Common Labelling Deficiencies for Prescription Drug Submissions

CAPRA 2024 Pharmaceutical Symposium

October 22, 2024

Labelling Division
Pharmaceutical Drugs Directorate

Health Canada Santé Canada

Canada

Overview

- General
- Brand Name Assessment
- Mock-up Labels
- Product Monographs
- Package Inserts
- Contact Information
- Questions?

General

Both **Regulatory Enrolment Process (REP) forms** should correctly identify when an Administrative submission / application versus a Submission with an administrative component is filed.

REP - Regulatory Transaction (RT) (REP-RT) form:	**Administrative (S)(A)NDS** (45 day screening only)	**(S)ANDS – Clin/C&M, Comp/C&M, Labelling Only**
Is this an Administrative Submission or Application?	Select "**Yes**" and enter the reason for the administrative change bundled in the submission	Select "**No**"

REP - Product Information (PI) (REP-PI) form:	**Administrative (S)(A)NDS** (45 day screening only)	**(S)ANDS – Clin/C&M, Comp/C&M, Labelling Only**
Question 6: Does this regulatory activity contain an administrative component?	Select "**No**" since the submission sub-type (Administrative) already identifies its purpose for filing	Select "**Yes**" and enter the administrative type change that is bundled with other post-NOC/DIN changes.

General (continued…)

- The **REP-PI** form should be kept up to date to reflect any submission information revised during review:
  - Brand name (align with labelling materials)
  - Medicinal ingredient (align with CPID and labelling materials)
  - Non-medicinal ingredient (align with CPID and labelling materials)
  - Expression of Strength (specify if calculated as base or as a salt)

This will help to avoid delays with the issuance of the *Drug Notification Form* and ensure accuracy of the Drug Identification Number (DIN) key product characteristics.

Brand Name Assessment: Proposed Proprietary brand names

- The Brand name assessment package is **encouraged to be filed at the original time of filing** to allow Health Canada sufficient time to review the data and provide feedback. Filing delays could impact the time remaining to submit an alternate name in the event the first name is rejected.

- All proposed drug names are subject to the Review of Drug Brand Names guidance document, section **2.2 Initial brand name review criteria**, with the exception of those only using the proper/common name of the drug.

- Proprietary names that are subject to further Look-alike (LA) Sound-alike (SA) should include:
  - ✓ A complete **Process Map** that is reflective of the proposed market conditions
  - ✓ A detailed **justification** when LASA pairs have been excluded from the **Failure Mode and Effects Analysis** (FMEA) review - especially in cases when panel members identify a strong LASA pair

Brand Name Assessment: Modifiers / New Abbreviations

- Common deficiencies include:
  - Lack of justification to support use of a new modifier. See section 2.2 and Appendix 2 of the Review of Brand Name guidance document.
  - Does not meet any of the criteria set out for modifiers in Appendix 2.
  - There is no benefit to repeating the product strength it in the brand name. Its removal is recommended in Appendix 2 since it already appears on the main panel.
  - Where a **risk minimization strategy** is needed, the generic product has not proposed the use of a modifier to differentiate formulations or has not adopted the same modifier as innovator product (where permissible while respecting copyright/trademark law) as recommended in Appendix 2.

Consult with Health Canada if there are potential inconsistencies around a proposed/existing modifier and the controlled vocabulary for the drug product impacted by Schedule B updates that can lead to confusion for end-users.

Mock-Up Labels: TALLman in Brand Names

- **When used effectively, TALLman lettering is a method to assist in the differentiation of look-alike, sound-alike (LASA) non-proprietary (proper or common) drug names through the application of UPPER CASE lettering to certain syllables or groups of letters within names.**

- Proposals for the adoption of TALLman lettering **must be filed** as a Level 1 Supplement, accompanied by a rationale, when filing to Health Canada. **This type of change is NOT permitted through the administrative pathway.**

- The rationale should critically assess whether the company has the LASA pair of concern which could necessitate the use of TALLman.

TALLman lettering is NOT the only risk mitigation strategy that can be used.

Other design features on the labels should be explored as well to aid in product identification/differentiation.

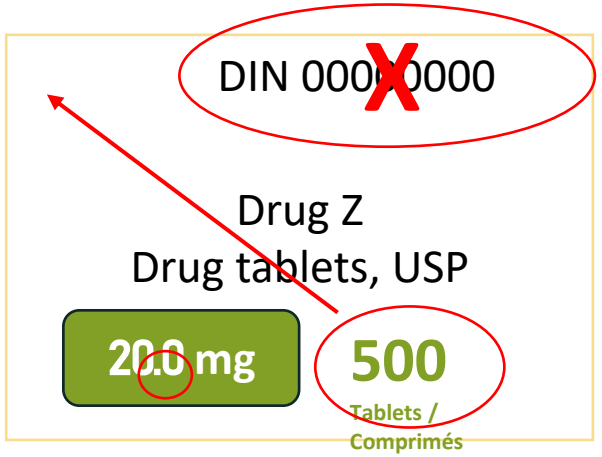
Example: Excerpt taken from ISMP Canada TALLman list

DACTINomycin / daptomycin*	ISMP (US)
DAUNOrubicin / DOXOrubicin	FDA
dexamethasone / dexmedeTOMidine	ISMP Canada
dilTIAZem / diazepam*	ISMP Canada
dimenhyDRINATE / diphenhydrAMINE	FDA
DOBUTamine / DOPamine	FDA

Mock-Up Labels: Strength vs Net Contents and DIN

- Avoid displaying numbers with a trailing zero as it can lead to harmful medication errors (i.e., a ten-fold dosing error if it is misinterpreted by the end-user).
- Avoid placing the drug strength (a numeric value) and the unit or pack size (another numeric value) in close proximity.
- DIN must be placed on the principle display panel (usually upper left or right section of the label).
- New DIN Placeholder should be listed as “DIN XXXXXXXX” (per Questions and Answers: Plain Language Labelling Regulations (PLL Q&A) Document, section 5.4).

Principal Display Panel



- Avoid Trailing Zero (20 can be misread as 200)
- Proactively relocate pack size numerical values away from drug strength
- Avoid using numerical place holders for the DIN

Mock-Up Labels: Font Style and Size

Brand Name
Non-proprietary name in final dosage form

20 and 18 point font size

- *Good Label and Packages Practices Guide for Prescription Drugs* (GLPPG)(section 3.3) recommends against using compressed, condensed or serif fonts.
- Reduced white space between letters can make words harder to read.

Brand Name
Non-proprietary name in final dosage form

20 and 18 point font size

- Include a Note to Reviewer in section 1.3.2 of your e-CTD filing to highlight font choices and sizes if what is proposed does not align with the GLPPG; and/or where existing flexibilities (include previously approved control number) continue to be sought and applied.

Mock-Up Labels: Colour and Contrast

Brand Name
Non-proprietary name
in final dosage form

- Maximize the legibility of text by ensuring good contrast between text and background (GLPPG 3.3.5).

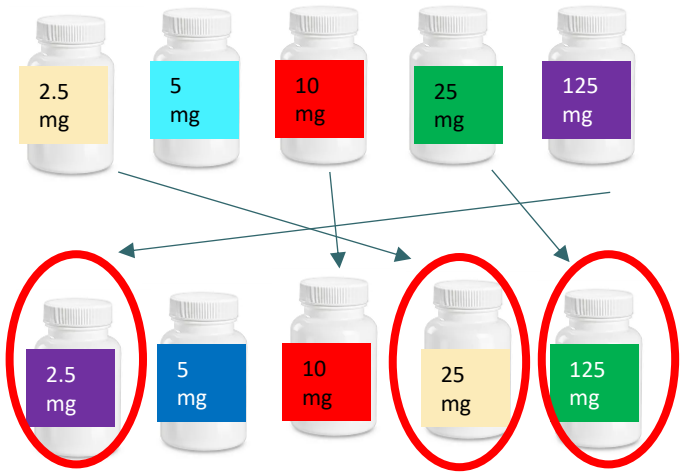
Brand Name
Non-proprietary name
in final dosage form

- To enhance differentiation among product strengths, use a colour with a different hue, rather than a different intensity or value of the same colour.

Brand Name
Non-proprietary name in
final dosage form

- Other design elements can be used besides colour to distinguish between products (e.g., colour bands, frames, etc).

Mock-Up Labels: Colour and Contrast (continued)



- Post-market label design changes should be evaluated to determine if the change could introduce an element on confusion.
- Avoid use of overlapping colours previously marketed for another strength within the same product line. This could create confusion / selection errors (including confirmation bias) where there is a market overlap period before old stock label is depleted/expires.
- Include a justification in the Level 1 Supplement that addresses any potential safety concerns around the use of overlapping colours that have already been used for other strengths if such applies.
  - Are there other new design features that could mitigate the risk?
  - Is this a high alert medication?
  - Is there a new company trade dress design that will also be introduced?

Mock-Up Labels: Parenteral Drugs

On the principle display panel:

- Route of Administration should be legible.
- Bilingual “Sterile (stérile)” notation per the Regulations is required.
- If no preservatives are present, state “Single use. Discard unused portion.”
- State “preservative-free” instead of “unpreserved”.

On secondary panels:

- Include dilution/reconstitution instructions if space permits. If not, refer to a package insert.
- If space permits, include in-use storage conditions. If not, refer to a package insert.
- Quantitative declaration of preservatives must be declared on the labels (FDR C.01.004 (2) (b))
- Visual inspection related statements should be listed on the labels or package insert.
- General handling instructions should be presented in close proximity to each other where possible.
    - CAUTION: Liquid in glass. Handle with care. Inspect syringe for damage prior to assembly.

Mock-Up Labels: Caps and Ferrules for Critical Warnings

- Mock-ups of caps and ferrules for certain drugs should be submitted for review:
  - **Neuromuscular blocking agents:** a **red ferrule with white lettering**, and **red cap with white lettering** is recommended. Restrict top (circle) surface of the ferrule or Cap overseal to only list critical statement, - "**Warning: Paralyzing Agent**" or "**Paralyzing Agent**"
  - **Potassium Chloride Concentrate**: A **black cap or ferrule** and **one or more black bands** above the constriction on ampoules. **Cap** of the container and the overseal of the cap must be black, and state "**Must Be Diluted**". Overseal may be of a clear plastic material where black cap is visible and the printing is readily legible.
- A rationale is required to address any safe concerns when a proposed mock-up label, cap or ferrule does not align with the recommendations in the *GLPPG for Prescription Drugs*.

Only the critical cautionary statement should appear on the top surface of any ferrule or cap overseal of an injectable product.

Refer to the GLPPG for the list of drug products that require additional critical warnings on their labels.

Mock-Up Labels: Other drug specific information

On the principle display panel, include Cytotoxic related **Special Handling instructions**:

- The bilingual Cytotoxic standards symbol should be displayed and not manipulated.
- For small/special container labels, when space is limited, display the text “Cytotoxic / Cytotoxique” only.

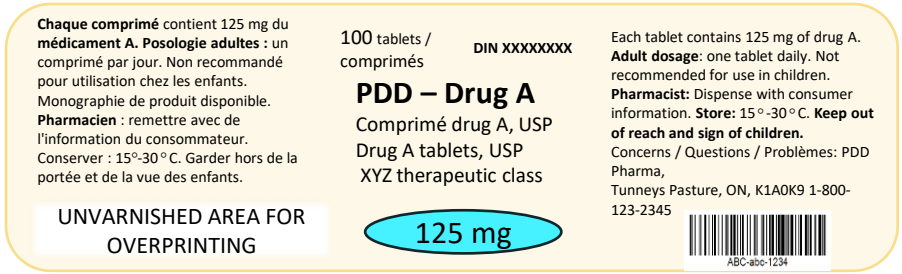
On any panel:

- As part of the dosage and administration instructions, ensure to include any special instructions such as “Do not crush tablet”, “Do not split tablet”, “Capsule contents can be sprinkled on […]”, etc.
- Consider including clinically relevant non-medicinal ingredients (listed in Part I of the Product Monograph) to promote patient safety (i.e., “Contains [peanut oil / lactose / …”]

Mock-Up Labels: Lot and Expiration Date Information

- Display both descriptor fields as required by the Food and Drug Regulations (FDR). Confirm the format used for the human readable labels:
  - Expiry date: Where “MM” is listed as a place holder for the month, clarify if it's in two digit or bilingual format
  - See PLL Q&A (section 5.5) for an expanded list of acceptable expiration date formats (beyond the GLPPG)
  - When details for human readable format and the QR coded format differ, include a Note to the Reviewer
- Include a Note to Reviewer (section 1.3.2) if the descriptor or format details are missing from mock-up labels.

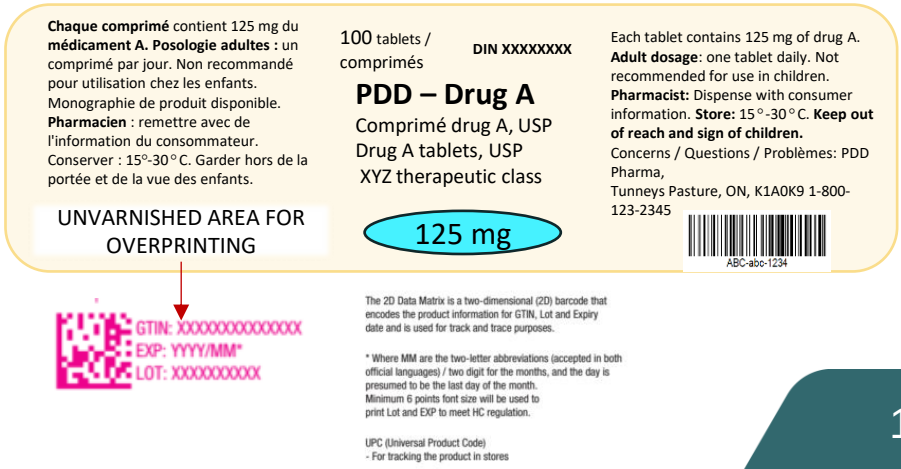
Example of incomplete details on mock-up label



Missing details should be included in section 1.3.2 as a Note to Reviewer in the e-CTD submission.

versus

Example of detailed mock-up label



Mock-Up Labels: Barcoding

- Specify the purpose of any automated identifiers appearing on package labels and package inserts.
  - Include with first Plain Language Labelling review, or when an existing barcode has changed to a matrix 2D barcode (QR code) bundled with other Level 1 changes.
  - Confirmation can be provided in a Note to Reviewer (section 1.3.2) or on the labels.

Are the 2D matrix codes only used for traceability purposes?

Updating and/or adding an electronic code (e.g., bar codes, QR codes, technical codes and any other inventory tracking codes) strictly for product traceability purposes (i.e. does not link to drug product information) that does not negatively impact the existing labels can be implemented as a Level III post-NOC change so long as the criteria in the PLL Q&A are met.

Mock-Up Labels:
PLL Q&A Questions and Concerns Statement

- The PLL Regulations require sponsors to provide at least one method of contacting the person in Canada, in both official languages:
  - A toll-free number,
  - Email address or
  - Website

- If space is restricted, the postal code can be used to satisfy both sets of regulations (C.01.004.01(1) PLL requirement) and existing manufacturers address in C.01.004.1(c)(i)).

"For questions or to report problems, please contact...", followed by the sponsor's contact information.

Where space is limited, the following abbreviated versions are acceptable:

- **"Questions or Concerns"**
- **"Concerns / Questions / Problèmes"** or
- **"Concerns / Questions / Préoccupations"**

Mock-Up Labels: Other common requested revisions

Standard of Manufacturing:

- C.01.004 (1) of the Food and Drug Regulations states that where a standard prescribed by the Regulations exists and applies to the specific drug product, it shall be included on the principal display (main) panel of the inner and outer labels.
    - Ensure the product monograph is also updated to ensure labelling materials align.

Pharmacist Dispensing Statement:

- When the PM is updated to a new template, the pharmacist statement on the labels should be updated to reflect the actual title of the Patient Medication Information or Consumer Information Leaflet (as applicable).

Product Monograph (PM): General

Table of Contents and Hyperlinks:

- Ensure Hyperlinks are working and included when sectional cross-references are made.
- Minimize inconsistencies in the details listed in the Table of Contents (e.g., page numbers and hyperlinks).

Other:

- For Generic drugs: Differentiate drug product brand name (e.g., COMPANY-Drug X or COMPANY-DRUG X) from proper/common name of the drug (drug X / drug X for injection) when third party data is referenced.
- Avoid error prone abbreviations (i.e., "µg" should be replaced with “mcg” for micrograms).
- Ensure dosing units is consistent throughout the PM including its Patient Medication Information (i.e., 240 mcg & 360 mcg”).

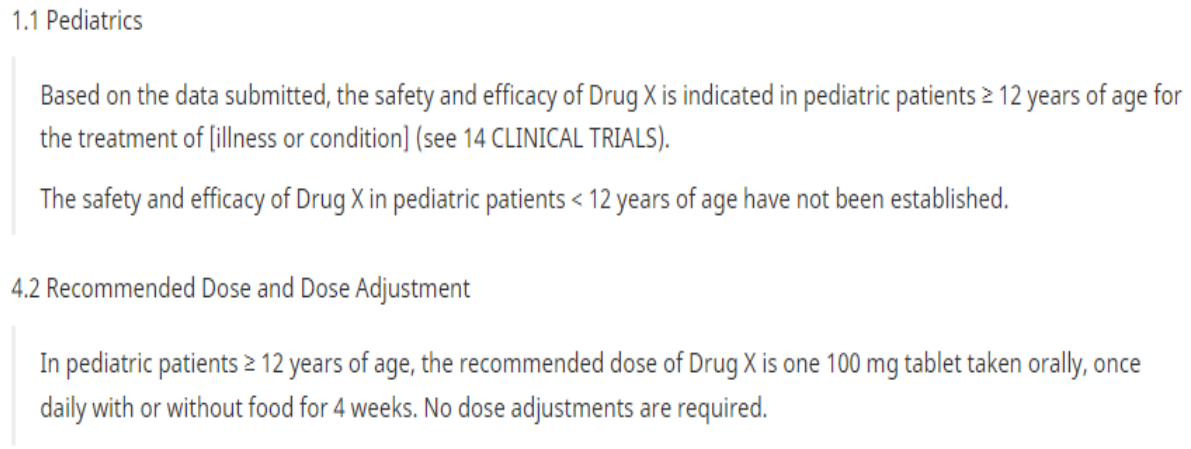
Response to Clarification Requests:

- In some Q&A responses, including the annotated PM, it states that the revised PM has been updated as requested but changes are still missing. All Health Canada clarifax comments should be fully addressed, including the changes in the attached revised annotated PM.
- There are revised PMs that include unsolicited changes as part of a response to Clarification Requests. Unsolicited changes should not be made. In cases where unsolicited alternate wording in the PM is proposed, a scientific rationale should be included for review.

Product Monograph:
Recent Major Label Change (RMLC) Table

- For supplements, ensure RMLC Table and their corresponding vertical line reflect the proposed PM changes to the key major label changes related to safety and efficacy:

1 INDICATIONS, 1.1 Pediatrics	02/2024
2 CONTRAINDICATIONS	02/2024
3 SERIOUS WARNINGS AND PRECAUTIONS	02/2024
4 DOSAGE AND ADMINISTRATION	02/2024
7 WARNINGS AND PRECAUTIONS	02/2024
~~7 WARNINGS AND PRECAUTIONS~~	10/2021



1.1 Pediatrics

Based on the data submitted, the safety and efficacy of Drug X is indicated in pediatric patients ≥ 12 years of age for the treatment of [illness or condition] (see 14 CLINICAL TRIALS).

The safety and efficacy of Drug X in pediatric patients < 12 years of age have not been established.

4.2 Recommended Dose and Dose Adjustment

In pediatric patients ≥ 12 years of age, the recommended dose of Drug X is one 100 mg tablet taken orally, once daily with or without food for 4 weeks. No dose adjustments are required.

- All Recent Major Label Changes must remain listed for at least 24 months after the date the label change was authorized.
- **Once the 24 month period expires,** the sponsor may choose to file a submission to remove the listing or wait until the next filing to remove it.

Product Monograph: Sectional Information

14 Clinical Trials:

- Renumbered and renamed to support the XML PM (see Notice dated June 24, 2021).
- For generics:
  - 14.3 Comparative Bioavailability Studies has changed to **14.2**.
  - Ensure comparative bioavailability study narrative and tabular summary align with PM Master Template format recommendations.

16 Non-Clinical Toxicology:

- Ensure correct title used. Some proposed PMs inadvertently retain the old header (16 DETAILED PHARMACOLOGY) from the previous PM.

17 Supporting Product Monographs:

- Should not include additional caveats/statements that make references to carved out indications/ conditions of use when listing the CRP's approved PM.
- CRP's last approved PM should be retained even when it's been discontinued.

Reference: **Notice: Product Monograph guidance - Formatting for clinical trials section and administrative updates** (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/product-monograph-guidance-formatting-clinical-trials.html)

Product Monograph: Patient Medication Information (PMI)

Section in PM	Recommendations
Read this for safe and effective use of your medicine…	• Include Scheduling symbol near the upper left hand corner of the brand name
Serious Warnings and Precautions	• This is a **boxed text** • Align with Part I: 3 Serious Warnings and Precautions box
To help avoid side effects and ensure proper use, talk to your healthcare professional before taking X…	• Align with Part I: 7 Warnings and Precautions section • Bullet listing related to pre-existing health conditions or conditions for which there is a medical history.
Other warnings you should know about	• Align with Part I: 7 Warnings and Precautions and 9 Drug Interaction sections, including relevant details under Monitoring and Laboratory Tests
How to take [Brand Name]	• Align with Part I: 4 Dosing Considerations and Recommended Dose and Dosage Adjustment
What are possible side effects from using [Brand Name]?	• Bullet list of self-limiting side effects (per Part I: 8 Adverse Reactions) • Do not include frequency headings in this section. Frequency reporting only in tabular listing (Serious side effects and what to do about them).
Serious side effects and what to do about them *(table)*	• Side effects listed in bulleted listing (What are possible side effects…) should not be included in the table. • List only those requiring medical attention in the table. • Frequency headings are to be included.

Ensure consistency in contents and sectional headers with the Product Master Template

Package Inserts

- To facilitate review, when a PM or mock-up label update impacts the contents of a package insert:
  - A revised mock-up package insert should be included with your filing when one exists.
  - Provide a rationale that addresses end-user needs when there are significant content changes to an existing insert (i.e., Abbreviated package insert (Part I) to a PMI or Instruction for Use (IFU) or vice-versa).
  - Provide the Control # and package formats that were previously granted a package insert waiver.
  - If a NEW request to remove an approved existing insert has been submitted, indicate for which packaging formats and include a rationale for review.
- Ensure attestations provided in the *Label and Packages Certification Form for Prescription Drugs* and information regarding the package insert for the product/provided in the submission is accurate and complete. Attestations regarding the fidelity of translation, its design elements, and that its final contents will be verbatim to the final approved PM/Prescribing Information will aid in the finalization of its mock-up review.

A Note to Reviewer in section 1.3.2 can be helpful to provide the reviewer with the history and/or reasons for the proposed changes to the existing package insert for your product.

Contact Information

Labelling Division of PDD

Email: pdd.bgivd.ld-dmp.bgmiv.de@hc-sc.gc.ca

Administrative Submissions Unit in LD, PDD

Email: pdd.bgivd.asu-dmp.bgmiv.usa@hc-sc.gc.ca

Questions ?