Health Canada Santé Canada

Therapeutic Products Directorate

Health Products and Food Branch

Direction des produits thérapeutiques

Direction générale des produits de santé et des aliments




Tips to Improve the Quality of Submissions

Kristen Zorn, Senior Regulatory Project Manager
Regulatory Project Management Division

Canada

Tips to Improve the Quality of Submissions

- Both pharmaceutical companies and Health Canada benefit from high quality submissions being filed.
- This presentation focuses on suggestions and tips for how to facilitate the processing, screening and review of submissions, how to avoid delays and negative decisions.
- Input is included from the Office of Submissions and Intellectual Property, the Regulatory Project Management Division and the clinical and quality review bureaus.

Tips to Improve the Quality of Submissions

- Agenda Topics:
  - General / Communication
  - Pre-submission Meetings
  - Quality
  - Drug Master Files
  - Safety & Efficacy
  - Product Monograph
  - Post NOC Changes
  - Screening Report

General/Communication

- The Cover Letter should clearly indicate the reason for the filing and correspondence with Health Canada prior to filing should be referenced in the cover letter and included in Module 1.
  - e.g., pre-submission meeting minutes, email correspondence about filing requirements or drug status, communication with the Marketed Health Products Directorate
  - Indicate if the submission is being filed in response to an Advisement Letter
  - Address a response to clarifax to the reviewer who issued it and include the clarifax date

- Include the international status of the product/submissions and anticipated global filing dates. In particular, explain if not filed with United States Food and Drug Administration or European Medicines Agency.
  - Notify the Regulatory Project Manager (RPM) of updates (filing, decisions, availability of foreign review documents).

General/Communication (continued)

- Ensure that responses to clarifaxes prepared by global affiliates respect the Management of Drug Submissions process (e.g., do not include new data).
- Provide a Company Core Data Sheet (CCDS).
- Ensure that hyperlinks in eCTD files are functional.
- Define abbreviations keeping in mind that different reviewers may be working on different portions of the submission.

General/Communication (continued)

- It is important to notify the RPM and send in a revised Drug Submission Application Form (HC3011) when the regulatory contact information changes.

- For Administrative Submissions complete boxes 54-69 on the Drug Submission Application Form (HC3011), medicinal ingredient, strength, dosage form, etc. If incomplete or referencing the parent submission, the file will be placed on Process Hold until a complete HC3011 is provided.

- Where possible, separate New Drug Submissions (NDS) should be completed for each medicinal ingredient before filing a combination. Any potential concurrent/parallel filings should be discussed in advance with Health Canada to determine the best approach.

General/Communication (continued)

- The Regulatory Project Manager (RPM) should be the contact for a submission or therapeutic area. The Senior RPM may also be contacted. Let the RPM know in advance if you plan to call with several people on the line/speaker phone.
- A brief written summary of teleconference discussions are appreciated.
- Bringing a Canadian clinician to pre-submission meetings (particularly pre-NDS) adds significant value.

Quality

- Include a detailed scientific justification where deviating from guidance documents or common scientific practices. For example, explain why stability batches tested/manufactured are the “worst case scenario” or how the data demonstrates the product was stressed.

- CPIDs at filing for NDSs facilitate review.

- CPID Sections 2.3.P.3.3 and 2.3.P.3.4 should not be oversimplified. Include details of the equipment, process parameters and controls of critical steps and intermediates as they are identified in the Master Batch Documents, along with Proven Acceptable Ranges (PAR)s or design space, where supported by development work.

Quality (continued)

- Ensure evidence of GMP compliance for required sites (or evidence of filing to the Inspectorate for previously compliant expired sites) is available prior to filing *(under discussion).*

  Submission Filing Requirements - Good Manufacturing Practices (GMP)/Establishment Licences (EL)
  http://hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/notice_gmp_el_avis_bpf_le-eng.php

- Summaries of stability data could be better presented in many submissions by including groupings to demonstrate what the data is showing rather than just summarizing results for each batch.
  - For example, if all batches show similar impurity trends, group together and list trends and maximum impurity levels.
  - Minimum and maximum assay values across the whole range of batches are illustrative if there are no trends.
  - Highlight different trends across strengths or packaging materials.

Quality (continued)

- To confirm study batches are representative of proposed market production (*Food and Drug Regulations* C.08.002(2)(m)) include English or French translations of
  - Complete Executed Batch Records (for pivotal Clinical/Bioequivalence) and
  - Master Production Documents (MPDs) from bill of materials to final packaging operations.

- MPDs should be provided for each strength, manufacturing site and proposed commercial batch size. Where there is significant redundancy (e.g., common blend compressed to different tablet sizes), reduced documentation can be provided (e.g., complete MBD for one strength and compression steps for remaining strengths), as long as it is ensured that each variation in manufacturing is fully described.

Quality (continued)

- Certificates of Analysis for pivotal clinical/bioequivalence batches supporting the submission should be included in drug product section 3.2.P.5.4 (batch analysis) in module 3.

- Also in section 3.2.P.5.4, it is extremely helpful to include overall summary tables clearly identifying and linking all drug product batches to their use in clinical, preclinical, comparative in-vitro and stability studies.
  - Include identification of API drug substance batch number and manufacturing site, batch size and manufacturing date for the drug product, and specific use of the product, including study number, where relevant.
  - Where different batch numbers are assigned to drug product intermediates or where a manufacturing batch is assigned a different number when used in a clinical study, the tabulated summary should include and link together these data.

Quality (continued)

- Process validation protocol should be included in drug product section 3.2.P.3.5.

- Information on packaging materials should be included in section 3.2.P.7, if it pertains to composition and specifications and in section 3.2.P.2.4 if it pertains to qualification of packaging materials.

- Information on development of the dissolution method should be included in section 3.2.P.5.3, and referenced, wherever relevant, within section 3.2.P.2. Also, when applicable, all raw dissolution data used to generate comparative dissolution profiles should be included in the submission along with corresponding f2 values.

Quality (continued)

- For Quality by Design (QbD), clearly identify in the Quality Overall Summary (QOS) Introduction what is being claimed/supported based on information and data from the QbD approach included in the submission
  - e.g., Design space(s), Proven Acceptable Range(s) (PARS), Omission of test(s) from specifications, Implementation of skip testing, Real Time Release Testing, Process robustness, Other
- When PARs have been established, be clear whether the combination of PARs is considered to constitute a Design Space.
- Use ICH Q8-9-10 terminology for QbD (e.g., key process parameter is not defined in ICH).

Drug Master Files

- Ensure that contact information is up to date and the contact numbers are available during Health Canada business hours; fax number functional at all times.
- If possible, use a Canadian agent to improve communication times.

- Applications should be filed separately and by DMF. Avoid submitting a new DMF with an amendment in the same package.
- All responses, updates and new DMFs need to be submitted electronically on CD for upload with an attestation. Emails with attachments are for convenience only.

Drug Master Files (continued)

- The sponsor should be aware of any bank transfer fees and ensure they are covered in advance so full payment is received by Health Canada. This will help avoid process holds for DMFs and Letters of Access.
- Proof of payment should be submitted with the fee form if fees are paid by wire.
- It is not necessary to repeatedly send Letters of Access for a product already authorized if the same product line and sponsor. The authorization is valid for the life cycle of the product.
- Always mention the name of the product line for which authorization has been granted in the Letter of Access.

Safety & Efficacy

- Supply all non-clinical study reports in a pdf format with copy-paste functionality.
- Look critically at whether to include nonclinical data that will not be included in the PM. This could be a topic for discussion at pre-submission meetings.
- It is helpful for initial submission scoping and assignment to include a summary table listing study number, title and module location of all studies included (clinical and non-clinical). The table of studies often omits several of the smaller studies (biopharmaceutics, PK, etc.)

Safety & Efficacy (continued)

- Include appendices for clinical trial data.
- Clearly identify which studies are considered pivotal and indicate whether these batches were manufactured according to the proposed method of manufacture. Be explicit explaining how every indication, strength and dosage form is being supported by the data package (e.g., if bridging, waivers or extrapolation are being relied upon).
- Explain the purpose of submitted comparative bioavailability studies to facilitate the decision whether review by Division of Biopharmaceutics Evaluation is appropriate with Comprehensive Summary: Bioequivalence (CS:BE) and data files.

Product Monograph (PM)

- Be aware of timing for submission finalization in order to be prepared to submit pristine PMs and certification without delay.
- Ensure that proposed PMs contain information relevant to the Canadian dossier (e.g., not dosage forms or indications that are not part of the submission).

Post-NOC Changes

- It is helpful if cover letters give a description of the reason for the submission
- When making safety updates, submit the data to support the changes, and not only the CCDS.
- The summary of changes (Note to Reviewers) and an explicit indication of how the changes link to the Post-NOC guidance (type of change, conditions fulfilled/unfulfilled for quality changes, and supporting data) are always very useful.

Post-NOC Changes (continued)

Health Canada Santé Canada

Summary of Post-Notice of Compliance Quality Changes to [Brand Name] (SNDS, Control No. xxxxxx)

Reference: Post-Notice of Compliance (NOC) Changes: Quality Document (Effective date: 2009/09/30)

Post-NOC quality change according to guidance document (Please indicate the number for each change)	Description of change	Conditions to be fulfilled for this change and reporting category based on Health Canada guidance document	Explanation of how each condition is, or is not, fulfilled	Based on fulfilment of the conditions, what is the corresponding reporting category? (i.e. Supplement or Annual Notification)	Supporting data required	Location of required supporting data within submission or reason for omission

Post-NOC Changes (continued)

- Ensure there are no implied claims (efficacy or safety) being filed in Notifiable Changes.
- Be cautious of revisions in NCs that are described as “editorial” or “to be clearer” and ensure that these are well justified in the submission.

Post-NOC Changes (continued)

- For generic sponsors, monitor the Product Monograph Brand Safety Updates table to ensure timely labelling updates.
  http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/pm_saf_mp_innoc/lab_safety_rep_rap_eval_etiq-eng.php

- Use the revised Label Safety Assessment Update – Sponsor Attestation (sample document comparison summary tables).
  http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/pm_saf_mp_innoc/lab_safety_att_eval_etiq-eng.php

- Check the Drug Product Database immediately before filing to ensure you are comparing against the most recent innovator PM
  http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp

- PM Document comparisons versus the Canadian Reference Product and previously approved generic:
  - Different/new information in the PM should be highlighted
  - Information removed should be marked with strikeout

Screening Report

Health Canada Santé Canada

NDS/SNDS Screening Report
(Including response to NON/NOD/SDN)

Brand (Proprietary) Name of Drug Product		
Proper, Common or Non-proprietary Name of Drug Substance		
Manufacturer / Sponsor		
Therapeutic Classification		
Dosage Form(s) and Strength(s)		
Route(s) of Administration		
Submission Type/Control Number		
Dossier ID/dB Sequence Number(s)		
Proposed or Currently Approved Indications		
Reason for Supplement		
Foreign Regulatory Status		
Current Issues re: drug or therapeutic area		
Relevant submissions currently in review		

Active Streams:		Submission Issues to Flag
	Regulatory	
	Quality	

Conclusion

- Increased awareness of common submission challenges should support review efficiency and reduce unnecessary delays.

Thank you