Health Canada Santé Canada

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22-108439-909

July 22, 2022

Subject: (1) Health Canada's extension of Step 3 deadline (changes to marketing applications) for human pharmaceutical products; (2) Request to MAHs for anticipated number of drug products requiring Step 3 supplemental drug submissions

Dear industry stakeholder,

On October 2, 2019, Health Canada issued a letter to all Drug Identification Number (DIN) and Drug Establishment Licence (DEL) holders informing them of their responsibilities to assess the risks and, if applicable, control the presence of nitrosamine impurities in human pharmaceutical products containing chemically synthesized active pharmaceutical ingredients (APIs). The current deadlines for Step 2 and Step 3 of the 3-step Call for Review process are October 1, 2022. Health Canada has received feedback from industry regarding challenges in meeting the deadlines for their drug portfolios within the current timeframe. As such, Health Canada is extending the deadline for Step 3 (changes to the Marketing Authorization) by one year. Therefore, the deadlines for Health Canada's Call for Review for human pharmaceutical products containing chemically synthesized and semi-synthetic APIs are now as follows:

- Step 1: risk assessments by March 31, 2021
- Step 2: confirmatory testing by October 1, 2022
- Step 3: changes to the market authorization by October 1, 2023

The health and safety of Canadians is of utmost importance; therefore, Market Authorization Holders that have identified a risk that requires changes to the marketing authorization are encouraged to take a risk-based appro

- maximum daily dose of the drug product
- duration of use
- indication and consideration of special populations, such as pregnant women and children
- toxicological profile of the API (for example, cancer therapies in which the API is a mutagen could be considered lower priority)
- market considerations such as the availability of product for sale on the Canadian market and number of patients being treated with the drug product
- the presence of structural elements in the API or conditions in the manufacturing and packaging processes for the API or drug product, which are conducive to nitrosamine formation (for example, presence of secondary or tertiary amine groups in the API)
- levels of a nitrosamine in an API or drug product are approaching or above an established acceptable intake (AI) through confirmatory testing (or, in the absence of an established AI for the nitrosamine, are approaching or above the class-specific threshold of toxicological concern (TTC) of 18 ng/day for nitrosamines)
- an API or a drug product has been found to contain multiple nitrosamines through confirmatory testing

An MAH with many drug products expected to progress to Step 3 should aim to submit those with higher risk factors or multiple risk factors within the first quarter following October 1, 2022. Drug products with a lower risk profile are to be submitted no later than October 1, 2023.

As Health Canada continues to respond to issues relating to the presence of nitrosamines in some pharmaceutical products, additional information is requested to assist in planning and managing related workload. As soon as possible, and no later than December 01, 2022, MAHs are requested to provide the number of Step 3 supplement(s) that you intend to file and their anticipated submission date(s) (e.g., by quarter) to bpsenquiries@hc-sc.gc.ca.

Sincerely,

Melissa Hunt
A/Director General
Pharmaceutical Drugs Directorate
Health Products and Food Branch
Health Canada

Natalie Page
Director General,
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Linsey Hollett
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