COMMENTS BY GPIM ON 2002 DRAFT EDITION
GOOD MANUFACTURING PRACTICES GUIDELINES
HEALTH PRODUCTS AND FOOD BRANCH INSPECTORATE

QUALITY MANAGEMENT SECTION

- Replace the expression < Quality Assurance > by a more neutral one such as < Quality Systems > throughout the text,
- In that section, add a note establishing the correspondence between the selected expression with < Quality Assurance > used in the PIC/S Guide to cGMP,
- Insert a paragraph stating that the existence of separate < Quality Assurance > and < Quality Control > units and the distribution of tasks between them is an operational issue, and that the < Quality Units > must assume all the responsibilities normally identified as that of QC, as it is done in section 2.16 of the ICH Consensus Guideline. Also the different tasks listed under < Quality Assurance > and < Quality Control > may differ from companies.

PAGE	ITEM N°	ACTUAL TEXT	PROPOSED CHANGE	REASON
6	QUALITY MANGEMENT Quality Assurance n° 3	Systems, facilities and procedures are adequate	Add: Qualified and competent personnel are employed. Add: Recall procedures exist.	
13	GLOSSARY	Re-test period: the period of time during which the drug substance can be considered to remain within the specifications and therefore acceptable for use in the fabrication of a given drug product, provided it has been stored under defined conditions; after this period, the batch is re-tested for compliance with the specifications and then used immediately. (Definitions taken from ICH document QA7;GMP for API)	Re-test period: the period of time during which the drug substance can be considered to remain within the specifications and therefore acceptable for use in the fabrication of a given drug product, provided it has been stored under defined conditions; after this period, the batch is re-tested for compliance with the specifications and then used within a 30 day period . Removed	As with Interpretation 11 of RAW MATERIAL TESTING C.02.009 on page 26, the expression “immediately” needs to be better defined. Need to take into account industry practice to assign new expiry date based on new data. The ICH reference is not appropriate

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16	PREMISES C.02.004 Interpretation 2.2	Receiving and shipping area(s) do not allow direct access to production areas.	There needs to be direct access from storage or warehouse to shipping and receiving. There may be need for doors. Clarify.	Rationale: Preventing contamination of the production area and means thereof.
16	PREMISES C.02.004 Interpretation 2.5	Engineering, boiler rooms, generators, etc., are separated from production areas.	Engineering, boiler rooms, generators, etc., are isolated from production areas in order to minimize risks of contamination. Engineering: may not be most appropriate expression	Numerous facilities have been upgraded over the years and sometimes generators and boiler rooms were part of the production area. The important point here is to minimize the risk of contamination that can be generated by those activities.
17	PREMISES C.02.004 Interpretation 7	Utilities and support systems are qualified and are subject to periodic verification.	Utilities and support systems are validated and are subject to periodic verification.	Qualification applies to equipment and validation refers to system. In the French section the term 'validated' is used.
20	PERSONNEL C.02.006 Interpretation 1.1 and 1.2	Hold a university degree or equivalent in a science related to the work being carried out; and Have practical experience in their responsibility area	Possess the appropriate education, training, and experience, or any combination thereof.	Equivalency of a university degree is not well defined and is subject to several interpretations and the proposed change gives some flexibility in combination of education and experience.
22	SANITATION C.02.007 Interpretation 2.9	Microbial and environmental monitoring procedures with alert and action limits in areas where susceptible products are fabricated or packaged	Clarify what is meant by <susceptible products >. We think you are trying to convey that some products may be more at risk to contamination.	

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25	RAW MATERIAL TESTING C.02.009 Interpretations 6.1, 6.1.1 and 6.1.2	6.1 Each container of a lot of an active pharmaceutical ingredient (API) is tested for the identity of its content. However, a composite sample is acceptable for identity testing as long as the following conditions are met: 6.1.1 the number of individual containers for each composite sample does not exceed 10; and 6.1.2 a potency test is performed on each composite sample to establish the mass balance of the composite for at least one key marker of the active ingredient.	6.1 Each container of a lot of an active pharmaceutical ingredient (API) is tested for the identity of its content. However, it is permissible to sample only a proportion of the containers where a validated procedure has been established to ensure that no single container of the active ingredient has been incorrectly labeled. 6.1.1 as is 6.1.2 as is Add: 6.2 It is possible that a validated procedure exempting identity testing of each incoming container of active pharmaceutical ingredient could be accepted when: 6.2.1 Active ingredients are coming from a single product (or dedicated) manufacturer 6.2.2 Active ingredients are coming directly from a manufacturer or in the manufacturer's sealed container, where there is an history of reliability and when regular audits of the manufacturer's Quality systems are conducted by the manufacturer of the drug product.	It achieves the same objective while allowing more flexibility. Borrowed from the Medicines Control Agency of the UK

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26	RAW MATERIAL TESTING C.02.009 Interpretation 11	Any API is quarantined, evaluated, and tested prior to use, if held in storage after the established retest date. This retest date is based on acceptable stability data developed under predefined conditions or any other acceptable evidence. A batch of raw material can be used immediately after the retest as long as it continues to comply with the specifications.	Delete the last sentence and replace by: A batch of raw material can be used within 30 days after the retest and the retest date can be extended based on supporting data.	Allow a company who has sufficient and satisfactory data to extend the retest date.
31	MANUFACTURING CONTROL C.02.011 Interpretation 27.4	The batch number and/or analytical control number as well as the quantity of each raw material actually weighed and dispensed (for active raw material, the quantity is to be adjusted if the assay value is less than 99% on "as is" basis and on which the master formula was based)	The batch number and/or analytical control number as well as the quantity of each raw material (for active raw material, the quantity is to be adjusted where necessary according to assay results) actually weighed and dispensed	The 99% assay value is arbitrary and has not been scientifically justified
35	MANUFACTURING CONTROL C.02.012 Control system for recall Interpretation 1.9	All Canadian and foreign establishments involved in the fabrication, distribution or importation of the recalled product be notified.	All Canadian and foreign establishments involved in the fabrication, distribution or importation of the recalled product be notified where appropriate.	Not all establishments need to be informed of every recall.

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37	MANUFACTURING CONTROL C.02.012 Sites located in non MRA countries Interpretation 3.6 and 3.6.3	3.6 GMP inspection report covers: 3.6.3 Evidence of validation as described in the document " Validation documentation requirements… " is available	At section 3.5.3 it says that a consultant may perform an inspection in a case where products are not considered as drugs in the foreign country. It is clear if the product is not considered as a drug, that the foreign firm will not comply with the validation requirements. In such a case, it should be sufficient to perform the complete testing of each imported lot and not require validation.	If the product is not considered as a drug in the foreign country, it will probably be a low risk product in Canada.
39 to 41	QUALITY CONTROL DEPARTMENT	Several interpretations	When written < by the person in charge of the quality control > add "or designee"	It is not always the person in charge that will perform all of those tasks but will designate qualified and experienced alternates. In some companies, Quality Assurance and not Quality Control may also perform some of those tasks.
41	QUALITY CONTROL DEPARTMENT C.02.015 Interpretation 6.6	All reagents and culture media are recorded upon receipt or preparation. Reagents made up in the laboratory are prepared according to written procedures and are labeled. Both positive and negative controls are applied to verify the suitability of culture media…	All reagents and culture media are recorded upon receipt or preparation. Reagents made up in the laboratory are prepared according to written procedures and are labeled. Both positive (once for each manufacturer lot) and negative controls (for each prepared batch) are applied to verify the suitability of culture media…	Ever since the change was introduced in the USP 23 (supplement 8), it has become a well-accepted and customary practice in the industry to test only each (manufacturer) lot for growth promotion as opposed to every reception. Negative test must be performed on each prepared batch.

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47	FINISHED PRODUCT TESTING C.02.019 Sites Holding a Canadian Establishment Licence Interpretation (2)	To demonstrate compliance with finished product specifications, distributors of drugs fabricated, packaged/labelled and tested at Canadian sites are only required to have a copy of the authentic certificate of analysis from the licensed Canadian fabricator. /...	To demonstrate compliance with finished product specifications, packagers and/or labellers and/or distributors of drugs fabricated, packaged/labelled and tested at Canadian sites are only required to have a copy of the authentic certificate of analysis from the licensed Canadian fabricator	As written, the reality of a licensed packager/labeller and distributor was not acknowledged.
49	RECORDS C.02.020 Regulation (1) (d)	Evidence establishing the period of time during which the drug in the container in which it is sold will meet the specifications for that drug	Add at the end of the sentence < as required by section C.02.027 >	Reference to the stability section
50	RECORDS C.02.022 C.02.023 (1) AND (2)	Every distributor, wholesaler and importer of a drug shall retain records of the sale of each lot… On receipt of a complaint respecting the quality of the drug, every distributor and importer… On receipt of any information respecting the quality or hazards of a drug, every distributor and importer…	Add fabricator and replace "and importer" by "or importer"	The fabricator shall also maintain records of distribution, complaints and information received related to the quality or hazards of a drug.
61	STERILE PRODUCTS C.02.029 Premises Interpretation 4.3	Parenterals are filled in an aseptic area of at least a Grade B environment or in a Grade A zone with at least a grade C background, before terminal sterilization	Parenterals are filled in a Grade C environment unless the products are unusually at risk to microbial contamination	To harmonize with the EU GMP requirements

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66	STERILE PRODUCTS C.02.029 Sanitation Interpretation 4	Disinfectants and detergents are monitored for microbial contamination and are sterile when used in grade A or B areas. Dilutions are kept for in previously cleaned containers and are not stored for long periods unless sterilized. Partly emptied containers are not topped up.	Disinfectants and detergents are monitored for microbial contamination if stored for long periods and that period should be validated. For use with aseptically filled products, disinfectants and detergents should be sterile. Dilutions are kept…	If disinfectants and detergents are prepared and used daily, it is not necessary to monitor their microbial contamination. The use of sterile disinfectants and detergents is not required for terminally sterilized products.
68	STERILE PRODUCTS C.02.029 Manufacturing control Interpretation 15.2.1	Both temperature and pressure controls…The reading of the independent temperature indicator is routinely checked against the chart recorder during the sterilization period. For sterilizers…	Remove the sentence: The reading of the independent temperature indicator is routinely checked against the chart recorder during the sterilization period.	This independent reading check is performed during validation but there is no need to perform that check for each cycle, the recorder and the indicator being part of the calibration program.