Updates from the Bureau of Pharmaceutical Sciences

CAPRA Pharmaceutical Symposium
October 22, 2024

Health Canada Santé Canada

Canada

Overview

Overview of BPS

Key Challenges and Initiatives

- Workload
- Nitrosamines
- Complex Generics
- First Review Cycle Performance
- E-Labelling and Labelling Inserts
- Enquiries

BPS Overview – Core Activities

Bureau of Pharmaceutical Sciences (BPS) is one of six Bureaux and three Offices that are part of the **Pharmaceutical Drugs Directorate (PDD)**

BPS is primarily responsible for the review of:

- Quality and chemical composition of brand name and generic drugs submitted for approval, and
- Comparative clinical studies that claim to show the bioequivalence of brand name and generic drugs, to ensure that new versions of the brand name drug are as effective as the original version

Approximately 100 full time equivalents (FTEs) (review and non-review staff) in the NCR with a satellite office in Toronto

BPS Overview – Additional Key Activities

Stakeholder engagement

- Responds to queries (700-800/year) from various stakeholders such as patients, Health Care Professionals, and industry stakeholders (e.g., providing guidance on how to make their drug available in Canada)
- Bilats with key stakeholders

Post-Market and Risk Issues

- Nitrosamine impurities, drug shortage issues & Health Risk Assessments (HRAs)

International Regulatory Cooperation and Work Sharing- Generic and Innovator Medicines

BPS Overview – Additional Key Activities

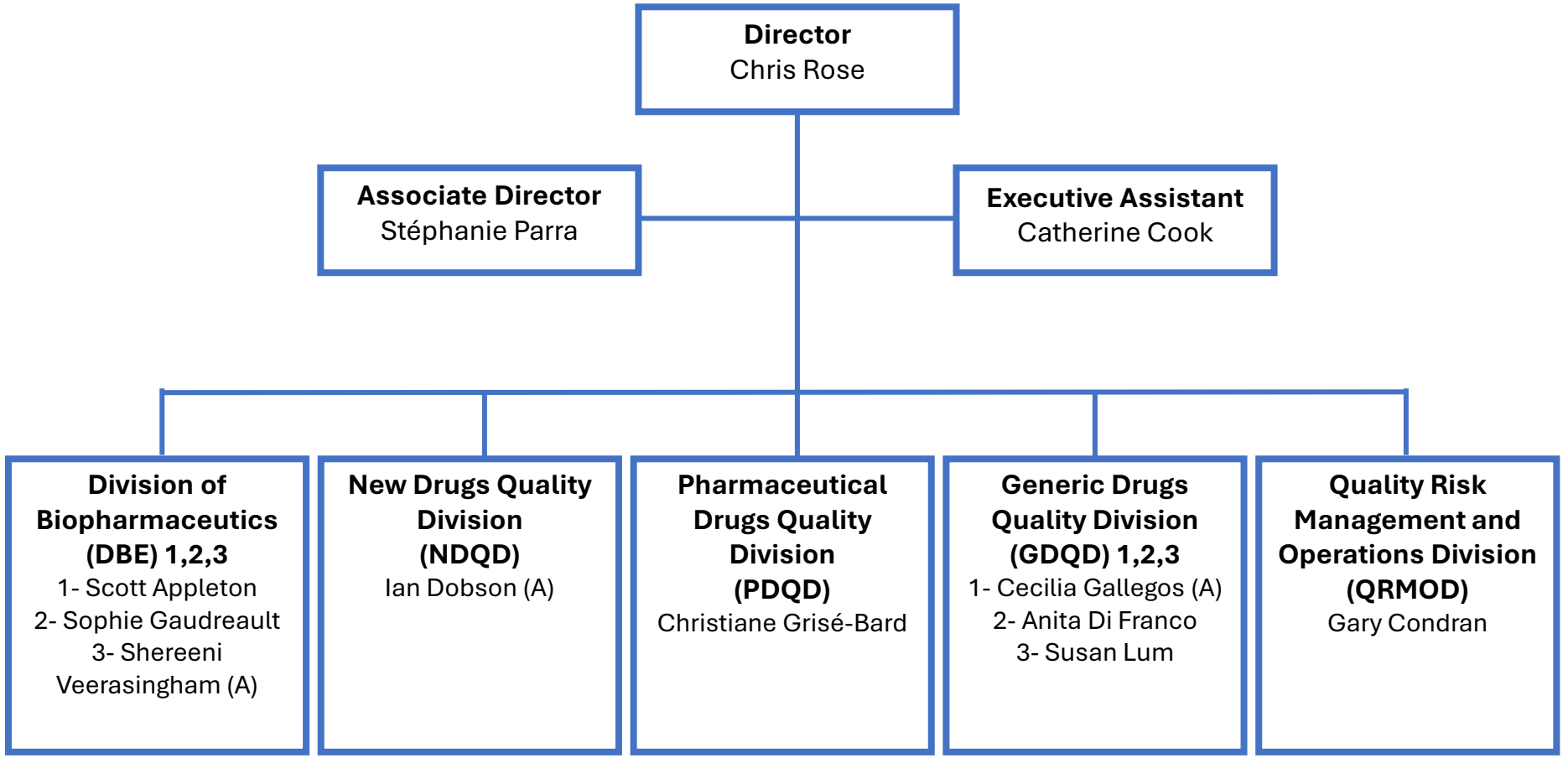
Contributes to and leads on modernization of policies & regulations

Develops and maintains guidance documents, regulatory tools, and scientific capacity

Collaborates and consults with intra-Departmental partners

- PDD's Risk Management Division, Marketed Health Products Directorate (MHPD, Regulatory Operations and Enforcement Branch (ROEB)
- Evaluation of drug/device combination products (with Medical Devices Directorate)
- Conducts bioequivalence reviews for the Natural and Non-prescription Health Products Directorate (NNHPD)
- Joint - reviews of quality (chemistry and manufacturing) data with the Biologic and Radiopharmaceutical Drugs Directorate (BRDD)

BPS Overview – Organizational Structure



Key Challenges and Initiatives

- Workload
- Nitrosamines
- Complex Generics
- First Cycle Review Performance
- E-Labelling and Labelling Inserts
- Enquiries

Workload

Context:

- BPS is continuing to receive unprecedented levels of submissions for generic drugs leading to performance standards not being met (i.e. "backlog") for some submissions

- FY2023/24 saw a 27% rise in new generic submissions compared to the 5-year average, with further increases expected in FY2024/25

- For the fiscal year 2022/23 and 2023/24 year to date 75 generic submissions have missed target

- There are several contributing factors including: the high volume of submissions, their complexity, their quality and staffing challenges

Workload

What we are doing:

- Planned indeterminate staffing of 8 quality reviewers and 8 BE reviewers (replacements and new needs), together with prioritization of the workload
- On-going engagement and communication with industry on the status of the workload
- Examining additional strategies to address the backlog
- Examining options to potentially provide earlier notification of potential negative decisions
- Undertaking an enquiries pilot

Nitrosamines

Context:

- Based primarily on animal studies, some nitrosamine impurities are known probable human carcinogens. This means that long-term exposure to a level above what is considered safe may increase the risk of cancer

- Several medications have been recalled in Canada and globally since 2018 due to the detection of nitrosamine impurities in the active pharmaceutical ingredient (API) or drug product above or close to the acceptable levels

- Generic drug companies have noted this as the most significant issue they currently face

Nitrosamines

What are we doing:

- Recently implemented the CPCA which is a new risk-based approach developed by international regulatory partners for the characterization of nitrosamines which was a significant step forward in the management of nitrosamines
- Stakeholder engagement via conferences and workshops
- Regularly update Health Canada’s Nitrosamines guidance document to provide timely information and recommendations
- Examining feedback from industry on submission requirements and the step 3 deadline of the Call for Review
- Continued leadership and international collaboration on the Nitrosamine International Strategic Group, its technical working groups and the ICH M7 discussion topic

Complex Generics

Context:

- Generics of complex drugs can be more difficult to develop and the generic industry is investing more in these products
- The scientific knowledge, guidance documents and regulatory roadmaps are continuing to be developed for these submissions

What are we doing:

- Development and implementation of key quality and bioequivalence guidance documents to provide clarity and transparency on technical requirements
- Creation of a third Division of Biopharmaceutics Evaluation (DBE3), dedicating resources to consider emerging and evolving methods for alternative bioequivalence approaches and stakeholder feedback
- Leveraging the Generic Drug Cluster to discuss products specific requirements with regulatory partners to resolve scientific issues

First Cycle Review Performance

Context:

- The overall first review cycle approval rate is low as major deficiencies continue to be found in submissions
- Major deficiencies regularly found for nitrosamines, biowaivers and Active Substance Master Files (ASMFs)

What are we doing:

- Communicating the analysis of negative decisions to industry associations and at conferences with the aim of improving the quality of the files submitted
- Company specific data shared with select companies with lower 1st cycle approval rates
- Pre-submission meetings

E-Labelling and Labelling Inserts

Context:

- As reported by industry, paper-based inserts present challenges due to the extra burden of publishing and cost leading to inefficiencies and decreased product availability
- Health care providers and their patients have become increasingly reliant on digital technologies

What are we doing:

- A draft guidance document on E-labelling (Electronic media in prescription drug labelling) was published for consultation in 2021
- Based on feedback received and additional considerations related to business delivery, PDD published a notice in Spring 2022, to provide additional information on how the Department intends to implement electronic labels for human prescription drugs in the near term

E-Labelling and Labelling Inserts

What are we doing, con’t:

- While physical label requirements are anticipated to continue for the foreseeable future, PDD remains open to continued dialogue with Industry on any potential proposals related to the use of electronic platforms as an extension to a drug’s package labels

- In Fall 2022, Health Canada established an internal HPFB Package Insert Working Group to determine the conditions and considerations for recommending the inclusion of a Package Insert for pharmaceuticals, and the development of work instructions oriented to Health Canada reviewers. This work instruction, on the process for granting waivers for package inserts for certain prescription drugs, has been drafted and approval processes have been initiated

Enquiries

Context:

- BPS responds to queries (700-800/year) from various stakeholders such as patients, Health Care Professionals, and industry stakeholders (e.g., providing guidance on how to make their drug available in Canada)
- Requests have become more complex and multi-faceted over the years, often requiring consultation with other bureaus and directorates
- The most common enquires relate to bioequivalence, quality-related questions, post-NOC changes and submission requirements
- Queries are being sent to multiple inboxes, which may add to coordination and response time
- Sponsors requesting guidance on multiple products/developments in one email
- Vague/hypothetical questions with little detail, results in challenges providing fulsome responses

Enquiries

What are we doing:

- In January 2024, BPS internally piloted a triage system, in which all incoming correspondence was sorted into two categories: Type I: Standard and Type II: Complex

- Results showed over a 6-month period 87% of standard enquiries were responded to within 60 days and 90% within 120 days

- Proposal is to implement different timelines for different categories of enquiries:
  - Type I: Standard – Respond to 90% of enquiries within 60 days
  - Type II: Complex – Respond to 90% of enquiries within 120 days

Type I: Standard- is correspondence sent to Health Canada, by or on behalf of a generic drug manufacturer or related industry, requesting information on a specific element of generic drug product development, such as: (a) submission requirements, (b) after a pre-submission meeting if the sponsor is seeking further feedback, (c) after issuance of a Notice of Compliance (NOC), (d) questions regarding a CRP or (e) clarifications on guidance documents

Type II: Complex- is correspondence which in addition to Type I, also involves: (a) evaluation of a bioequivalence protocol, (b) evaluation of alternative BE approaches (e.g., pharmacokinetic, in vitro, clinical), (c) evaluation of chemistry, manufacturing and controls (CMC) plans, or (d) requires internal consultation with another bureau or directorate

How to contact us:
BPS enquiries: bpsenquiries@hc-sc.gc.ca (for pharmaceuticals)