only as ' USP mixture'. A complete description such as 'the mixture contains 10% Oxygen USP, and 90% Nitrogen USP' should be stated on the label.

Only mixtures which have USP Monographs may be labelled as USP.

2.14.13 WHAT ARE TPP's EXPECTATIONS REGARDING SPECIFICATIONS FOR NON-SCHEDULE B MEDICAL GASES ?

TPP's expectations regarding specifications for medical gases which are not found in any Schedule B publications are as per sub-section 10(3) of the Act, where a standard for a drug has not been prescribed and no standard for the drug is contained in any publication mentioned in Schedule B, no person shall sell such a drug, unless it is in accordance with the professed standard under which it is sold, and it does not resemble, in a manner likely to deceive, any drug for which a standard has been prescribed or is contained in any publication mentioned in Schedule B. Where applicable, specifications for this type of product include the identity, potency and purity of the gas or gas mixture.

The finished product specifications for non-compendial medical gas mixtures should include an identity and potency test for each of the individual gases.
Eg. Lung Diffusion Test Mixtures contain several actives.

The USP does not require quantitation of Oxygen and Balance gas ie. Nitrogen for Medical Air, however TPP strongly encourages the fabricator to quantitate all constituents on one sample per batch , particularly if the mixture is prepared synthetically.

2.14.14 WHAT IS THE EXTENT OF DOCUMENTATION REQUIRED TO BE MAINTAINED BY A MEDICAL GAS DISTRIBUTOR FOR (1)NEW CYLINDERS AND VALVES (2)RETENTION OF GC CHARTS ?

Section C.02.016 and C.02.017 of the Good Manufacturing Practices Regulations (GMP) specify testing requirements for packaging materials and Section C.02.020 of the GMP specifies the information respecting packaging material testing which is to be maintained.

In those instances where new packaging components are inspected and approved at the component manufacturing site by another government department (e.g. Transport Canada in the case of new cylinders) it is sufficient to maintain evidence that specific cylinders have been tested and found to comply with established specifications. Notwithstanding the foregoing, it is expected that written specifications are available which outline the checks which are to be performed on empty cylinders prior to filling and that a record of those checks is maintained.

Section C.02.020 of the GMP specifies that records and evidence relating to the testing of a drug and a raw material are to be maintained.

GC charts are considered to be records/evidence of testing and must be maintained for the time period specified under Section C.02.021 of the GMP.

3.0 REFERENCE DOCUMENTS

3.1 Records of questions and answers from meetings with pharmaceutical trade associations.

3.2 GMP Interpretation Documents.

3.3 Records of Questions and Answers from Foreign Regulatory Authorities.

3.4 SOP-0053: How to obtain and record a GMP Interpretation Decision

APPENDIX 1

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