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ISMP Canada Safety Bulletin

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Safer Labelling of Repackaged Active Pharmaceutical Ingredients for Pharmacy Compounding

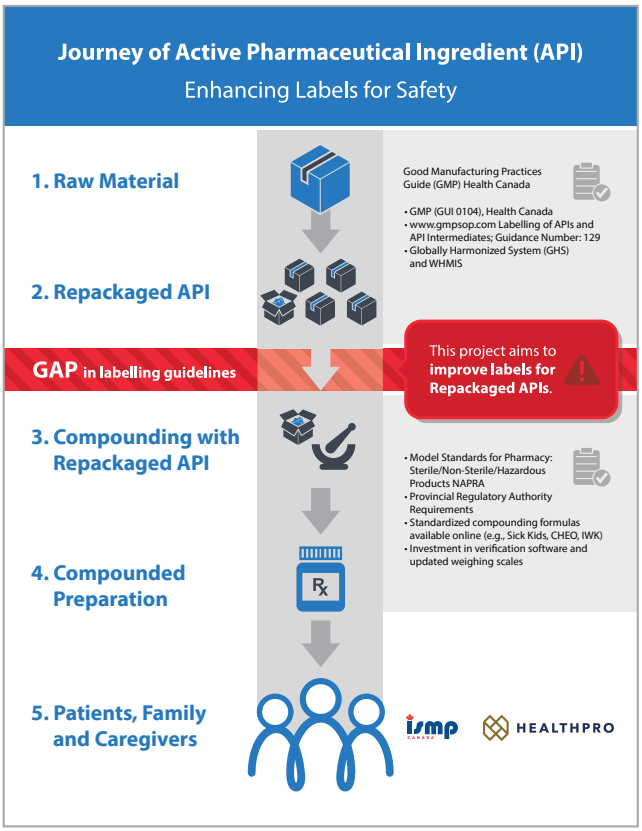
A child's death resulting from a compounding error, described in an ISMP Canada Safety Bulletin,[1] has reinforced the need for a focus on safety in pharmacy compounding. Recommendations set out in that bulletin included the use of unique chemical identifiers and automated identification (e.g., bar codes) for ingredients used in compounding.

ISMP Canada and HealthPRO Procurement Services Inc. partnered to lead an initiative[2,3] to improve the labelling of repackaged active pharmaceutical ingredients (APIs). They worked with an API Advisory Panel* that included regulators, API repackagers, community and hospital pharmacists, and compounding associations from across Canada. This bulletin shares recommendations for safer API labels, as well as examples to illustrate improved label content and design.

BACKGROUND

When medications are not commercially available, a pharmacy may be able to prepare compounded products for patients. Compounding may involve the use of APIs. Many APIs are imported by manufacturers in bulk quantities and then packaged into smaller containers by repackagers for subsequent use by pharmacies (Figure 1).

FIGURE 1. Infographic depicting the "journey" of an active pharmaceutical ingredient (API).



* Apotex; Association of Compounding Pharmacists of Canada; Canadian Association for Pharmacy Distribution Management (CAPDM); Canadian Generic Pharmaceutical Association; Galenova Inc. – Gentès & Bolduc pharmaciens; Medisca; Mohawk Medbuy; Ontario College of Pharmacists; Professional Compounding Centers of America (PCCA); Lower Mainland Pharmacy Services; Providence Health; Vancouver Coastal Health; and practicing pharmacists, including compounding pharmacists, hospital pharmacists, and community pharmacists.

There is limited direction on safe label design for repackaged APIs, unlike the guidance provided by the Good Label and Package Practices Guides for prescription drugs, natural health products, and non-prescription drugs.[4,5] Many decisions about label content and design are left to the quality control and marketing departments of the repackager. Although repackagers work with their partners to make improvements to labels, there is consensus that good label and package practices for APIs are needed to facilitate improvements. At the same time, it is recognized that better labelling is only one step towards improved safety and is not sufficient on its own to prevent harmful errors.[6]

SAFE LABELLING DESIGN CONSIDERATIONS

The API Advisory Panel reached consensus on a set of safe labelling design considerations (Box 1) for repackaged APIs, which are complementary to the requirements set out by Health Canada (GUI-0104)[7] and the Workplace Hazardous Materials Information System (WHMIS). Examples of leading work to improve labels are presented in alphabetical order by company name in Figures 2, 3, and 4.

FOLLOW UP ACTIONS TO DATE

Integrating use of the Chemical Abstracts Service (CAS) Registry Number into practice and workflow are examples of knowledge transfer efforts to enhance safety.

- HealthPRO added the CAS number to its online contracting criteria and published an article describing its work to advance safety. This was done to encourage the use of unique CAS numbers on product labels and improve clarity in the contracting process.[9]
- In 2021, the Ontario College of Pharmacists published an article about the potential for unique CAS numbers to reduce medication errors.[10]
- The National Association of Pharmacy Regulatory Authorities (NAPRA) has included the CAS number as an example of a unique identifier in its Master Formulation Record template.[11]
- A Canadian health care organization recently shared that they have integrated the CAS number into the drug description record used in their electronic system for dispensing and compounding.

Safety bulletins have continued to raise awareness of the risks associated with compounding and the opportunities for continued improvement.[12,13] A newsletter for consumers provided tips for parents whose children need medications that must be compounded.[14]

BOX 1. Safe labelling design considerations for repackaged active pharmaceutical ingredients (APIs)

A. Include automated identification (e.g., GS1-compliant barcoding).[4]

B. Use i) the largest possible type size that can be read easily by a variety of users (minimum 6 points for key information), ii) sans serif type style, and iii) mixed-case lettering (i.e., lower-case letters with capitalization for proper nouns).[4]

C. Display the chemical name of the API in larger type size than the name of the manufacturer/repackager.

D. Stack a long, multiword name, so that the full name can be read without the need to rotate the package.

E. Include the Chemical Abstracts Service (CAS) Registry Number for the API as an additional product identifier. This is analogous to including the Drug Identification Number (DIN) or Natural Product Number (NPN) on drugs and natural health products, respectively.

F. Avoid dangerous abbreviations, symbols, and dose designations (see ISMP Canada's "Do Not Use" list[8]).

G. Use one of the following formats for expiration dating: EXP 2020-JA-11 or EXP 11-JA-2020.[4]

H. Present potency, if applicable (e.g., X mg erythromycin activity per Y grams erythromycin stearate) on the front panel in a manner that simplifies any needed calculations.

I. Consider the use of more than just colour to distinguish between products. Examples of other distinguishing features include the use of frames or keylines (boxes around text).[4]

J. Use colour to draw attention to important label information, such as the API name, or to enhance or bring attention to warning statements.[4]

FIGURE 2. Sample label displaying select safe labelling design considerations A, B, C, D, E, F, I, J from Box 1.

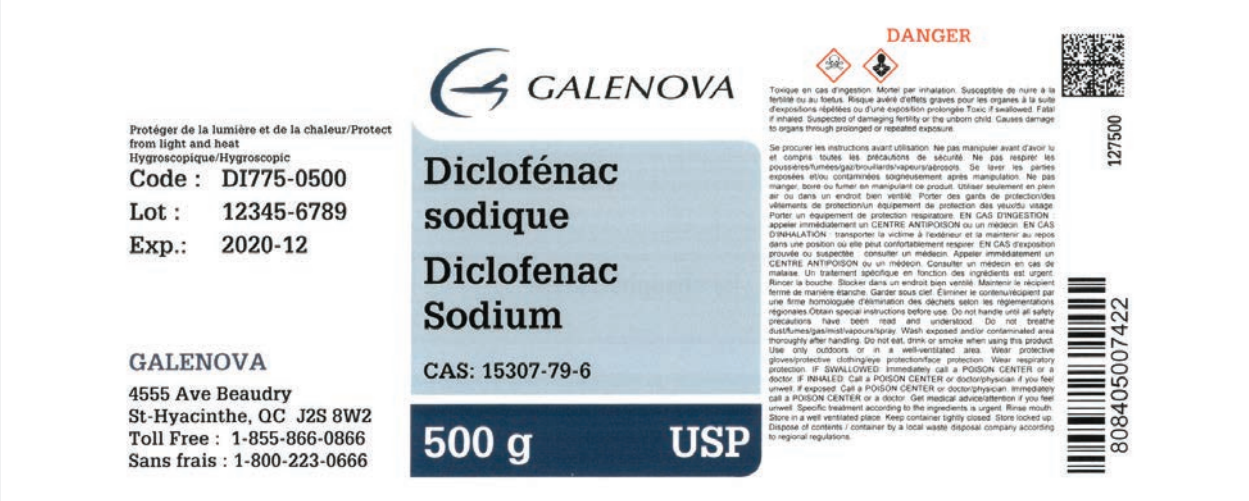
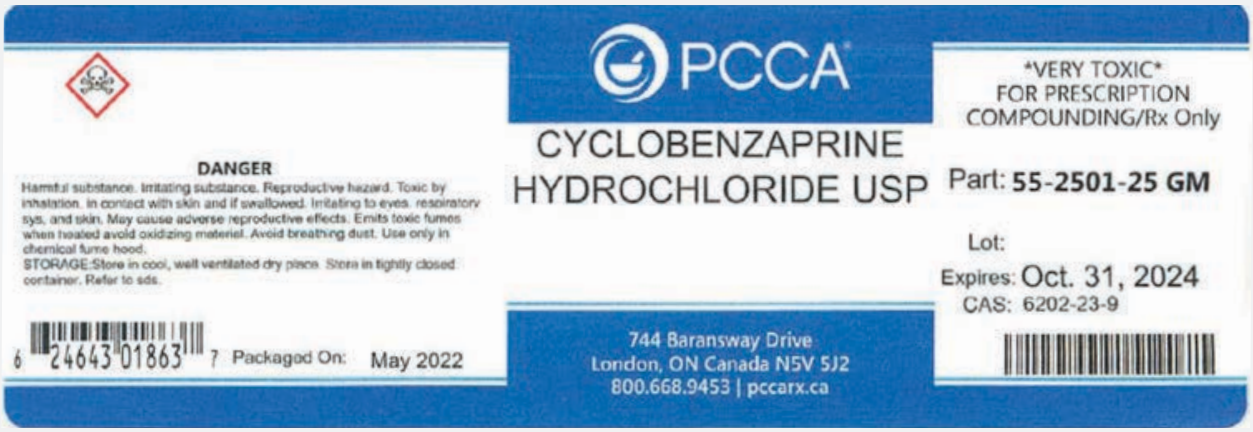


FIGURE 3. Sample label displaying select safe labelling considerations A, C, D, E, I, J from Box 1.

FIGURE 4. Sample label displaying select safe labelling considerations A, D, E, F, J from Box 1.



CONCLUSION

Next steps include knowledge dissemination and knowledge translation to continue to advance safe labelling for repackaged APIs and integrate safety measures into compounding practices. ISMP Canada is supporting a multistakeholder approach to increasing safety for patients who need compounded medications. Interested parties are welcome to join the collaborative efforts by contacting info@ismpcanada.ca.

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Ambiguity and Errors in Master Formulation Records Impact Multiple Patients

The National Association of Pharmacy Regulatory Authorities (NAPRA) Model Standards for Pharmacy Compounding of Non-sterile Preparations state that each product that is compounded must have an accompanying master formulation record (MFR).[1] When an MFR contains an error or is easily misinterpreted, the incorrectly prepared product(s) can harm multiple patients.

INCIDENT EXAMPLE:	A change in the MFR of a prescription suspension led to an error that caused finished products to be double the intended concentration. The error went unnoticed for several months, affecting many patients.
Contributing Factor:	**Lack of communication regarding a change in formula** It is unclear if the changes to the MFR were clearly stated in the document or if staff were notified of the changes.
Recommendation:	When changes are necessary, document them on the existing MFR with supporting rationale. Notify all compounding staff. Review the MFR at least yearly, or when new information becomes available, to ensure continued accuracy and availability of ingredients.[1]
Contributing Factor:	**Inadequate independent double checks** Following changes made to the MFR, verification of the MFR and the prepared compounds failed to detect the error.
Recommendation:	*Independently* reproduce all calculations required to compound the final product to ensure mathematical accuracy. Once the calculation has been verified, use appropriate tools (e.g., spreadsheet) to automatically calculate changes if an adjustment to the final quantity/volume is needed. An ISMP Canada Safety Bulletin provides additional information needed to implement independent double checks in practice.[2]

INCIDENT EXAMPLE:	The recipe for a compounded product required the anhydrous form of the active pharmaceutical ingredient (API) but did not specify this detail. A batch compound was prepared using the hydrous form of the API. The incorrectly prepared product may have reached hundreds of patients.
Contributing Factor:	**Missing information in the MFR** The formula did not specify that the anhydrous form of the API was required.
Recommendation:	Evaluate MFRs for error potential. Provide appropriate guidance to the user to reduce the risk for error. For example, highlight the existence of confusable salts or forms of an API. To clearly distinguish ingredients that can be confused, consider strategies such as bar coding, highlighting, or TALLman lettering.
Contributing Factor:	**Lack of API identifier** APIs did not have product-specific identifiers to support the verification process.
Recommendation:	See the Safe Labelling Design Considerations for Repackaged APIs (Box 1) on page 2 of this Safety Bulletin, which includes the recommendation to incorporate the Chemical Abstracts Service (CAS) Registry Number as an API identifier.

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NEW Controlled Substances Diversion Risk Assessment Program

The diversion of controlled substances from hospitals affects patients, the public, health care workers, hospitals, and the health care system as a whole. The recognition of drug diversion as a patient safety concern is gaining awareness; however, systematic approaches to both understanding the vulnerabilities involved and developing corresponding mitigation strategies lag behind efforts to address other patient safety matters.[1]

The NEW controlled substances diversion risk assessment program was developed in Ontario and designed to help Ontario hospitals identify diversion vulnerabilities in medication-use processes. The program was developed using the same platform as ISMP Canada's Medication Safety Self-Assessment (MSSA) programs, and therefore provides comparative options for analysis by users. Risk points highlighted in this resource include handling tasks associated with selecting and procuring, storing, prescribing and transcribing, preparing and dispensing, transferring, administering, and disposing of controlled substances.

The Canadian Society of Hospital Pharmacists – Ontario Branch (CSHP-OB), HumanEra, and ISMP Canada collaboratively developed the resource, which was informed by published literature, in-depth feedback provided by a panel of hospital pharmacists drawn from CSHP-OB, and feedback from a survey of all CSHP-OB members. A national version of the resource, which will incorporate a broader scope, more detailed assessment, and an expanded reference guide, is in development, with anticipated publication in 2023.

The assessment resource is accessible here: https://mssa.ismp-canada.org/diversion
For more information, contact mssa@ismpcanada.ca.

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