

**HEALTH CANADA - HEALTH PRODUCTS AND FOOD BRANCH
BILATERAL MEETING PROGRAM**

RECORD OF DECISIONS		
GROUPEMENT PROVINCIAL DE L'INDUSTRIE DU MÉDICAMENT (GPIM)		
LOCATION: 1600 Scott Street, Holland Cross, Tower B, 2 nd Floor, Boardroom 2048, Ottawa		
DATE: Wednesday, November 22nd, 2006	START TIME: 1:30 p.m.	END TIME: 3:30 p.m.

HEALTH CANADA PARTICIPANTS	GPIM PARTICIPANTS
<p>Omer Boudreau, Director General, TPD, Co-Chair Ellen Birnbaum, OBT Jacques Bouchard, BGIVD Gail Gervais, Liaison Unit, OBT Thea C. Mueller, BGIVD Nick McCandie Glustien, BPSIP Denise Quesnel, Liaison Unit, OBT Heather Sutcliffe, MHPD Vincent Tong, HPFB-Inspectorate Alan Viau, BPS</p> <p>Observers Joseph Benoliel, OCT Jenny Lee Choon, MHPD Natasha Kuran, BGIVD Matthew Ryan, OBT</p>	<p>Pierre Morin, Director General, GPIM, Co-Chair Manon Audet, Erfa Canada Caroline Fréchette, Omega Richard Marchand, Solumed Grégoire Hovington, Solumed Stéphane Lévesque, Solumed Adriana Petruilian, Neopharm (Warnex)</p>

1. Welcome and Introductions

Mr. Omer Boudreau, Director General of the Therapeutic Products Directorate welcomed everyone and Mr. Pierre Morin, Director General, GPIM, thanked TPD for the opportunity to meet on a bilateral basis. A roundtable of introductions followed.

2. Review of Agenda

The Agenda was accepted as presented.

3. Review of Minutes of May 24th, 2006.

Minutes were approved as presented.

GPIM wanted an update on Good Guidance Practices (GGP) and Good Review Practices (GRP). Although not the project lead for GGP or GRP, Ellen Birnbaum accepted to provide the update. With respect to GGP, she mentioned that at this time, each Bureau in TPD has identified their priority for guidance development, however resources may be an issue regarding the development of these guidance documents. The external consultation phase on the draft *Good Guidance Practices Manual* has now been completed.

With respect to GRP, HC is determining the required competencies for all types of reviewers, which would then help determine the type of training required for reviewers. Mr. Morin mentioned that industry should be trained to the same standards as internal reviewers and that industry would be willing to pay for external training, for example via CAPRA. GPIM is surprised by the high number of submissions that are going through second review. Mr. Boudreau confirmed that there was an increase in NONs/NODs, and that HC was looking at trends, hoping that a solution will be found. The goal is to ensure that HC is getting quality submissions in.

4. Progressive Licensing Framework (Homologation progressive)

Mr. Boudreau provided an overview of this project. He explained that the development of a drug licensing framework was based on sound risk management that supports access to promising new drug therapies while continuously monitoring and reassessing for potential safety, quality, efficacy and effectiveness concerns throughout the product life-cycle. He stated that the current framework is outdated (was developed in the 1960s) and has many regulatory gaps. The public expectations of the regulator are increasing and other jurisdictions have outpaced Canada in adopting new approaches. It is time for Canada to update its model.

Mr. Boudreau explained the drivers for change. Health Canada has little regulatory power after authorization, and little regulatory flexibility for assessing conditions or granting emergency use. The current linear model is not actual representation of real-world drug development and regulation. The needed framework is progressive in that it will address today's needs and will be adaptable to future needs. It adopts an approach to drug regulation as a product progresses through its life cycle. There is a natural progression of increasing information about a drug throughout its market life that needs to be assessed and conveyed to users.

There was a discussion on the definition of *efficacy* and *effectiveness*, as both have the same terminology in French, but have a very different meaning.

Specific questions on the concept and approach will be addressed during the consultation that is planned on November 29th. GPIM will be consulted.

Action: GPIM will be consulted throughout the development process, as one of the stakeholders.

5. Guidance Document for Industry – Reporting Adverse Reactions to Marketed Health Products

Heather Sutcliffe, Marketed Health Products Directorate provided a brief overview on the Draft Guidance Document for Industry - Reporting Adverse Reactions. The document was posted at the end of October (for a 60 day period) on the Health Canada website for public consultation. The closing date for comments is December 29th. It is an update of the current Guidelines for the Pharmaceutical Industry on Reporting Adverse Reactions to Marketed Drugs and communicates Health Canada's expectations concerning the reporting of adverse reactions to marketed health products. The Draft Guidance Document will be amended where applicable as a result of the consultation exercise and subsequent deliberations within Health Canada. Ms. Sutcliffe invited GPIM to visit the website for consultation.

English :

http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/guide/consult_guide-ldir_indust_e.html

Français :

http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/guide/consult_guide-ldir_indust_f.html

Mr. Morin shared his concern about postings on MedEffect. GPIM finds that it is not user friendly and does not serve Industry well. Ms. Sutcliffe acknowledged that the GPIM's comments would be forwarded to the MedEffect Manager. Ms. Sutcliffe mentioned that MHPD will be in a position to implement electronic reporting in 2007-2008, following deployment of the new database. ICH standards will be used.

6. Upgrading Requirements for Antiseptics for Professional Use: Tabling a Draft Guidance Document

GPIM provided a timetable of progress in preparing guideline for professional use antiseptics. These guidelines would accelerate the rate of the approval as well as ensure consistency. Dr. Thea C. Mueller, Manager, Nonprescription Drug Evaluation Division, BGIVD, mentioned that HC was hoping that GPIM could expedite the process so that a final version would be available in March of 2007. GPIM is requesting a workshop to address the scientific issues.

Dr. Mueller noted that the recent posting of the NHPD/TPD monograph for Antiseptic Skin Cleansers which excludes professional use antiseptic skin cleansers is recognition of the fact that antiseptic skin cleansers used in a professional setting- hospitals, food establishments, child/nursing care institutions, etc., require a higher degree of regulatory scrutiny as compared to products intended for personal care and which are granted market authorization via a monograph system. It is acknowledged that lack of efficacy in the aforementioned settings poses a serious public health concern.

There is cooperation to move forward. Dr. Marchand will provide Dr. Mueller with an initial draft document before the end of the year. TPD will collaborate with NHPD to develop joint regulatory requirements for professional use antiseptic products since, for the time being, such products also fall under NHP's jurisdiction. It was indicated that the guidelines will be subject to Good Guidance Practices. Once the document has been approved by the respective DGs, it will be posted on the website for broader consultation. After having collated, and given due consideration to, all stakeholder comments, a workshop may be convened, if deemed necessary, in order to resolve outstanding controversial issues.

Actions: Thea Mueller to provide comments to Dr. Marchand regarding the initial draft document after having consulted with NHPD.
GPIM to address the comments submit a finalized document by March 2007.

The finalized document will then be subjected to GGP's.

7. Material Changes in the Manufacturing Process - GMPs and Validation

Vincent Tong, Drug GMP Inspection Unit, HPFB Inspectorate addressed this issue. GIPM indicated that C.02.011 requires that a manufacturer shall have written procedures to ensure that the drug meets the specifications for use of that drug. This entails qualification and validation of equipment. When a unique and central piece of equipment is replaced, qualification of installation and qualification of the equipment is carried out, but little is said of the validation process.

Mr. Tong invited GPIM to visit the guidance document entitled “Validation Guidelines For Pharmaceutical Dosage Forms (GUI-0029)” (available online on Health Canada’s Compliance and Enforcement website - http://hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/validation/gui_29_tcm e.html) addresses process validation, in the event that a unique piece of equipment is replaced, through the change control section.

GPIM wishes to remain in control of the validation, and Vincent confirmed that the validation team has control over the process. Commitment of the company to control all changes to premises, supporting utilities, systems, materials, equipment and processes used in the fabrication/packaging of pharmaceutical dosage forms is essential to ensure a continued validation status of the systems concerned.

Upon evaluation of a change request, the assessment will determine the need and depth of the re-validation. The justification for conducting concurrent validation (process validation carried out during production) must be documented and the protocol must be approved by the Validation Team. A report should be prepared and approved prior to the sale of each batch and a final report should be prepared and approved after the completion of all concurrent batches. It is generally considered acceptable that a minimum of three consecutive batches within the finally agreed parameters, giving the product the desired quality would constitute a proper validation of the process.

There was a question from GPIM: what if only one batch per year is produced? How would we go about producing validation batches? The response from Health Canada is that a minimum of three consecutive batches within the finally agreed parameters, giving the product the desired quality would constitute a proper validation of the process. Therefore the concurrent validation process would take three years, if it takes that long to produce three consecutive batches.

GPIM suggested that Health Canada should have a Q&A section on Manufacturing. Alan Viau, Associate Director General, Bureau of Pharmaceutical Sciences, TPD informed the group that his office was indeed working on such a document (Frequently Asked Questions).

8. a) Reference Standards Other than USP/EP: Responsibility

Vincent Tong, Drug GMP Inspection Unit, HPFB Inspectorate addressed this issue. GPIM wanted some guidance on the Reference standards used by the Industry other than USP/EP primary standards. GPIM would like to know where the Quebec people from pharmaceutical manufacturing areas assess "complete confirmatory testing", and about the responsibility in terms of purity, when the standard is supplied by another manufacturer. Mr. Tong has sent the request to the GMP Committee.

The guidance document entitled “Good Manufacturing Practices Guidelines, 2002 Edition, Version 2 (GUI-0001)” (available online on Health Canada’s Compliance and Enforcement website - http://hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/guide-ld-2002/2002v2_e.html) pertains to reference standards. Interpretation 6.7 under section C.02.015, Quality Control Department, states:

“6.7 Reference standards are available in the form of the current reference standards listed in Schedule B to the *Food and Drugs Act*. When such standards have not been established or are unavailable, primary standards can be used. Secondary standards are verified against a Schedule B reference standard or against the primary standard and are subject to complete

confirmatory testing at predetermined intervals. All reference standards are stored and used in a manner that will not adversely affect their quality. Records relating to their testing, storage, and use are maintained.”

With respect to reference standards or primary standards, a pharmaceutical company has to evaluate the source of the reference standard or the primary standard, and determine/justify what is necessary to demonstrate the suitability of a reference standard. With respect to secondary standards, the pharmaceutical company must verify the standard against a Schedule B reference standard or against a primary standard, and perform complete confirmatory testing at predetermined intervals. "Confirmatory testing" is testing performed to demonstrate that a material conforms to all of its approved specifications. A pharmaceutical company is responsible for performing these tests and determining/justifying the appropriate intervals to perform the tests.

Action: Adriana Petruilian (GPIM) to contact Vincent Tong, HPFB-Inspectorate.

8. b) Classification of Aseptic and Clean Areas

GPIM wanted some guidance on the quality control of sterilized products. Vincent Tong, Drug GMP Inspection Unit, HPFB Inspectorate, explained that the guidance document entitled “Good Manufacturing Practices Guidelines, 2002 Edition, Version 2 (GUI-0001)” (available online on Health Canada’s Compliance and Enforcement website - http://hc-sc.gc.ca/dhp-mps/compl-conform/gmp-bpf/guide-ld-2002/index_e.html) contains a table describing the basic environmental standards for the manufacture of sterile products. Note 5, which refers to the “at rest” columns of this table, states:

“5. The particulate conditions given in the “at rest” column are to be achieved after a short clean-up period (20 minutes) after the operation has been completed.” Therefore, for routine monitoring, the particulate conditions for the “at rest” state are achieved after a short clean-up (20 minutes) after the operation has been completed.

8. c) Good Manufacturing Practices / Good Laboratory Practices

GPIM wanted guidance on the analysis that are been carried out under GMP compliance and GLP compliance. The issue was how chemical and microbiological testing be conducted as part of a GCP study.

GPIM gave an example of a service provider that is GMP compliant rather than GLP compliant. It receives samples for analysis that come in from different sources linked to clinical studies but, are not always part of a clinical study nor is it always mentioned that the sample is chemical or biologic.

HC has not designated a national authority for GLP licensing, but is currently examining the options.

9. Performance Review

Pierre Morin congratulated TPD for reducing the backlog. GPIM enquired about the ongoing efforts to reduce review timelines.

Jacques Bouchard, Director, Bureau of Gastroenterology, Infection and Viral Diseases, provided the update on this project. He stated that as of October 31st, 2006, there were 151 submissions under the DINA review category. In BGIVD, 22 (29%) submissions were in backlog (Average: 34 days). In BPS, 9 (41%) submissions were also late (average: 82 days).

In BGIVD, the increase in DINA review backlog is mainly due to an unforeseen reduction in staff and normal reduction of activities in summer due to annual leaves. Additional resources have been transferred to NDED to improve the performance review of DINA. BGIVD is anticipating that one senior officer will return to work on December 01, 2006 which will greatly reduce the pressure on NDED. The DINA review performance should be out of backlog by the end of the fiscal year. BGVID is also streamlining the process for screening of the DINF/ Labelling standards submissions. The implementation will be January 2007.

Omer Boudreau stated that there is some initiative on the way at the Branch level to request additional money in order to address the resources issue.

10. Roundtable:

a) Mr. Morin wanted TPD to comment on the book entitled Pharmaceutical Quality that he presented to Omer Boudreau and Dr. Siddika Mithani (former Associate Director General for TPD), in May 2005. Dr. Supriya Sharma will be forwarding her comments to GPIM.

Action: Dr. Sharma to comment on the book entitled Pharmaceutical Quality.

b) Stéphane Lévesque, GPIM expressed his concerns on the backlog and resources. Omer Boudreau mentioned that TPD was presently doing an analysis of the use of resources and does not foresee any cuts.

11. Adjournment: Meeting adjourned at 3:30 p.m.

12. Next Meeting: Wednesday, May 30th, 2007, at 1:30 p.m.

Original signed by

Omer Boudreau
Director General
Therapeutic Products Directorate