DEL Q&As – Anti-Microbial Resistance Regulatory Amendment

1. **Regulations have been posted in Canada Gazette Part II regarding veterinary drugs and Antimicrobial Resistance. What's changed?**

   On May 17, 2017 the *Regulations amending the Food and Drug Regulations (Veterinary Drugs-Antimicrobial Resistance)* were published in the Canada Gazette Part II (Vol 151, No 10). Upon coming in to force, these regulations introduce a number of changes. Additional information specific to each change relating to drug establishment licensing is available throughout this document.

   - Active pharmaceutical ingredients (API) for veterinary use must, as of May 17, 2018 meet the good manufacturing practices (GMP) and drug establishment licence (DEL) requirements – the DEL requirements are subject to the transition provision described in Question #4 below.
   - The introduction of List A, an administrative list entitled "List of Certain Antimicrobial Active Pharmaceutical Ingredients", that is published by the Government of Canada on its website, and will be amended from time to time - https://www.canada.ca/en/public-health/services/antibiotic-antimicrobial-resistance/animals/veterinary-antimicrobial-sales-reporting/list-a.html
   - A new category of drug will be added to C.01A.008 Table II and named, "Active pharmaceutical ingredients set out in List A that are for veterinary use"
   - Veterinary Health Products are defined as a separate category of veterinary drugs with a different level of oversight
   - A change will be introduced to the drug establishment licensing exemption of API for the purpose of compounding of drugs by veterinarians and pharmacists containing *Active pharmaceutical ingredients set out in List A that are for veterinary use*
   - Some drugs that were previously non-prescription have become prescription. This may require some people who were exempt from the DEL requirement to now need a DEL for Wholesale.

2. **When do I need to apply for a Drug Establishment Licence for fabrication, packaging, labelling, testing or importation of veterinary APIs?**

   You may begin applying for a DEL starting **May 17, 2018.** As of May 17, 2018 when the DEL and GMP requirements come into force, some companies who currently hold a DEL may need to amend their DEL within the mentioned time frame to reflect the updated regulations. Applicants are expected to be ready for an inspection at the time they submit an application.

3. When do the GMP requirements for veterinary API come into force?

As of May 17, 2018, if you are a veterinary API fabricator, packager/labeller, tester, importer, distributor, or wholesaler you are required to comply with GMP requirements. Importers of drugs in dosage form must ensure that imported drugs are fabricated using APIs that are fabricated, packaged/labelled and tested in buildings that comply with API GMP requirements.

The transition period is only applicable to obtaining an establishment licence — not GMP compliance. Should a GMP compliance risk be identified during the DEL transition period, or at any time thereafter, Health Canada will take appropriate compliance and enforcement action proportional to the risk.

You can find more information on veterinary API GMP requirements in Health Canada's Good Manufacturing Practices (GMP) for Active Pharmaceutical Ingredients (APIs) (GUI-0104). You can use the current version of this guide while Health Canada completes an update to include veterinary API within the scope of the guide.

4. What is the transition period for the DEL requirements?

The transition period lasts 14 months beginning **May 17, 2018** until **July 17, 2019**, but the transitional provisions differ depending on your licensing status and the activities you conduct as of May 17, 2018. Two scenarios are outlined below.

a. Companies conducting activities prior to May 17, 2018:

If you fabricate, package/label, test or import an API for veterinary use (including List A) before **May 17, 2018** you may continue to do so without an establishment licence so long as you submit a complete drug establishment licence application by July 17, 2019. If a complete application is submitted prior to July 17, 2019, you can to continue to conduct activities without a DEL until a decision is rendered on your application.

As per the normal DEL application and amendment process, you are expected to be ready for an inspection at the time you submit an application.

b. Companies that are not conducting activities before May 17, 2018

If you are **not** conducting activities with respect to API for veterinary use **before May 17, 2018,** the transitional provisions included in the regulatory amendment do not apply to you. As such, you cannot conduct licensable activities until you obtain the appropriate drug establishment licence.

5. My drug establishment licence already includes activities for the API drug category. Will I need to amend my licence to add API for veterinary use?

The drug category Active Pharmaceutical Ingredient that is listed on your DEL will authorize activities for API for veterinary use and human use. It will not, however, authorise activities with respect to the new drug category Active pharmaceutical ingredients set out in List A that are for veterinary use. Therefore, if you conduct activities with respect to API set out in List A that are for veterinary use, you will need to amend your DEL to add the drug category "Active pharmaceutical ingredients set

out in List A that are for veterinary use" for the necessary activities, this will appear on your licence as "List A APIs for veterinary use".

If you import API for veterinary use or finished dosage form veterinary drugs, you will need to submit a DEL application that includes Table A to update your Active Pharmaceutical Ingredient Foreign Building Annex to add the API(s) for veterinary use that you import or that are used in the fabrication of the finished dosage form veterinary drugs you import. This information must be submitted when you are submitting your application for an amended licence. If transition provisions are applicable you must submit this information by July 17, 2019.

Detail listings of the DEL requirements for importers are available in Questions #9, 10, 11, and 12 below.

Note: Drugs in their Finished Dosage Form (FDF) or FDF-intermediate form, that are fabricated using an *Active pharmaceutical ingredients set out in List A that are for veterinary use* should have their appropriate FDF drug category listed in FRM-0033, and not one of the two API-related categories.

6. Has the Drug Establishment Licence Application form (FRM-0033) changed to accommodate the information required by the new regulations?

A revised *FRM-0033* and Table *A: Foreign Buildings Conducting API-Related Licensable Activities* has been developed and will be required for all Drug Establishment Licence applications.

The revised *FRM-0033* now requires information regarding the drug class to indicate if the drug is for human use, veterinary use, or use in both human and veterinary drugs. **All applications will need to submitted using the revised FRM-0033 following its release shortly before May 17, 2018 on the Health Canada website.** The revised FRM-0033 will be announced via DEL Bulletin when it is posted on the Health Canada Website.

The revised *Table A: Foreign Buildings Conducting API-Related Licensable Activities* adds two new columns to capture the drug class and category of drug information along with a series of quality and usability improvements that will make Table A more user friendly.

Importers of APIs for veterinary use and List A for veterinary use are required to submit their application using the revised Table A. To request a copy of the latest version of Table A, please email DEL_Questions_LEPPP@hc-sc.gc.ca.

7. I fabricate, package/label, and/or test APIs for veterinary use in Canada, what do I need to apply for?

For the activities of fabricate, package/label, and/or test conducted with respect to APIs for veterinary use, you require a DEL for the appropriate activities and for the drug category "Active Pharmaceutical Ingredients".

If you fabricate, package/label, and/or test drugs in the new drug category of *API for veterinary use set out on List A*, see Question #8 below.

8. **I fabricate, package/label, and/or test, in Canada, *APIs for veterinary use that are set-out on List A*, what do I need to apply for?**

   For the activities of fabricate, package/label, and/or test conducted with respect to *APIs set out in List A that are for veterinary use*, you require a DEL for the appropriate activities and for the drug category, "List A APIs for veterinary use".

   Note: if you only conduct activities with respect to *List A APIs for veterinary use*, you are not required to have the drug category "Active Pharmaceutical Ingredients" on your licence if you only deal with veterinary use drugs. The drug category "List A APIs for veterinary use" is sufficient.

   If you import APIs for veterinary use that are set-out on *List A* refer to Question 9.

9. **I import *Active Pharmaceutical Ingredients for veterinary use that are set-out on List A*, what do I need to apply for?**

   You are required to hold a DEL for the activity of Import for the drug category *Active Pharmaceutical Ingredients for veterinary use that are set-out on List A* and your licence must include an *Active Pharmaceutical Ingredient Foreign Building Annex* listing all the foreign building that fabricate, package/label and/or test A*ctive pharmaceutical ingredients set out in List A that are for veterinary use* that you import.

10. I am a pharmacist or veterinarian and I import API for veterinary use, do I need a DEL?

   Healthcare professionals in the practice of pharmacy or medicine that import active pharmaceutical ingredients on List A to compound drugs for veterinary use will need to obtain a Drug Establishment Licence for the importation activity.

   Before the coming into force of these regulations, health care professionals in the practice of pharmacy or medicine did not require a drug establishment licence to import an API for use in their compounding practice.

   This remains the same after these regulations come into force with one exception. As of May 17, 2018 a health care professional in the practice of pharmacy or medicine will need to obtain a DEL if they import an API that is set out on List A to compound drugs for veterinary use.

   If you have imported API for compounding purposes on or before May, 17, 2018 you are subject to transition period. Please refer to Q#4 on when you must submit an application.

11. **I import drugs for veterinary use in their finished dosage form, what do I need on my DEL?**

   You are required to hold a DEL for the activity of Import for the drug category "pharmaceuticals". Your licence must include an *Active Pharmaceutical Ingredient Foreign Building Annex* listing all the foreign buildings that fabricate, package, label and/or test the API(s) used in the fabrication of the veterinary drugs you import.

12. I import drugs for veterinary use in their finished dosage form that are made using APIs that are set-out on List A, do I need to add the new category, *Active pharmaceutical ingredients set out in List A that are for veterinary use*, to my DEL?

The new category, *Active pharmaceutical ingredients set out in List A that are for veterinary use*, only applies to activities conducted with respect to the APIs. Finished dosage form drugs, even those that contain List A APIs for veterinary use, are not subject to the new category.

You will, however, need to complete the revised Table A to list the foreign buildings where the fabrication, packaging/labelling, and testing occurs with respect to the API(s) that you import in your Finished Dosage Form Drugs, indicating the drugs are for veterinary use, and that the API(s) are set-out on List A. The revised Table A will have Columns added to the end to allow for the entry of this information.

13. I fabricate, package/label, and test a FDF at the same establishment in Canada where I fabricate the API used in that FDF, what do I need on my DEL?

In addition to requiring a DEL for the relevant activities for the drug category "pharmaceutical" you will also need the drug category *Active Pharmaceutical Ingredient* and/or A*ctive pharmaceutical ingredients set out in List A that are for veterinary use* for the relevant activities.

14. I fabricate, package/label, and test a veterinary Finished Dosage Drug in Canada and I source my API from a Canadian company, do I need to amend my DEL?

No. You are not conducting any activities with respect to API for veterinary use. You are only required to hold a DEL for the activities you conduct on Finished Dosage Form pharmaceutical drugs.

15. I wholesale APIs for veterinary use, do I require a DEL?

No. Wholesaling of APIs, including wholesaling of *APIs set out in List A that are for veterinary use*, is not a licensable activity. You must, however, meet the Good Manufacturing Practices requirements of the *Food and Drug Regulations*.

16. The products I import, distribute, fabricate, package/label, test, and/or wholesale are Veterinary Health Products as defined in C.01.001(1) of the Foods and Drug Regulations or active pharmaceutical ingredients that is used in the fabrication of a veterinary health product. Do I need a DEL to conduct activities with respect to Veterinary Health Products?

No, you do not require a DEL to conduct activities related to the Veterinary Health Products (VHPs).

VHPs are low risk drugs in dosage form. They are used to maintain or promote the health and welfare of companion and food-producing animals. They are not for use to treat, prevent or cure disease.

VHPs contain ingredients such as:

- vitamins
- minerals

- traditional medicines

For more information on VHPs, please refer to the following Health Canada website - https://www.canada.ca/en/public-health/services/antibiotic-antimicrobial-resistance/animals/veterinary-health-products.html

17. I am a compounding pharmacist or veterinarian that imports APIs for compounded drugs that are used in food-producing animals; do I now need a DEL?

Pharmacists or health care practitioners (e.g. veterinarians) that import active pharmaceutical ingredients on List A to compound drugs for veterinary use will need to obtain a Drug Establishment Licence for the activity of import. The DEL requirement applies to all veterinary drugs whether they are intended for pets or food producing animals.

If you have imported API for compounding purposes on or before May, 17, 2018 you are subject to transition period. Please refer to Question #2 and #3 for information on dates applicable to submitting an application.

18. As an importer, can I sell API to pharmacists and/or veterinarians that do not have a DEL?

Yes. As an importer, you may sell APIs for veterinary use for compounding to veterinarians or pharmacists including those APIs that are on List A.

19. **Is GMP evidence required for APIs for veterinary use or APIs set out in List A that are for veterinary use? What GMP evidence is required?**

Yes, GMP evidence is required for foreign API buildings supplying APIs for veterinary use or APIs set out in List A that are for veterinary use. As stated in section C.02.003 of the *FDR*, no importer shall sell a drug unless it has been fabricated, packaged/labelled, tested and stored in accordance with Division 2 of Part C of the Food and Drug Regulations (GMP requirements). Also, as stated in C.02.003.3, no person shall use an active ingredient in the fabrication of a drug unless it is fabricated, packaged/labelled, tested, and stored in accordance with GMP requirements.

As per the revised GUI-0080 published on January 18, 2018, you must not apply to add a foreign building to your DEL (API FB Annex) if you do not have GMP evidence that supports the foreign building's compliance with Division 2 of the *FDR*. The GMP evidence you indicate on Table A must meet the evidence requirements as outlined in Section 5 of GUI-0080.

20. Will Health Canada allow API Foreign Buildings to submit GMP evidence directly, on behalf of an importer, due to confidentiality reasons?

Health Canada may request at any time that importers submit evidence to demonstrate the foreign building's GMP compliance.

Health Canada encourages importers to maintain all evidence of GMP compliance of API foreign buildings on site so that the importer is able to provide this within the time period specified if GMP evidence is requested. However, Health Canada will accept evidence directly from the foreign API manufacturer under the following conditions:

- The evidence is submitted after the API importer has received a request for GMP evidence
- The evidence must be submitted to: foreign_site_etranger@hc-sc.gc.ca clearly referencing the name and DEL# of the importer as well as the subject line of Health Canada's request to the importer.

Although evidence can be sent directly from the foreign building, it is important for importers to continue to fulfill their requirements as outlined in the *Food and Drug Regulations*. Health Canada strongly recommends that written agreements between importers and foreign buildings include provisions to ensure importers are able to fulfill their regulatory obligations, including provisions that compel the foreign buildings to provide importers with sufficient information necessary to demonstrate compliance with Canadian regulatory requirements.

21. **Which requirements and guidelines should I use for the manufacture of an active ingredient sold as finished dosage form (i.e., an API that does not go through any further manufacturing process before being sold)?**

If the finished product is an active ingredient that is sold as a drug in dosage form then you must appropriately satisfy expectations as it relates to both the active ingredient and the finished product. You can find more information in Health Canada's Good Manufacturing Practices Guidelines (GUI-0001) and Good Manufacturing Practices (GMP) Guidelines for Active Pharmaceutical Ingredients (API) – (GUI-0104).

As per the July, 2015 Notice to Stakeholders entitled "Updates to drug establishment licence applications and good manufacturing practice evidence requirements for active pharmaceutical ingredients", in cases where the API and the FDF are the same, or where the manufacturing process is continuous, the foreign buildings should be included only on the DEL Foreign Building Annex, not in Table A. This means that consistently with the guidance How to demonstrate foreign building compliance with drug good manufacturing practices (GUI-0080), GMP evidence would need to be submitted with your DEL application.

22. What are the requirements of Quality Agreements for veterinary APIs?

API importers, FDF importers, and FDF fabricators importing API for use in manufacturing should establish written quality agreements with foreign suppliers. These agreements should clearly identify the foreign API fabricator and the GMP responsibilities of each party. The key areas to be covered for FDF importer and API importer agreements are outlined in Health Canada's *Good manufacturing practices guide for drug products (GUI-0001)* - (GUI-0001) and *Good Manufacturing Practices (GMP) Guidelines for Active Pharmaceutical Ingredients (API)* - (GUI-0104), respectively.

Where applicable, written agreements should include (but are not limited to):

- Provisions requiring that the Canadian importer be notified of any change to the API manufacturing process and/or supplier and/or specifications.

- Provisions that the Canadian importer is notified of any recalls and/or other regulatory actions such as statements of non-compliance, warning letters or import alerts/bans that originate at any foreign buildings where FDF and/or API activities are conducted.
- Provisions, where applicable, requiring that upon request, a copy of the foreign API fabricator's Annual Product Quality Review (APQR) is to be provided to the API importer, as well as the Canadian FDF importer via the foreign FDF Fabricator.
- Provisions, where applicable, requiring that upon request the foreign API fabricator to provide on-going stability to the API importer, as well as the Canadian FDF importer via the foreign FDF Fabricator.
- For FDF importers, provisions requiring that foreign FDF fabricators use APIs manufactured at GMP-compliant buildings.
- For FDF importers, provisions requiring foreign FDF fabricators to ensure that the API supplier buildings are compliant with Canadian GMP or ICH Q7 guidelines. This should also enable foreign FDF fabricators to conduct GMP corporate audits on the other buildings used and/or request the relevant GMP compliance evidence.