

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

<b>RECORD OF DECISIONS</b>		
<b>GROUPEMENT PROVINCIAL DE L'INDUSTRIE DU MÉDICAMENT (GPIM)</b>		
LOCATION: 1600 Scott Street, Holland Cross, Tower B, 2 <sup>nd</sup> Floor, Boardroom 2048, Ottawa		
DATE: <b>Wednesday, May 24<sup>th</sup>, 2006</b>	START TIME: 1:30 p.m.	END TIME: 3:05 p.m.

HEALTH CANADA PARTICIPANTS	GPIM PARTICIPANTS
Supriya Sharma, Associate DG, TPD, Co-Chair Ellen Birnbaum, OBT Laura Freeman, OBT Gail Gervais, Liaison Unit, OBT Thea Mueller, BGIVD Joyce Pon, BPSIP Denise Quesnel, Liaison Unit, OBT Marilyn Schwartz, SIPD Caroline Vanneste, OBT Johanne Veenstra, HPFB-I  Observer Alice Hui, OBT	Pierre Morin, GPIM, Co-Chair Annie Arbour, ProDoc Jovette Deschênes, ProDoc Caroline Fréchette, Oméga Marco Hamel, Oméga Grégoire Hovington, Solumed Dr. Richard Marchand, Solumed

**1. Welcome and Introductions**

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

Dr. Sharma presented the TPD's Strategic Planning Exercise for 2006-09. The goal is to position TPD to better respond to anticipated challenges. She identified two strategic areas: Modernization of the Regulatory Framework and Performance. There are also three enablers: Relationship Management, People and Governance. She stressed that TPD's commitment is to continue the high levels of performance that have been achieved. Mr. Morin is pleased to hear about the succession plan.

**2. Review of Agenda**

The Agenda was accepted as presented.

**3. Review of Minutes and Actions Items: May 18, 2005**

Minutes were approved as presented.

**Review of previous action items:**

- a) Follow-up on Good Guidance/Good Review Practices Process

Ms. Laura Freeman addressed **Good Guidance Practices**. The Good Guidance Practices working group has drafted the GGP Manual, intended to be a resource for issue analysis and guidance development in TPD/BGTD. The Manual is divided into Chapters, and includes guiding principles, definitions, procedures for issue analysis and guidance development, and templates. Internal consultations on the draft Manual have been completed and external consultations will proceed in June.

Ms. Caroline Vanneste addressed **Good Review Practices**. The Good Review Practices project is continuing. Recent projects include a Standard Operating Procedure and new templates for writing safety and efficacy review reports (effective June 1, 2006), Good Review Guiding Principles, and an intranet for reviewers.

In 2006-2007, the focus will be on reviewers' training. SOPs and other material on conducting reviews will be posted on the TPD website. Mr. Morin would like industry members to be invited to the training sessions. Ms. Vanneste agreed to explore the possibility of similar sessions with CAPRA (for non-members also as not everyone is a member).

**Action:** Ms. Caroline Vanneste to contact CAPRA concerning training. (Ms. Vanneste will be speaking at a CAPRA dinner meeting in Toronto on June 19<sup>th</sup>, and Elizabeth Prosen will be speaking in Montreal on June 20<sup>th</sup>. Ms. Vanneste will also be contacting Mr. Morin about how to reach non-CAPRA members.)

#### **b) Follow-up on Old Drug/New Drug Determination**

Ms. Joyce Pon explained that work has been started to assess the usefulness of the list and to identify the issues that have resulted since the publication of this list. This analysis will assist in determining if the list will be updated and maintained on the Health Canada website. The updating of the "New Drugs List" involves the addition of all substances and formulations on the basis of an application to market or further to promotion of products for medical purposes for which a Notice of Compliance has been issued. The "new drug" definition in Part C, Division 8 of the *Food and Drug Regulations* is used in the determination of the drug status of all drug products. The Notice of Compliance (NOC) database posted on the Health Canada website provides the most current listing of drug products that have been issued an NOC; sponsors could use it as a guide in determining the status of subsequent market entry drug products.

Mr. Morin expressed concerns about the addition of drugs regulated under Division 1 to the New Drug List, and questioned the rationale behind the determination of the status of drugs. Ms. Pon re-iterated that any product for which a NOC has been issued is considered to be a New Drug as per the "new drug" definition in the *Regulations*. If a sponsor is not sure of the status of a proposed product, they should contact the Senior Regulatory Project Manager servicing BPS (Alice Hui).

Dr. Thea Mueller stated that the New Drug List was helpful to find out for which drug products a NOC had been issued, but not it would not help industry to determine which drugs regulated under Division 1 may be converted to New Drugs for reasons of safety, efficacy and/or quality. Under these circumstances, the industry should contact the Bureau dealing with the product in question (generally BGIVD for GPIM members) to obtain a drug status determination. HC has to see the manner in which the drug will be promoted and any labelling before a status decision can be made as it is not always dependent upon the ingredients contained in the product. Generally speaking, any new indication made for a Division 1 drug may place it in New Drug status.

**c) Follow-up on NOC Database and Inclusion of DIN Data**

Ms. Marilyn Schwartz, Director of Submission and Information Policy Division (SIPD) mentioned that the NOC Database was officially launched on November 17, 2005. She explained that due to the lack of funds and resources allocated to TPD for this year, SIPD will be unable to pursue the inclusion of DIN data.

Two online databases (NOC Database and the Drug Product Database (DPD)) are currently available on TPD's website. SIPD will be considering the possibility to include the DIN data in either database in the following fiscal year. GPIM was invited to provide comments.

Mr. Morin expressed concerns about the formulation of products. The issue about animal sources was brought up approximately 2 years ago, and he would like an update. Ms. Schwartz mentioned that the voluntary reporting proved to be successful. The database is being populated, but would like to see it regulated so it would be mandatory.

**Action:** Mr. Pierre Morin will consult the GPIM members and provide comments to TPD.

**4. a) Inspectorate Policy Interpretation: Sometimes at odds**

Mrs. Johanne Veenstra, A/Drug Specialist, Drug GMP Inspection Unit, Health Products and Food Branch Inspectorate, provided some background on the guidance.

Mr. Morin stated that a modification was brought to policies to the effect that a drug imported into Canada for packaging could only be re-exported to the country of origin. Some members have developed a good business packaging drugs destined to multi site clinical trials. This modification has eliminated whatever economic advantage was theirs without notice nor consultation notwithstanding the provisions of section 37 of the FDA. Mr. Morin also stated that under the current guidance, goods that come in Canada for packaging had to return to their country of origin.

Ms. Veenstra informed GPIM that the Inspectorate has met with TPD on several occasions throughout this past year to discuss the guideline entitled "Conditions for Provision of Packaging/ Labelling Services for Drugs Under Foreign Ownership (GUIDE-0067)". No consensus has been reached with respect to companies that provide contract packaging/labelling services for drugs destined to multi site clinical trials. Discussions are still ongoing within Health Canada.

Mr. Richard Marchand reminded the group that some drugs do not handle transportation well, therefore limited shipping is recommended.

Mr. Morin also mentioned that in this specific situation, the drugs brought into Canada for contract packaging/labelling are destined for Canadian clinical trial sites for which the clinical trial applications have been submitted to Health Canada.

The intent of the guidance is not to apply to clinical trial drugs. Mrs. Veenstra mentioned that the guideline could have an additional bullet indicating that the guideline does apply to clinical trial drugs. GPIM is invited to provide comments.

#### **4 b) Upgrading Requirements for Antiseptics for Professional Use**

Mr. Morin reported that Quebec hospitals were experiencing difficulty in controlling nosocomial infections. He expressed the view that the antiseptic products currently on the Canadian market are not being evaluated in sufficient detail to establish effectiveness against the variety of organisms/infections claimed in the labelling. NDED in TPD had commenced to develop guidelines to address this issue and has received expert guidance from Dr. Richard Marchand. However, not much progress in finalizing the guidelines has been made in the intervening two years, limited resources being a factor, but mainly because two of the more important ingredients that would be subjected to these guidelines, namely alcohol and iodine, have been converted to NHP status and no longer are under the jurisdiction of TPD. Consequently, TPD will have to collaborate with NHPD to develop a common guideline. GPIM recognizes that NHPD deals mostly with low risk products and has no experience in dealing with professional use type products, such as the antiseptics used in food preparations and health care institutions, or for surgical scrubs, patient preoperative skin disinfection, etc. Dr. Mueller invited GPIM to present a draft guideline that would elaborate upon the original version and which would incorporate the best practices of US FDA/ASTM and European methodologies. It is likely that NHPD would be receptive to adopting such guidelines but they would need to be consulted during ongoing discussions as well.

**Action:** GPIM to prepare draft guidelines to establish safety, quality and efficacy criteria for professional use antiseptic products.

### **5. Implementing the Guidelines for Temperature Control of Drug Products during Storage and Transportation**

Mr. Pierre Morin explained that GPIM members have started implementing the guidance document by first dealing with the cold chain. While this is, in a way, the simplest approach, for it requires refrigerated storage and transport, it also raises a number of issues as to how, and at what cost, the process can be validated. When GPIM ventures into other areas than the cold chain, the degree of uncertainty greatly increases to the extent validation does not appear feasible while costs rise by an exponential factor. Members would like to sit with Inspectorate acting in an advisory capacity to explore what is feasible both technically and economically and to prioritise implementation.

Mr. Morin stated that the technology is available and should be introduced sooner in the validation process.

Mrs. Johanne Veenstra, A/Drug Specialist, Drug GMP Inspection Unit, Health Products and Food Branch Inspectorate, mentioned that there are two sections regarding transportation and storage conditions of drug products in the Food and Drug Act and Regulations.

Specifically, sections C.02.015. (1) and C.02.019 of the Food and Drug Regulations and their interpretations of these sections with respect to transportation and storage can be found in the Canadian Good Manufacturing Practices Version 2 published in 2002. From this, Guide-0069 on temperature control for drugs was written and published in October 2005.

This guideline applies to all drugs including drug samples, and drugs intended for clinical study. Some products are obviously more temperature sensitive than others. Some products are extremely perishable when thawed. Creams and ointments may separate if frozen. Some powders may clump if the humidity is too high. Some drugs must be stored at room temperature.

There are many methods to ensure that temperature sensitive products are maintained within their recommended storage conditions: Active temperature controls in mapped and validated warehouses, validated primary insulated packaging, continuous monitoring, passive heat/cold packs, etc. The method used will depend on the type of product, quantity of product, size of the company, shipping conditions, etc. The Inspectorate does not dictate and does not act in an advisory capacity as to how industry should achieve this. It is up to the company to decide which methods is most suitable for that situation and it is up to the company to show proof to the inspectors that the cold chain is maintained.

Pierre Morin asks if an approach that consists in documenting all of the current practices of storage and transportation completed by a series of measurements to ensure that real conditions are known to effect corrective measures and then followed by a program of control measurements would be acceptable. Mrs. Johanne Veenstra indicates the approach sounds acceptable and would be controlled through regular inspections carried out by the Inspectorate.

Health Canada will enforce these guidelines through our regular inspection program. Licenced companies are inspected every 2 to 3 years depending on their activity, or when a risk or GMP deficiency comes to Health Canada's attention. When an inspector is on-site, he/she will look for documentation, SOPs, training records, monitoring devices, calibration records and schedules, quality agreements between the company and contractors, evidence that shows temperature of inbound and outbound shipments are monitored appropriately. This list is not exhaustive.

Observations of deficiencies during an inspection will require a feasible corrective action plan. Corrective actions will be verified upon reinspection. Deficiencies observed during an inspection in this area require corrective actions and responses from companies. The Inspectorate understands that implementing a validated cold chain system where one did not previously exist is a lengthy process, therefore expects responses to observations to be reasonable and timelines for full implementation to be realistic.

Mr. Morin stated that during the next inspection, inspectors will find proper documents (SOPs, training records, etc.).

## **6. Upgrading Rules Relative to Compliant Drug Products Awaiting Patent Termination**

Mr. Morin presented the issue. New compliant product launch may be delayed for need to upgrade product monograph. Patent holders have been known to file amended product monograph on their product a few days prior to expiry of patent. Should this situation occur once a bioequivalent product is on the market, sponsor would be requested to upgrade its product monograph. In cases where compliant bioequivalent products have not been launched and are awaiting patent expiry, the delay in upgrading product monograph can create havoc with production schedules and be extremely costly. Unless the amendment in the patented product monograph clearly involves a change in the product's safety or efficacy, a deadline of at least 60 days should be set before the launch of a bioequivalent product. Should the deadline not be respected, the product launch would proceed and monograph would be updated as if the product were on the market.

Ms. Ellen Birnbaum, Manager, Regulatory Project Management Division, explained that unfortunately, the Therapeutic Products Directorate is unable to accommodate GPIM's proposal. When a generic product is approved, its Product Monograph (PM) must reflect the most recently approved innovator PM (with the standard differences such as product name and bioequivalence tables). It is the sponsor's responsibility to ensure that they are aware of the most recent version of the innovator PM and to update their PM via the appropriate submission type while their product is still on patent hold. For more information, please refer to the policy entitled *Filing of Supplemental New Drug Submissions, Supplemental Abbreviated New Drug Submissions, Notifiable Changes and Cross-Referenced Submissions*.

To facilitate clarity with respect to which is the most recently approved version of the innovator PM, sponsors can contact the Regulatory Project Manager for the submission to determine the date of the most recent innovator PM. This will ensure that the sponsor is aware of changes to the innovator PM that occurred as a result of a Notifiable Change, thereby ensuring that their PM is up to date. Ms. Birnbaum introduced Ms. Alice Hui, as Senior Regulatory Project Manager servicing the Bureau of Pharmaceutical Sciences, RPMD. Ms. Birnbaum also invited GPIM to visit the Health Canada website for an upcoming related notice (since posted on May 29, 2006 regarding the release of Product Monographs directly to requesters).

7. **Roundtable:** At the last meeting, Mr. Morin presented the book entitled Pharmaceutical Quality to Mr. Omer Boudreau. He would like TPD to provide some comments.

**Action:** TPD to provide comments to Mr. Morin.

8. **Adjournment:** Meeting adjourned at 3:05 p.m.
9. **Next Meeting:** Wednesday, November 22<sup>nd</sup>, 2006 at 1:30 p.m., in Montreal (in French).

Dr. Supriya Sharma  
Associate Director General  
Therapeutic Products Directorate