

TRANSCRIPTION - Q&A
“One Day Workshop - GMP Guidelines 2002 edition”
Organized by the PSG, the CVG and the Inspectorate

Montreal, December 4, 2002
Toronto, December 5, 2002
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TRANSCRIPTION - Q&R
“Un atelier d’un jour - Lignes directrices sur les BPF 2002”
Organisé par le PSG, le CVG et l’Inspectorat

Montréal, 4 décembre 2002
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PREMISES / LOCAUX**C.O2.004**

For a self-contained facility it has been stated that personnel are to be separate. What about quality control or engineering staff who may sample or do maintenance in both facilities daily, thereby travelling between them daily? What if one facility makes a live vaccine, and the other makes another drug product?

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

EQUIPMENT / ÉQUIPEMENT**C.O2.005**

Est-ce que les équipements (ou procédés) achetés avant l'année 2000 nécessite une validation ou non?

Oui.

PERSONNEL**C.O2.006**

Qu'entend-on par diplôme universitaire pour délégation de tâche? Un certificat est-il suffisant ou le BAC est requis? Aussi, faut-il: diplôme et expérience ou diplôme et/ou expérience adéquate?

Tel qu'indiqué à l'Interprétation 1.4, les tâches et responsabilités doivent être déléguées à une personne qui rencontre les exigences décrites à l'Interprétation 1.1 et 1.2 i.e. détenir un diplôme universitaire dans une discipline appropriée ET posséder une expérience pertinente.

Is a company required to notify Health Canada if there is a change in key personnel? For example, the production manager or quality assurance manager is fired and replaced with somebody else, or he/she decides to leave the company.

No. However, the new person should meet the requirements of Interpretation 1 or 3 depending on the activities performed.

SANITATION / HYGIÈNE**C.O2.007 - C.O2.008**

Est-ce que le gouvernement Canadien prévoit introduire une réglementation concernant le

contrôle microbiologique de l'environnement pour les produits non-stérile et aussi l'évaluation microbiologique des produits finis non stérile.

Quoique générale, une telle exigence est énoncée à l'Interprétation 2.9 sous C.02.007. En ce qui concerne l'évaluation microbiologique, une telle exigence doit être incluse dans les spécifications pour les formes posologiques susceptibles, telles les liquides, gels, crèmes et onguents.

Is it acceptable to have 2 levels of garmenting in the primary manufacturing area (solid dose, liquids, topicals)? i.e. one level for operators (fully gowned with coveralls) and another level of garmenting for quality assurance auditors or regulatory inspectors? What environmental monitoring data is required to support this practice?

There should be basic clothing requirements for any person entering the manufacturing areas, such as hair, mustache and beard covering as well as a protective garment. However, a firm may decide to apply more stringent requirements for operators such as dedicated shoes, etc. , Contrary to the sterile suites, there is no specific environmental monitoring requirements regarding clothing for the primary manufacturing areas.

What are the guideline expectations for non-sterile dosage forms related to micro assessment in:

- environmental monitoring**
- monitoring/validation of clean equipment**
- monitoring/validation of process (coating solutions, binding solutions, granulations, finished products)**

As per Interpretation 2.9 under C.02.007, environmental monitoring for micro would be required in areas where forms susceptible to contamination are manufactured, whereas Interpretation 3.3 under the same section provides the requirements for the cleaning and storage of equipment with regard to microbial proliferation. For in-process and finished product, this aspect should be assessed in the stability program.

RAW MATERIAL TESTING / ANALYSE DES MATIÈRES PREMIÈRES
C.02.009 - C.02.010

Regarding identification of a Raw Material on a Vendor Certification Program. Do all ID tests need to be performed if there are ID results on the Certificate of Analysis (C of A)? ie. If the specifications indicates an IR and an HPLC ID, can IR only be performed?

As stated in Interpretation 2 under C.02.010, one specific ID test needs to be performed after receipt of the raw material on the premises of the person that formulates the raw material into dosage forms.

C.02.009: Please clarify the statement: Inactive raw material is tested prior to use if the material has passed the expiration date as determined by the stability data or any other documented evidence. Would the Certificate of Analysis (C of A) be considered

documented evidence? Does this basically mean that inactives need not be tested prior expiration date?

When the vendor is certified according to C.02.010, the C of A obtained from the vendor is considered as acceptable evidence that the raw material meets its specification. However, as required by Interpretation 2 under C.02.010, a specific ID testing must be conducted on all lots of any raw material received on the fabricator's premises. This being said, inactive raw material subject to changes must be retested before use when the expiration date is reached. This retesting may include only those parameters that are subject to change.

Does the manufacture of non-sterile skin cleaners (soaps) require purified water as a raw material? Previous manufacture utilizes municipal water supply, which conforms to provincial drinking water regulations and is monitored regularly for microbiological parameters. The water lines are sanitized. The soaps we manufacture are of both drug & non-drug nature. Product formulations do not specify type of water - just "water".

In line with the new Interpretation 4 under C.02.009, if the use of potable water (or tap water) has been specifically mentioned in your drug submission (DIN application) and, following review, has been approved and is stated in your marketing authorization, then it can be used. Otherwise, if it is not, you must use PW.

Est-ce qu'un contrat devrait aussi être signé avec un fournisseur d'excipients? (C.02.010). Ceci est bien difficile vu que souvent ils sont achetés chez un courtier. Habituellement, la plupart des excipients rencontrent les pharmacopées.

Si le produit est acheté chez un courtier, voir Interprétation 3 sous C.02.010.

Par contre, si vous voulez certifier la source originale, le courtier ou grossiste devrait avoir signé un contrat avec la source originale couvrant les exigences requises à l'Interprétation 1.1 de C.02.010 et devrait vous fournir cette information.

C.02.010: If we are transferring raw materials and packaging components between affiliated (sister sites) is Identity testing still required? If these materials are still in their original containers?

If the sister site is located outside Canada, the ID test will have to be repeated upon receipt on the premises of the fabricator or packager/labeller. However, if the sister sites are both located in Canada, the ID testing performed by one site would not have to be repeated by the manufacturing packager/labeller site if the conditions of transportation and storage are met as per Interpretation 5 under C.02.010 or Interpretation 7 under C.02.017.

Testing of a lot: Can you do an identity test on a composite Active Pharmaceutical Ingredient (API) sample, rather than on each container?

Two approaches can be used to identify an API. The first option is to individually test each container using a specifically discriminating ID test. The second option is to use composite samples where each container must be opened, sampled and weighed in equal amount to form the composites. And you also have to perform the assay to establish the Mass Balance (i.e. the limits for the potency permit to establish this MB) and the number of containers must be less

than 10. See Interpretation 6.1.1 and 6.1.2 under C.02.009.

If a product is considered a food product not a Din product, for instance saw palmetto, do you still have to do identity tests? What would you perform if the product is not found in USP? What would you identify it for then?

Products that are foods are regulated by the Canadian Food Inspection Agency (CFIA). For herbal preparations that are considered drugs, a new GMP guidelines will be soon issued by the Natural Health Products Directorate which should address this point.

If the Active Pharmaceutical Ingredient raw material vendor is certified, does identity testing have to be conducted on every container of a lot received or each composite of 10 containers (of all the container received). In other words, would all containers have to be sampled in a lot received?

Yes: the ID test must be performed according to the conditions described in Interpretation 6.1 under C.02.009, i.e. each container must be opened, sampled and tested. Or when composite samples are used, an equal quantity from each container is weighed to form the composites and those composites are tested for ID and assay to establish the Mass Balance and the number of containers must be less than 10.

Can you explain re-test date, retest period. Example: Raw Material A received with manufacturers expiry date of 3 years. Therefore (Dec 1, 2004). Re-test date = Dec 1, 2004. Re-test period = date of receipt until Dec 1, 2004. On Dec 2, 2004, material successfully passes retesting and can be used immediately (within 30 days). A new retest date/period can NOT be assigned. If material is not used Dec 1, 2006 immediately on quantities are sufficient that use will pass 30 days. Therefore the material can be reused if it is re-tested prior to each use.

After the retest date assigned by the vendor (fabricator) of the Active Pharmaceutical Ingredient (API), an API may still be used if it is tested and found to comply with its specifications. As mentioned in Interpretation 8 under C.02.009, it must be used within 30 days after the retesting.

Can the testing of raw material be done by a lab outside of Canada e.g. USA?

Yes. But this site has to be included on your Establishment Licence.

Retest date for excipients - needs clarification

Inactive raw material (excipients) should bear an expiry date when they are subject to chemical, microbiological or physical changes. The expiry date should be based on acceptable stability data. After the expiry date, a material can be used if the retest shows that it still complies with its specifications. Based on a sufficient number of retests, a new expiry date can be assigned.

C.02.010, Interpretation 1.2. re_audit reports non available

- > open door to consultant?
- > contrary to conditions of acceptance
- > to be looked at the next version

The question is not clear but Interpretation 1.2 under C.02.010 addresses the compliance of an API fabricator with the ICH Q7A document “GMP for API”. The scope of the document “Conditions of acceptance of foreign inspection reports” does not include Raw Materials. Given that the ICH Q7A document “GMPs for APIs” is recent, the Inspectorate will consider consultant reports as acceptable evidence to demonstrate compliance with this Guidelines when an audit report from a qualified Regulatory Authority is not available or older than 4 years.

Re-test period (raw material). Is complete testing required or can re-testing be limited to stability indicating criteria?

The retesting can be limited only to the parameters that are subject to change, either chemical, microbiological or physical.

Do you mean that active ingredients can only be tested once?

An Active Pharmaceutical Ingredient (API) may only be tested once. The fabricator has the choice to conduct full testing after the receipt of a lot of API on his premises or he may rely on the vendors results of analysis when this vendor is certified. However, ID testing of every container must be conducted after receipt on the fabricator’s premises (even if this test has been previously performed by the vendor) and this test must be in accordance with Interpretation 6.1 under C.02.009.

Active Pharmaceutical Ingredient (API) sampling of every container at the pharmaceutical manufacturing site in Canada: Does it apply when the API is manufactured by the same pharmaceutical manufacturer that formulates the drug product when

1) API manufacturer is located in Canada (at a different location)

2) API manufacturer is abroad

in all cases, container are labelled tamper evident packed.

As answered above, if the sister site is located outside Canada, the ID test will have to be repeated upon receipt on the premises of the fabricator or packager/labeller. However, if the sister sites are both located in Canada, the ID testing performed by one site would not have to be repeated by the manufacturing packager/labeller site if the conditions of transportation and storage are met as per Interpretation 5 under C.02.010 or Interpretation 7 under C.02.017.

MANUFACTURING CONTROL / CONTRÔLE DE LA FABRICATION **C.02.011 - C.02.012**

Does an Active Pharmaceutical Ingredient quantity adjustment (when assay at less than 98%) apply to imported product as well? *Yes.*

Pour la fabrication de produit de biotechnologie, combien de jours avant le début de son usage est-ce qu’une matière première peut être pré-pesée et gardée dans un contenant intermédiaire? / For the manufacture of biotech products, how many days before it is used can a raw material be weighed and kept in an intermediate container?

The fabricator must be able to demonstrate that the raw material still conform to its specifications and that the intermediate container does not have any deleterious effect on the material.

Who is responsible for validation of the process for manufacturing/packaging? Is it the holder of the DIN or the third party contract manufacturer?

The Distributor (DIN holder) is responsible as well as the manufacturer and packager.

For a custom manufacturer, is it necessary to test the raw materials offered by client? If the client does not ask for a test report for final products, is it necessary to test the products?

Interpretation 3.2 under section C.02.012 covers the written agreements with regard to the fabrication, packaging / labelling or testing among the parties involved. If no such agreement is in place, the observation will be made against the party responsible according to the GMP. For example, testing of a raw material is the responsibility of the fabricator. But an observation will not be made against the fabricator for omitting to test a particular raw material if this is excluded by way of the contract with his client.

Is the contract manufacturer responsible for validation of utility systems/cleaning validation etc. or is it the responsibility of the DIN Holder?

The contract manufacturer is responsible for the validation of utilities and systems and for cleaning validation. With regard to process validation and test method validation, if a written agreement is signed by both parties that excludes the responsibility of the contract manufacturer or contract packager to perform validations activities, the contract manufacturer/packager will not be penalized but only the DIN Holder (Distributor). We have made an addition in the 2002 GMP under C.02.012, Interpretation 3.2.3 regarding the responsibilities for process validation and test methods validations.

How will Health Canada ensure that wholesalers comply with recall requirements? (“In record time” as quoted by Ms Krepps)

Health Canada should be notified by a wholesaler of his decision to conduct a recall as soon as this decision is made, although there is no formal requirement to this effect in the Guidelines.

What is “record time” or acceptable timing?

I probably shouldn't have said “record time”, The Guideline says “rapid and complete”.

QUALITY CONTROL DEPARTMENT / SERVICE DU CONTRÔLE DE LA QUALITÉ
C.02.13 - C.02.014 - C.02.015

Rework: Does the requirement for a “notifiable change” also apply to Drug Product in addition to sterile & Biologics/Genetics.

Yes, notification is required.

Par un “reworking”, comment peut-on libérer un lot avec le résultat d’un seul lot, ce qui est contraire à une validation normale (3 lots)? Dois-t-on vraiment notifier au gouvernement?

Il n’est pas nécessaire de notifier la reprise d’un lot à Santé Canada. Par validation, on entend une série de mesures additionnelles approuvées par le service du contrôle de la qualité et normalement, ceci implique des analyses supplémentaires en cours de reprise pour assurer que la qualité du produit fini ne sera pas compromise. Par exemple pour une forme solide comme un comprimé ou une capsule, il y aurait lieu de prélever des échantillons aux diverses étapes du mélange des poudres et lors de la compression ou de l’encapsulage selon le plan suivi pour les lots de validation afin de vérifier l’uniformité du mélange.

It is generally accepted in the industry to perform process validation on three consecutive lots. How does Health Products and Food Branch view validation when reworking is required (i.e. three consecutive incidents will never happen)?

A reworked batch would not be considered as representative for consistency of manufacture for process validation purposes. The validation of a reworked lot would imply supplementary testing during the reworking operations to ensure that the quality of the final product is not compromised. For example, for a solid form such as a tablet or a capsule, validation would mean to take samples at the various steps involved in the mixing operations for powders and during the compression or encapsulating according to the plan followed for the validation lots in order to verify the uniformity of the blend. However, several reworks would mean that the validation studies performed are not sufficiently detailed and probably did not represent the worst case scenario.

Standard qualification: When qualifying secondary standards, what is the rationale for full monograph testing? Standard will only be used for specific assay i.e. potency, so for example OVI levels - why would we worry if these levels were outside of limits as long as potency meets requirements?

Standards are used usually to determine potency - often variable bioassays - therefore their standardization through full testing is required.

Standard qualification: Standards are not used as marketed drugs and are not used for human use so full monograph testing seems as though it is not contributing to rational productivity - too many unnecessary tests are being performed.

Tests are not unnecessary particularly with bioassays.

Standard qualification: What is it the regulatory requirement? Can we rationalize scientifically why we do not perform the additional release monograph testing?

The testing conducted to establish the potency of a secondary standard can be limited to those that are specific to this effect.

À la fin de la date d’expiration d’un standard, on le reteste par rapport à un autre standard et en général on extensionne la date d’expiration de 1 an. Avec la nouvelle

réglementation, doit-on utiliser le standard retesté tout de suite?

Les mêmes principes que pour les ingrédients pharmaceutiques actifs s'appliquent, p. ex. lorsque la date de réanalyse est dépassée, l'ingrédient pharmaceutique actif qui doit servir de standard doit être réanalysé. Toutefois, cette date d'expiration peut être allongée basée sur des réanalyses antérieures effectuées sur un nombre suffisant de lots.

PACKAGING MATERIAL TESTING / ANALYSE DU MATÉRIEL D'EMBALLAGE
C.02.016 - C.02.017

Is it necessary to include in a specification for a packaging component (eg. plastic bottle) a chemical identification (eg. IR)? Must this chemical Identification be conducted for each lot received? Would Vendor Certification be considered an acceptable substitution for testing upon receipt?

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

C.02.017: Can supplier of Printed Material (i.e. labels) be part of a Vendor Certification Program?

Yes, but the requirements of section C.02.017(2)(b) and Interpretation 8 must be met. The labels and other printed packaging material shall be examined or tested in order to ensure that they comply with their specifications.

Analyse du matériel d'emballage: Quels sont les tests d'identité acceptés?

-bouteille HDPE, film PVC, etc.

-Infrarouge?

-Transmittance? (As for USP)

L'infrarouge est un test acceptable mais toutes autres méthodes spectrophotométriques ou chimiques pourraient être aussi valables. Par contre, si le type de matériau est décrit sur le CA émis par le fournisseur et si ce test a été effectué par celui-ci pour confirmer l'identité du polymère utilisé pour la fabrication d'un lot spécifique, il n'est pas nécessaire de répéter le test d'identité chimique ou spectrophotométrique.

FINISHED PRODUCT TESTING / ANALYSE DU PRODUIT FINI
C.02.018 - C.02.019

Est-ce acceptable comme "unique identifiant" d'utiliser le lot imprimé sur l'étiquette de la bouteille si le full testing est effectué après l'emballage et que la description sur les spécifications demande d'inscrire le numéro de lot lu sur l'étiquette?

Non.

Emballage d'un produit sur le site A → transport → site B Distributeur. L'identification se fait: au site A après l'emballage? Après réception au site B? Et si A et B sont dans des pays différents?

Lorsque l'emballer/étiqueteur et le distributeur sont situés au Canada, le test d'identité doit être normalement fait après le conditionnement par l'emballer/étiqueteur et le distributeur n'est pas tenu d'effectuer un test d'identité, sauf si les accords contractuels entre les parties exemptent l'emballer/étiqueteur d'effectuer ce test. Le distributeur serait alors responsable d'effectuer le test d'identité après réception dans ses locaux. Lorsque le fabricant ou l'emballer / étiqueteur ou le laboratoire d'analyse est situé dans un pays avec lequel nous avons un Accord de Reconnaissance Mutuelle (ARM), aucun test n'est exigé incluant l'identité. Si le produit provient d'un pays avec lequel nous n'avons pas d'ARM, les exigences sont décrites à l'Interprétation 5 sous C.02.019, p.ex. identité de chaque lot après réception au Canada (soit par une méthode chimique / biologique ou selon le principe de l'identificateur unique), obtention du Certificat d'analyse (CA) du fabricant et analyse périodique de confirmation.

Un produit fini qui se retrouve dans une pharmacopée doit-il absolument être déclaré comme tel et donc analysé comme tel? Si oui, s'il se retrouve dans plusieurs pharmacopées différentes, a-t-on le choix de la pharmacopée que l'on va déclarer?

Si un produit se retrouve dans plusieurs pharmacopées, vous pouvez utiliser celle de votre choix à condition que cette pharmacopée soit incluse à l'Annexe B de la Loi. L'analyse devra être effectuée selon la monographie choisie et devra donc comprendre tous les paramètres inclus dans celle-ci.

Analyse Produit Fini: (non ARM) Afin et avant de parvenir à l'analyser par le fabricant de 1 est 1 forme poso./année, existe-t-il des exigences analytiques (comme X analyses complètes en comparaison entre le fabricant et distributeur)? Si des exigences analytiques sont requises, y a-t-il une période requise afin de refaire ces analyses? (A chaque X année?)

La question semble porter sur la certification du fournisseur. L'obligation d'effectuer une analyse complète sur un certain nombre de lot pour un produit fini afin de certifier un fournisseur n'existe plus. Lorsqu'un site étranger situé dans un pays non signataire (avec lequel il n'y a pas d'Accord de reconnaissance mutuelle (ARM) en vigueur) est inclus sur la licence d'un importateur (signifiant que des données suffisantes ont été reçues et évaluées pour démontrer sa conformité générale aux BPF), il suffit de rencontrer par la suite les exigences des Interprétations 5 et 7 sous C.02.019, p. ex. identité de chaque lot après réception au Canada (soit par une méthode chimique / biologique ou selon le principe de l'identificateur unique), obtention du Certificat d'analyse (CA) du fabricant et analyse périodique de confirmation d'un lot / année/ forme posologique / fournisseur.

What are the documentation responsibilities and expectations for transportation for Importers and Distributors? Is the stability documentation required to be on site for Importers and Distributors?

As per Interpretation 2 under section C.02.019, evidence must be available at the receiving site

that the shipping requirements have been met. Some companies are using indicators within their containers to this effect.

Yes to the second question.

Canadian Establishment Licenced sites: Does this mean if sites (non-Mutual Recognition Agreement) are on your Establishment Licence that we do not need to do any identification testing, and that only a copy of an authentic Certificate of Analysis would suffice?

No, this only applies to products fabricated/packaged labelled in Canada, not those imported which have been fabricated in a non-MRA country.

Do “validated” methods apply to the cosmetic industry?

No, provided that the product is truly a cosmetic and not a cosmetic-type drug such as sun screens, fluoride toothpastes, etc.

In Daryl Krepps’ presentation, I have heard that we can release a product only by doing identity. Then later on we can conduct full testing on that lot. I understood this is acceptable, please advise if I have understood this correctly.

The question is probably for the lot used for complete periodic confirmatory testing once a year. It is acceptable to release this lot for sale after the identification test is done and to perform shortly thereafter the remaining tests described in the specifications. _____

A Certificate of Analysis for an imported (non-MRA) finished product should include Unique Identifier. What does this mean in practice? Is it sufficient that it is the normal routine description of the product: for example “Description: A round biconvex, white tablet...engraved with xxx-123” Is it acceptable the above appears without further elaboration as to what constitutes the Unique Identifier?

The acceptable unique identifier principles are described in Interpretation 7 under C.02.019. The principle you are describing (engraved tablet with a unique marking) appears acceptable providing the other conditions are met.

RECORDS / DOSSIERS

C.02.020 to C.02.024

Does Health Canada plan to adopt 21 CFR Part 11, Electronic Records & Signatures in whole or in part for Canadian companies? If not, do you plan in the foreseeable future to provide more specific guidance on controlling electronic records?

No. At this time, no such document is being prepared.

Is Canada’s “Electronic Evidence Act” to be used for electronic records and signatures?

You are probably referring to the “Personal Information Protection and Electronic Documents Act”. It is not a specific requirement to meet the dispositions of this Act when GMP records are maintained electronically, although some of the principles described may be used.

What is the value added or the usefulness in getting executed batch records from a non-MRA country, especially if the document is in a non-official language? Most batch records in English or French are provided.

This provides evidence that the fabricator is really completing the “Manufacturing Batch Document” in line with the current Master Production Document.

How does C.02.021 apply to blood establishments who need to keep records indefinitely for lookbacks/tracebacks? C.02.021 only requires a 1 year or 5 year retention period.

Respecting lookbacks/tracebacks which specifically apply to the blood component used as the starting material for the blood product please refer to the guidelines for Good Manufacturing Practices for Schedule D Drugs, Part 2, Human Blood and Blood Components where records are required to be kept indefinitely.

With respect to the requirement under C.02.021 that records be maintained for at least one year after the expiration date of a drug, what is the requirement when there is no expiration date for biotech products in clinical trials?

Biotech products have an expiry date sheet. Documents should be retained. Further information with respect to Good Manufacturing Practices for drugs used in clinical trials is under development and will be available on the Health Canada web site.

As they are separate entities and have their own establishment licences, pharmaceutical companies are reliant on their wholesalers in the event of a recall.

It is a requirement for wholesalers to maintain records of sale under C.02.022. Any distributor should ensure, through a written agreement or contract, that a wholesaler will participate in a recall.

With respect to Interpretation 4.5 under records, are detailed plans and specifications for buildings required for fabricators only? Does this include packaging buildings? (Eg. fabrication would include packaging.)

Yes, fabrication includes packaging in this Interpretation.

What are the responsibilities for the importer in terms of validation, if the product is imported from a parent company? If the importer is responsible for validation, is the importer required to maintain validation data on site? Or can it be supplied as per request?

The requirements in terms of validation are described in the document “Validation Documentation Requirements and Responsibilities for Drug Fabricators, Packagers/Labellers, Distributors and Importers”.

SAMPLES / ÉCHANTILLONS

C.02.025 - C.02.026

Why is there a difference in the retention time for samples for distributors and fabricators?

Distributor - 1 year after expiry

Fabricator - 2 years after use

Could result in fabricator discarding samples earlier than distributor does.

The prescribed retention period for the distributor or importer applies to the finished product whereas the retention period for the fabricator is for the raw material only. A fabricator is not required to retain a sample of the finished product manufactured for a client.

With respect to raw material testing and sample retention, when a subcontractor is charged with the production, packaging and labelling of a product - all subject to the parent company's approval and approbation - but not with the quality of the raw materials used (ie. the raw materials are purchased, analyzed, released for use and pre-weighed by the parent company, then sent to the subcontracting company, who is contractually obliged to only effect the production and packaging - the parent company is responsible for all final product testing and releases), then is the subcontracting company still required to retain raw material samples used in the production processes?

Even if the parent company is responsible for the purchase, testing and release and excludes the subcontractor from these tasks by contract, the subcontractor (the fabricator) is required to retain a sample of all raw materials, according to section C.02.025.

Since the alternate retention site should be included on the Establishment Licence for category IV products, does this require all supporting Good Manufacturing Practices documents? Or is this included on the licence for information only?

It is not necessary to send any supporting Good Manufacturing Practices data. The inclusion on the Establishment Licence of the list of products for which an alternate retention site has been granted may be reviewed at time of inspection.

If an application for retained sample exemption was made in 1998, do we have to re-apply as part of the Establishment Licence renewal for 2002?

No.

STABILITY / STABILITÉ

C.02.027 - C.02.028

Do we need to maintain a full stability test schedule for natural products?

For natural health products, the stability program should include microbial tests and tests for potency if a representation relating to potency is declared on the label of the product. Other parameters should be addressed by GMP guidelines that will be developed by the Natural Health Products Directorate.

Est-ce qu'un distributeur est tenu de faire des tests de stabilité sur des produits provenant de France et d'Allemagne si ces tests sont faits par eux? (Accord de reconnaissance

mutuelle)?

Les exigences de stabilité s'appliquent à tous les distributeurs et importateurs, que les produits proviennent ou non de sites situés dans des pays avec lesquels nous avons un Accord de reconnaissance mutuelle (ARM). Tel qu'indiqué aux Interprétations 1.4 sous C.02.027 et 1.3 sous C.02.028, les données de stabilité développées par des manufacturiers étrangers sont acceptables si elles rencontrent les exigences énoncées dans les différents documents de référence.

Des échantillons peuvent-ils être gardés en stabilité par un laboratoire autre que celui du manufacturier?

Oui, si les conditions d'entreposage sont conformes à celles spécifiées par le programme de stabilité.

With respect to Interpretation 1.1 under section C.02.027, does this Interpretation still allow a company to market a product with an expiration date supported by only accelerated stability based upon label storage?

For new drugs, the stability data to be submitted are according to the specific requirements of the review Bureaux involved, either in the Therapeutic Products Directorate or the Biologics & Genetic Therapies Directorate. For "old" drugs, accelerated data only could be considered based on acceptable recognized principles for the extrapolation of data. But the pilot lots involved in the establishment of the expiry date through accelerated studies should also be enrolled in long term studies.

Is there a minimum time required when performing accelerated stability and then utilizing bracketing and matrixing? (ie. Product at 40°C +/- 2°C, Time = ?)

As mentioned, for new drugs, the data will be required by the appropriate review Bureaux. Usually, the data to submit are in accordance with the relevant guidance documents such as the ICH and TPD guidelines.

Interpretation 2(b) under section C.02.028 states that a single primary stability batch of the drug should be tested for antimicrobial preservative effectiveness (in addition to preservative content) at the end of the proposed shelf life for verification purposes. Does this statement mean that the preservative effectiveness is to be performed on the routine stability program (minimum one lot/year/presentation) at expiry, one time only or on a normal basis?

No. This test is to be performed only once on one regular production batch at the end of the proposed shelf-life.

Is it acceptable to use an excipient, such as albumin, that is close to its expiration date, in the formulation of a biologic where the expiry date for the biologic extends beyond the expiry date for the excipient?

Yes.

Can products be grouped into one stability protocol (ie. same active & excipients, same closures/containers, stoppers/vials, different sizes) or must each have a separate protocol as specified in the regulations?

As mentioned in Interpretation 1.1 under C.02.028, the principle of bracketing and matrixing as described in ICH guidance document Q1A(R) is allowed.

With respect to section C.02.028 of the regulations, please clarify “package in which it is sold”. Individual cartons or shipper corrugated boxes.

Under most circumstances, consideration is given only to the packaging materials that are in direct contact with the product. Outer packaging such as cartons or corrugated shippers are not considered unless they have a direct impact on the stability (for example, if they are used as insulating material).

Please clarify if accelerated studies are sufficient for transport.

Yes, if they include or reflect the actual transportation conditions.

STERILE PRODUCTS / PRODUITS STÉRILES

C.02.029

Dans une salle d’habillage en situation non opérationnelle, doit-on mesurer les particules et les bactéries viables?

Oui. Voir l’Interprétation 8 à la section “Locaux” sous C.02.029.

Cleanroom monitoring: Should the monitoring of pressure, temperature and humidity be performed on a continuous basis, if not how frequent?

There is no requirement to monitor these parameters on a continuous basis. However, the procedures in place must ensure that these parameters are always kept within limits.

C.02.017: particle Count Monitoring: “At Rest” should the primary packaging components (container/closure) be present in the room during the particle monitoring at rest. Specially in the case of plastic components and known to shed particles.

The “at rest” condition is described in Interpretation 5.1 under the General section of C.02.029. as the condition where the installation is complete, including fabrication equipment installed and present in an operational condition but not in use and with the operating personnel absent. Normally, the “at rest” condition does not include the packaging components in the room. However, if packaging components are introduced in the working zones prior the start of the monitoring for the “at rest” condition, there should be a cleaning time allowed for the removal of particles generated by such packaging components.

Frequency of sterile monitoring programs: how often should importers of sterile products obtain reports of simulated files validation of sterilization process, particulate matter monitoring, etc.?

The requirements in terms of validation documentation for importers are described in the document “Validation Documentation Requirements and Responsibilities for Drug Fabricators, Packagers/Labelers, Distributors and Importers”.

Regarding recommend units of microbial contamination, is it acceptable to expose settle plates for 1 hour as a standard practice?

Yes. But the results should be extrapolated to reflect the actual requirement of 4 hours.

Are we required to retain sufficient samples to allow sterility testing, pyrogens, endotoxin particles, etc.?

Please refer to Interpretation 4 under C.02.025 - C.02.026.

Does the Health Canada web site have a definition of Grade A, B, C & D areas for sterile manufacturing?

Specifications for these room classification are included in Interpretation 9 under the General chapter of C.02.029 of the GMP Guidelines 2002.

Sterility: If a product is released based on process parametric release (PPR) by a foreign site and Health Canada has not reviewed nor authorized parametric release, is the distributor required to perform sterility testing upon receipt in Canada?

Yes. But to be accepted in Canada, PPR for an imported product from non-MRA countries must be supported by a submission covering all the information requested by the PIC/s guidance document, which has been accepted by Health Canada and became effective on September 1st, 2001 and posted on the Inspectorate Web site. This evidence must be available that this submission has been evaluated by a qualified Regulatory Authority (PIC/s, MRA, FDA) according to the PIC/s guideline and found acceptable. This information must be submitted to the National Coordination Center of the Inspectorate for evaluation.

For products that have been filled aseptically, samples must be taken from: the first and last containers filled. My point of view is that the middle is missing since it is representing the real mean since the first and last it is where problems occurs, so the middle reflects the mean.

The main goal of the sterility test is not to get a satisfactory result but to detect even one contaminated unit. Usually, the first and last units filled as well as those filled after significant work interruptions represent the worst case condition (higher probability of being contaminated) and therefore should be selected for the sterility test.

Dans une hotte laminaire, peut-on avoir une classe A (micro ou particule) autour de la zone de remplissage et une classe B aux extrémités de la hotte?

Pour être de classe A, la zone doit rencontrer les standards décrits au tableau de la section C.02.029 que ce soit au repos ou en opération. S’il s’agit d’un remplissage aseptique, il faut que la zone rencontre les critères d’une classe A. Par contre, si le produit est stérilisé en phase terminale, il serait acceptable que certaines parties de la hotte laminaire soient de classe B.

MEDIA FILLS: If a number of units are filled equal to the batch size, is the 95% confidence interval applicable or is the 0.1% limit applicable alone? This might be true since a “sample” is not being taken but rather the whole lot quantity is being tested. The 0.1% limit alone does not apply anymore. It must be used with the 95% confidence limit.

**MUTUAL RECOGNITION AGREEMENT (MRA) / ESTABLISHMENT LICENCE -
ACCORD DE RECONNAISSANCE MUTUELLE (ARM) / LICENCE
D'ÉTABLISSEMENT**

Fabricator Batch Certificate: Without any reference to the master issue, this certificate is incomplete and do not assure quality. Please comment.

In this document, a certification statement is included to the effect that the product batch/lot has been manufactured in full compliance with the GMP requirements of the local Regulatory Authority and with the specifications in the Marketing Authorization of the importing country. We believe and as agreed with our MRA partners that this statement is sufficient to ensure that the product batches/lots are being manufactured in accordance with the current updated version of the Master Production Documents.

What's the difference between “Certificate of analysis” and “Batch Certificate”?

The term “Fabricator’s Batch Certificate” is used in the framework of the MRA for the exchange of information required for each lot sold. Basically, the Certificate of Analysis or a statement of all the required tests with the results obtained and the methods used is included in the Fabricator’s Batch Certificate.

I understand the importance of harmonization - MRA. However, are we upgrading our GMP to meet those of the EU and Switzerland, or are we “giving” in to them? Are we ignoring the USA in the process?

During the confidence building phase of the MRA process with Switzerland and the EU, the equivalency of the regulations governing the GMPs and the compliance activities have been assessed. No major discrepancies were noted. The ones noted were addressed in our revised GMP guidelines. With regard to the US, although a MOU (Memo of Understanding) is in place regarding the exchange of certain information, the signing of a MRA is not foreseeable in the near future.

If Canadian company A imports product into Canada and Canadian company B distributes it, who has to list the foreign site in section 5 of their drug establishment licence? “A” is packager/labeller. Whose name is on label “B”?

Normally, the foreign site is listed on the Establishment Licence of the Canadian importer. In this instance, the importer is also the packager/labeller. The name of the distributor (Company B) must appear on the label.

On the Establishment Licence, the GMP compliance expiry rating is site specific as opposed

to dosage form specific. This creates confusion. For example, our Establishment Licence may state that a site is GMP compliant, however, we have experienced times when Therapeutic Products Directorate (TPD) has informed us that we are no longer GMP compliant for a specific dosage form at that site and that we are required to supplement updated GMP information. Is there any plans to make the GMP compliance expiry rating dosage specific for each site?

Situations like the one you describe are exceptional and are usually brought to our attention by foreign Regulatory Authority following specific problems investigated. Such situations of non-compliance may occur during the validity period of the data to support the listing of a foreign site on your Establishment Licence.

Re_Evidence to demonstrate the continuing competence of contractors: Would a Swiss audit report on a UK site really rate higher than a MRA current report on the same site?

At this time, the only operational MRA is the one signed with Switzerland. If a MRA was operational in both countries, the only evidence needed to demonstrate the GMP compliance would be the GMP compliance certificate and not the full audit report. An MRA report used in the context of a MRA agreement confidence building exercise or when the Operational phase is started is an audit report of the Regulatory Authority Inspectorate to ensure the Authority is properly inspecting the site. It is not a report of the site.

For the addition of a new site to an Establishment Licence, what is the time-line for review of the GMP documentation?

For MRA countries, the GMP compliance certificate must be issued within 30 days when an inspection report is still valid and within 60 days when no inspection report is available. For sites located in non-MRA countries, for amendments the information submitted is to be reviewed within 3 weeks (or 15 calendar days) and during renewal time (December to March) the information submitted is to be reviewed within 7 weeks.

A company which was last inspected 1995. Establishment Licence issued 1998. Health Canada made inspected (last) 1998 instead 1995 and issued Establishment Licence. Now under inspection (Nov. 28/2001), is there any grace period to update our validation or complete (Air, MFG).

The validation requirements are not a new issue: those were first included in the main GMP guides in the 1996 edition. These new requirements were then discussed and presented to industry at many occasion during discussion sessions. At this time, it is expected from manufacturing sites that a validation master plan is in place with most systems and equipment qualified and cleaning and process validation is well in progress.

We are currently importing drugs from EU countries expecting to be part of MRA. Are we required today to conduct identity testing on each batch? When does this requirement disappear for MRA countries? January 2002? When the MRA is official?

Yes you are required to perform an ID test as well as periodic confirmatory testing for lots imported from EU.

The retesting exemptions provided by a MRA will not be applicable until the MRA with EU is operational.

As mentioned during one session, the operational phase of the MRA with EU is not expected before a year or so.

Has the MRA status of the US changed?

There has been no change.

If not, must product sourced from the US comply with all the requirements outlined for non-MRA countries?

Yes.

Will inspection of a non-MRA manufacturer by the Regulatory Authority of an MRA country enable the importer to discontinue identity testing?

No.

From non-MRA sites we have to show GMP compliance if we use fabricators test results. We show evidence of GMP compliance to get that site listed on the Establishment Licence. Is this enough or are you looking something else to show GMP compliance if something else is required please specify what.

The accepted evidence to demonstrate the GMP compliance of a foreign site for the purpose of listing this site on the Establishment Licence of the Canadian importer are described in the document "Conditions for Acceptance of Foreign Inspection Report".

GMP certificate: What must an importer/distributor do if a foreign site had a MRA GMP certificate but it expires and a new GMP certificate is unavailable?

The situation should be brought to the attention of the Inspection Unit of the National Coordination Center in Ottawa. A new GMP compliance certificate will be requested. If none is available, it may indicate compliance problems with this foreign site and proper action, depending of the situation, will be implemented.

Pays non-ARM: Pour relâcher les produits en provenance de ces pays nous devons avoir:

-Certificat d'analyse

-Certificat de fabrication du lot

et une fois par an par produit

-"Executed batch document" dans la langue d'origine.

Est-ce bien exact?

Oui. Cependant toute documentation exigée par Santé Canada pour fins d'évaluation est fournie dans l'une des langues officielles.

When will the MRA come into effect?

You are probably referring to the MRA with the EU. As mentioned during the workshop, this MRA is not expected to be operational before a year or so.

What are the validation document requirements for a product imported from a non-MRA country.

The requirements in terms of validation documentation are described in the document “Validation Documentation Requirements and Responsibilities for Drug Fabricators, Packagers / Labellers, Distributors and Importers”.

OTHERS - AUTRES

Does the “GMP committee” need industry/stakeholders participation?

The Inspectorate considers the participation of the stakeholders as an essential component in the development and implementation of new guidance documents. This participation is achieved by consultation through webposting, meetings, discussion sessions, etc.

Can you describe the functions/mandate of the GMP Committee?

The main function of the Committee is to coordinate the development and maintenance of GMP Guidelines and Policies and to provide guidance on technical issues to the Inspectorate and other stakeholders. It also evaluates the effectiveness and identifies issues related to GMP Regulations and acts as a forum to evaluate proposals from sources internal and external to the Inspectorate.

Plans for 2002: did not hear any reference to sanitizer (hard surface cleaners) guideline excluding these products from the GMPs. (Originally due to be finalized in spring 2002). Why?

A new draft of the document “Standard for the Fabrication, Control and Distribution of Antimicrobial Agents for Use on Environmental Surfaces and Non-Critical Medical Devices” will be published for comments.

Note: this document has been published on the Inspectorate Website in January 2002.

Will validation requirements be discussed within framework of GMP 2002? I do not see it specifically on the agenda.

Validation was not discussed during these GMP workshops since all Interpretations related to validation and qualification are identical in the GMP 1998 edition and in the GMP 2002 edition. A specific workshop for validation requirements was given to industry in 1999.

When will these new GMP 2002 Guidelines be official?

Jan. 1, 2002.

Would you be able to describe the process for these guidelines to be official?

In this particular case, the process involved the publication of a preliminary draft which was submitted for a limited consultation by the associations. Following this 2 day consultation session, a draft was published on the Therapeutic Products Directorate (TPD) website for comments. Where deemed appropriate, the comments received were incorporated in the final

version which was subsequently published on the Inspectorate website on December 1st, 2001.

Representatives of the radiopharmaceutical industry have claimed that the GMP Guidelines are an impediment to the pursuit of clinical trials and to the marketing of radiopharmaceuticals in Canada. Is there support for their opinion from the industry represented here today - or any evidence of this from those who have performed inspections?

These guidelines do not apply to the drugs manufactured for clinical trials. Concerning the marketing of radiopharmaceuticals, the Inspectorate gives consideration to the fact that, sometimes, the quantities manufactured are limited compared to regular drugs. In those instances, the application of the GMP requirements will be exercised with discretion.

Does a “contractor” include foreign site wholly owned by the same company as the Canadian importer (subsidiary)?

Yes.

Is there a transition period before the 2002 GMPs changes are enforced?

No.

C’est quoi la règle “grand father”?

Ce sont les équipements achetés et en place depuis plusieurs années. La Qualification d’installation n’est pas obligatoire si l’évidence documentée démontre que:

- l’entretien en fonction des échéances est respecté;*
- les équipements n’ont pas été modifiés.*

On peut passer directement à la Qualification opérationnelle.

GMP compliance expiry rating for foreign sites database published on internet?

There is no plan to publish such a document.

When will we see “computer validation” guidelines from Health Products and Food Branch Inspectorate (HPFBI)?

There are no such guidelines in preparation by the Inspectorate. However, guidance documents developed by other Regulatory Authorities with whom we have signed agreements, such as the PIC/S or Mutual Recognition Agreement (MRA) authorities, could be considered for implementation in Canada.

Is there any or will there be any guidelines on the following:

- 1) use of electronic signatures on documentation records?**
- 2) validation of softwares for documentation records?**
- 3) use of Intranet websites for documentation records?**

Is there any specific guideline around the following:

- 1) the use of electronic signatures on documentation records?**

2) documentation (e.g. SOPs) in the intranet website?

3) Documentation softwares?

No such guidelines are presently being developed by the Inspectorate.

Ephedra use: When & why? Therapeutic Products Directorate (TPD) move towards withdrawing products containing greater than or equal to 8 mg of ephedra per dosage unit. Does this include oral nasal products, that have been approved with 8 mg per dosage?

On January 9, 2002, information has been published on the Health Canada website providing more information. The information can be accessed at:

http://www.hc-sc.gc.ca/english/protection/warnings/2002/2002_01e.htm

Shall we use purified water for natural products?

The requirements for the water to be used in the manufacture of natural health products should be included in the soon to come GMP guidelines which are presently being developed by the Natural Health Products Directorate.

Shall we do process and test methods validations for natural products?

For the time being the answer would be “yes” for natural health products that are currently considered to be drugs. Since this is a major undertaking, you may wish to wait for the new GMP guidelines that will be developed by the Natural Health Products Directorate.

Nous sommes une entreprise de produits de santé naturels. Sommes-nous assujettis aux normes de BPF de l’atelier d’aujourd’hui ou seulement des BPF qui seront ou sont issues de la Diresction des Produits de Santé Naturels? Aussi comme la structure à Santé Canada est assez complexe, svp, pourriez-vous nous classer dans les Produits naturels et non dans les drogues.

Le cadre réglementaire qui est présentement en cours de préparation pour ces produits inclura une définition du terme “produit de santé naturel”. Ce cadre comprendra aussi des lignes directrices spécifiques sur les BPF. Celles-ci s’appliqueront à vos produits si la définition du terme “produit de santé naturel” englobe tous vos produits. Toutefois, plusieurs firmes fabriquent à la fois des produits de santé naturels et des produits pharmaceutiques réguliers. Dans ce cas, les 2 guides seront applicables.

Are all the regulations for pharmaceutical products also suitable for natural products?

In theory, yes, but until the new regulations for natural health products come into effect, the Inspectorate will enforce current regulations with common sense. The proposed Natural Health Products Regulations were published in Canada Gazette Part I on December 22, 2001.