FEB 2 2 2018

Health Canada / Santé Canada

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Adele Fifield, O.Ont., CAE, BA, B.Ed
Executive Director
National Association of Pharmacy Regulatory Authorities
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Dear Ms. Fifield,

Thank you for engaging Health Canada on the topic of dose-splitting of Eylea and Lucentis as described in your November 21, 2017 letter.

Health Canada considers dose-splitting of these drugs to be a practice that would increase the adverse effects that occur with intraocular injection. Even with the best of precautions these include infections that can lead to blindness, intraocular hypertension, and, if the dose is inaccurate, lack of efficacy (lower than recommended dose) or systemic side-effects (dose higher than recommended).

The marketing authorisation and manufacturer's directions for use clearly indicate that these drugs are for single use only.

Eylea labelling indicates the following:
The EYLEA vial (DIN 02415992) is for single-use only. The vial contents should not be split or further compounded. Use of more than one injection from a vial may increase the risk of contamination and subsequent infection. EYLEA vials do not contain any preservative agent.
THE VIAL IS FOR SINGLE-USE ONLY. EACH VIAL IS TO BE USED ONLY FOR THE TREATMENT OF ONE EYE WITH 50 microliters (2 mg) OF EYLEA.

Lucentis labelling indicates the following:
Single-use vial (DIN 02296810) or single-use pre-filled syringe (DIN 02425629) for intravitreal use only. Use of more than one injection from a vial can lead to contamination and subsequent infection. LUCENTIS (ranibizumab injection) vials and pre-filled syringes do not contain any preservative agent.
It is important to note that Health Canada does not view the preparation of a drug when performed in accordance with approved directions for use provided by the drug manufacturer to be drug manufacturing. It is an activity that falls outside the scope of the Food and Drug Regulations.

You have raised the following question:

Based on the criteria outlined in Policy 0051, is dose-splitting of single-use products into multiple doses for distribution to health professionals or other pharmacies considered manufacturing by Health Canada?

As you're aware, there are many factors for consideration when determining if an activity is manufacturing or compounding as outlined in Health Canada's *Policy on Manufacturing and Compounding Drug Products in Canada (POL-0051).* Distinguishing between compounding and manufacturing activities is made on a case-by-case basis, taking account of the particular facts at hand.

Health Canada would support any Provincial regulator that holds the position that the dose splitting reported for Eylea and Lucentis present a risk to patient safety and that such activities are drug manufacturing as they fall outside the acceptable limits to the practice of pharmacy or medicine. The Department would support Provincial regulatory bodies to exercise compliance and enforcement actions or undertake compliance promotion activities to ensure that healthcare professionals authorized to practice under provincial jurisdiction continue to comply with acceptable limits to their practice. Health Canada is prepared to likewise seek compliance with the *Food and Drug Regulations* in such cases.

Putting future regulatory safeguards such as commercial compounding aside, Health Canada will look forward to bilateral discussion based on current frameworks to better understand the position of Provincial regulators and the actions that provincial regulators may be considering to ensure that healthcare professions continue to conduct preparation activities in accordance with acceptable limits to their practice.

Finally, should there be evidence of a lack of safety or efficacy and regardless of whether an activity is considered manufacturing, compounding or preparation of a manufactured drug according to directions; Health Canada may still apply Section 8 of the *Food and Drugs Act* in the interest of patient safety.

8. No person shall sell any drug that (a) was manufactured, prepared, preserved, packaged or stored under unsanitary conditions; or (b) is adulterated.

We look forward to understanding the position of Provincial regulators and any actions that may be considered to address the safety concerns that have been raised on dose-splitting.

Sincerely,

Kimby N. Barton

Kimby N. Barton
Director
Health Products Inspection and Licencing Division
Regulatory Operations and Regions Branch