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04-119517-720

TO: STAKEHOLDERS

Re: Creation of a regulatory framework for the implementation of good manufacturing practices for active pharmaceutical ingredients

This is to provide you with an opportunity to comment on Health Canada's proposed regulatory framework for the purpose of implementing the International Conference on Harmonization (ICH) guideline Q7A. Q7A is an internationally recognized guideline that was developed to provide internationally harmonized guidance regarding good manufacturing practices (GMPs) for active pharmaceutical ingredients (APIs). The primary aim of creating a regulatory framework for GMPs for APIs is to ensure that activities involving APIs, including imported APIs for use in dosage form drugs, and those used in clinical trial drugs, meet good manufacturing standards expressed in Q7A. A stakeholder consultation took place on May 26-27, 2004 on the elements of a regulatory framework for implementing Q7A and the feedback received at this session was essential in the creation of the following proposed regulatory framework. Health Canada proposes to create a regulatory framework with five key elements as its foundation. These proposed elements are as follows:

1. Incorporating Q7A into regulation using an approach similar to *Divisions 1A* and *2* of the *Food and Drug Regulations*.
2. Creating regulatory prohibitions that appropriately manage risk related to APIs, as well as provide for a level playing field for domestic and foreign manufacturers.
3. The inclusion of supplemental labelling requirements to foster traceability of the API product from the original manufacturer to the dosage form manufacturer.
4. The use of establishment licensing (EL) as the site authorization mechanism.
5. A tailored scope of Q7A, which takes into account the Canadian regulatory context within which Q7A will be implemented.

The Q7A guideline is available, under the section on active pharmaceutical ingredients, at http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/drugs_e.html.

Description

1. *Division 2* of the *Food and Drug Regulations* outlines the good manufacturing practices for dosage form drugs. A comparison of Q7A and *Division 2* has been completed by Health Canada to identify the gaps between Q7A and *Division 2*. The finding was that using *Division 2* as the regulatory foundation for GMPs for APIs would be appropriate as long as a number of revisions were completed. This approach would see all applicable sections in *Division 1A* and *2* have an API-specific equivalent in regulation either as new Divisions in the *Food and Drug Regulations* or as subsections under current *Division 1A* and *2* provisions. Most of the revisions required in order to make *Division 2* applicable to the API industry are minor.

   High level requirements would be drafted to supplement *Division 2* in particular instances where Q7A requirements are not currently present in *Division 2*. These requirements principally relate to APIs for use in dosage form drug for use in a clinical trial (chapter 19), cell culture and fermentation (chapter 18) and distribution practices for APIs (chapter 17).

2. A single regulatory prohibition would not provide an adequate foundation for appropriate management of the risk related to APIs. Thus, a multi-pronged approach is necessary in order to effectively manage risk. The proposed prohibitions are[1]:

   - No person shall sell a dosage form drug not manufactured with Q7A compliant APIs. Thus, the sale of dosage form drugs, both domestically manufactured and imported, would be prohibited unless that drug was manufactured with APIs from a Q7A-compliant site.

   - Dosage form manufacturers must use only APIs that were manufactured at a Q7A-compliant site in the fabrication of dosage form drugs.

   - No person shall, except with an establishment license, manufacture, package/label, distribute or import, and any other activities that fall within the scope of Q7A, an API. This would have the indirect effect of requiring Q7A compliance, due to the fact that API GMP compliance would be assessed by Health Canada prior to the issuance of an EL.

[1]The wording used here is merely an approximation of the concept that is proposed to be reflected in regulation. This wording is provided in order to better facilitate understanding of Health Canada's direction, but does not purport to be a precise expression of the final prohibition.

- No person shall sell an API intended for pharmaceutical purposes unless the API has been manufactured in accordance with Q7A. This prohibition would capture all APIs to be used in or as a dosage form drug while excluding APIs to be used for industrial purposes, to be used in a natural health product or any other purpose that does not fall within the scope of Q7A.

3. Q7A contains API labelling requirements. However, additional labelling requirements in the regulations could better facilitate the traceability of APIs. The supplemental labelling requirements would include a site number on the product label and a requirement for a party responsible for the APIs in Canada. First, a site number on the label would provide a link between a shipment of API product and the origin of the manufacturer. The site number could be integrated with existing structures so that the establishment licensing number could also serve as the site number. Second, a party responsible for the APIs would be required in Canada, similar to the requirement for dosage form drugs under *C.01.004.1* of *Division 1A* of the *Food and Drug Regulations*.

4. Compliance with drug GMP requirements is assessed by conducting inspections of those establishments pursuant to the powers provided in the *Food and Drugs Act* and its *Regulations*. These inspections and the determination of compliance with drug GMP requirements are the basis for the issuance of establishment licenses to domestic sites. Foreign sites are assessed for compliance with drug GMP requirements and may be listed on the importer's Canadian establishment license. It is proposed that this system be extended to API manufacturing sites as a key component of a regulatory framework for the implementation of Q7A.

5. The regulatory framework must clearly define the scope of Q7A as it applies to the Canadian specific context. Elaboration on the scope of Q7A could be supplemented with further clarification in policy and guidance documents.

   - *Veterinary drugs*: In December 2003, the Veterinary Drugs Directorate of the Health Products and Food Branch wrote to stakeholders advising them of its intention to adopt GMPs for APIs for veterinary use.

   - *Category IV monograph products*: Category IV monograph products are over-the-counter products that present a different risk than other dosage form drugs. Health Canada is looking at options that would provide the needed flexibility that takes into account the risk presented by this category of products.

   - *Natural health products*: A regulatory framework for natural health products (NHPs) came into effect January 1st, 2004. This regulatory framework outlines good manufacturing practices for natural health products, which will continue to apply to NHPs. However, Q7A will apply to starting materials that are considered an NHP, but are used as an active ingredient in the manufacturing of a dosage

form drug. Health Canada will create a regulatory framework that mitigates overlap between the two sets of GMPs.

- *Bulk process intermediates*: Bulk process intermediates (BPIs) are defined as a drug under *Division 2* of the *Food and Drug Regulations*, and as such have a history with respect to the application of GMPs. The status quo will continue for BPIs, which means that *Division* 2 will continue to apply as the GMPs for BPIs.

Original signed by
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