



# GUIDANCE DOCUMENT

## Post-Notice of Compliance (NOC) Changes: Safety and Efficacy Document

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**Health Products and Food Branch**

<p>Our mission is to help the people of Canada maintain and improve their health.</p> <p style="text-align: right;"><i>Health Canada</i></p>	<p>Health Products and Food Branch’s mandate is to take an integrated approach to the management of the risks and benefits to health related to health products and food by:</p> <ul style="list-style-type: none"> <li>• minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and,</li> <li>• promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.</li> </ul> <p style="text-align: right;"><i>Health Products and Food Branch</i></p>
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## FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document *may be* acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this guidance, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidances.

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## 1. INTRODUCTION

### 1.1 Objectives

- (a) To assist with the classification of safety and efficacy changes made to a new drug that has received a Notice of Compliance (NOC).
- (b) To provide sponsors with recommendations on the data to support a change which would be considered sufficient to allow a determination of the impact of the change on the safety, efficacy and/or effective use of the new drug.

### 1.2 Scope and Application

This guidance document applies to sponsors intending to make changes to new drugs that have received a NOC pursuant to section C.08.004 of the *Food and Drug Regulations*. These new drugs may include pharmaceuticals, biologics, and radiopharmaceuticals for human use and pharmaceutical and certain biotechnological products for veterinary use<sup>1</sup>. This guidance document also applies to those submissions for which a NOC has been recommended but issuance of the NOC has been placed on hold.

This guidance document should be read in conjunction with the associated Health Canada guidance documents entitled *Post-Notice of Compliance (NOC) Changes: Framework* for further background information including a list of policies and guidance documents that will be superseded, *Post-Notice of Compliance (NOC) Changes: Quality* as well as other related Health Canada guidance documents. Information regarding general submission requirements and target performance standards may be found in the Health Canada guidance document: *Guidance for Industry: Management of Drug Submissions* for drugs intended for human use and *Guidance for Industry: Management of Regulatory Submissions* for drugs intended for animal use.

## 2. GUIDANCE FOR IMPLEMENTATION

### 2.1 Reporting Categories

The following criteria and examples are meant to provide guidance with respect to the classification of a safety or efficacy related change. For assistance in classifying a change, sponsors are advised to contact Health Canada. Contact information is provided

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<sup>1</sup> The Veterinary Drugs Directorate (VDD) should be consulted to determine if the submission constitutes a veterinary biotechnological drug under the *Food and Drugs Act*.

in *Guidance For Industry: Management of Drug Submissions* (drugs for human use) or the *Guidance For Industry: Management of Regulatory Submissions* (drugs for veterinary use).

When filing an update to the labels (for example [e.g.], Product Monograph or Package Insert for veterinary drugs) for a Subsequent Entry Product to be in line with the currently approved labelling of the Canadian Reference Product, sponsors should follow the same reporting category that the reference product was submitted as.<sup>2</sup>

### 2.1.1 Level I - Supplements

#### Criteria

A Level I change is defined as a change to the label of a drug that has the potential to increase the exposure levels of the drug, either by expanding the population that is exposed, or by increasing individual exposure. The label changes that can result in increased exposure levels of the drug include:

- a) The addition or expansion of a safety claim or efficacy claim, whether explicit or implicit.
- b) The addition of a new route of administration, new dosage form, new strength, or increase in recommended dose/dosing range.
- c) The deletion or reduction of existing risk management measures.

This level also includes those changes that do not meet the above criteria but require the issuance of a new NOC:

- d) The brand name of the new drug has been changed.<sup>3</sup>
- e) An existing indication has been withdrawn in its entirety.
- f) An existing route of administration, dosage form and/or strength has been deleted due to safety reasons.

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<sup>2</sup> Not applicable to biologics.

<sup>3</sup> Only if there is a change in the product name but the same Drug Identification Number (DIN) is retained. For all other changes in Manufacturer's name and/or product name, refer to the "*Changes to Manufacturer's Name and/or Product Name Policy*"(2001) and "*Drug Name Review: Look-alike Sound-alike (LA/SA) Health Product Names Guidance*"(2005).

- g) Results of confirmatory clinical trials (either intermediate or final) specified in the Letter of Undertaking.<sup>4</sup>

### 2.1.2 Examples

Examples of Level I related changes include but are not limited to the following:

Any change to the existing text of the labels (including Package Insert<sup>5</sup> or Part III of the Product Monograph) that refers to any potential benefits of the drug, implicit or explicit, including claims regarding the safety profile or efficacy. This includes changes in text with reference to sub-populations and species (for veterinary drugs), and any reference to possible claims regarding side effects.

A new indication has been added, including reintroduction of an indication that had received a Notice of Compliance and was subsequently withdrawn, or the existing text of an indication has been revised (other than changes to improve risk management as per Level II (90 day) Risk Management criteria).  
For drugs for veterinary use, addition of a new species.

Any change regarding the mechanism of action of the drug as detailed in the ACTION AND CLINICAL PHARMACOLOGY (CLINICAL PHARMACOLOGY for veterinary drugs) sections of the Product Monograph/Package Insert that results in an explicit or implicit claim.

Any change to the CLINICAL TRIAL (SAFETY AND EFFICACY STUDY INFORMATION for veterinary drugs) sections of the Product Monograph/Package Insert which results in a new claim, explicit or implicit (e.g., listing of additional outcome measures, or revision to the description of study design such that a new benefit is implied for a specific sub-population).

A new route of administration has been added.

A new dosage form has been added.

A new strength has been added.

Change in condition of use from prescription to non-prescription status.

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<sup>4</sup> Refer to the “*Notice of Compliance with Conditions Policy*” (2007).

<sup>5</sup> Equivalent document to the Product Monograph for Veterinary drugs.

An existing contraindication, warning or cautionary text anywhere in the Product Monograph/Package Insert, has been deleted in its entirety, has been altered so as to reflect a reduction or diminishment in risk, and/or in a risk management measure. For veterinary drugs, this also includes a reduction or diminishment to an existing withdrawal/withholding period. These may result from a range of supporting data (e.g., post-marketing data, safety studies, pharmacokinetic data etc.).

Existing text regarding an adverse event or set of events has been altered to reflect, in any way, an apparent reduction in risk. This includes changes related solely to animal data (for human drugs), or non target species data (for veterinary drugs), but excludes changes solely to a percentage appearing in an adverse event table where there is no associated cautionary text in the Product Monograph/Package Insert.

The existing text of the label (e.g., Package Insert or Part I or Part III of the Product Monograph) have been deleted, reworded and/or otherwise altered so as to diminish a risk management measure. This would include any a change as a result of new pharmacokinetic data related to a special or sub-population or new species (for veterinary drugs).

### **2.1.3 Submission Filing**

The changes included in this reporting category shall be filed, with Health Canada as a Supplemental New Drug Submission (SNDS) or Supplemental Abbreviated New Drug Submission (SANDS) along with the recommended supporting data.

### **2.1.4 Level II (90 day) Notifiable Changes**

#### **Criteria**

A Level II (90 day) **Risk Management Change** is defined as a change to the label that has the potential to improve the management of risk to the population currently indicated for use of, or in any other way exposed to, the drug by:

- a) The identification or characterization of any adverse events, addition or strengthening of risk management measures for the adverse event;
- b) The identification of subgroups, or conditions of use, for which the benefit to risk profile of the new drug has the potential to be less favourable; and
- c) The addition or strengthening of risk management measures, including instructions on dosing or any other conditions of use.

As per Level 1 criteria, changes which concern a safety related claim are excluded.

### **2.1.5 Examples**

Examples of Level II (90 day) Risk Management related changes include but are not limited to the following:

Addition to, strengthening or clarification of text anywhere in the sections: CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS (CAUTIONS for veterinary drugs) and ADVERSE EVENTS of the Package Insert or Part I or III of the Product Monograph, including changes as a result of an advisory. These changes may include the provision of recommended risk-management actions (e.g., required testing prior to initiation of the drug, specific monitoring during product use, ensuring patient awareness of certain risks, etc.), or the identification of a specific sub-population as being at greater risk such as those with a concomitant condition, those taking concomitant medicine, or a specific age group.

The instructions for use including dosage and administration, anywhere in the Package Insert or Part I or Part III of the Product Monograph, have been reworded and/or otherwise altered with respect to optimizing the safe use of the drug.

An existing indication has been altered for risk management purposes including reduction in scope.

A new drug interaction has been added, or an existing drug interaction has been better characterized, that alters the conditions of use in terms of risk management (e.g., a precautionary statement is added as the result of the new data).

New overdose symptom(s), or overdose treatment(s) has been added.

The existing text of the labels (e.g., product monograph, package insert, inner and outer labels) that have has been revised to add clarity as it relates to the safe use of the drug, but without expanding, explicitly or implicitly, the claims of the drug.

A change made only to the text of the Consumer/Client Information section of the Product Monograph/Package Insert (e.g., to improve the clarity of the message to consumers).

### **2.1.6 Submission Filing**

The changes included in this reporting category should be filed, along with the recommended supporting data, to Health Canada as a Level II (90 day) Risk Management Change.

### **2.1.7 Level II (120 day) Notifiable Changes**

#### **Criteria**

A Level II (120 day) change is defined as any change to the label that does not affect the conditions of use (i.e. does not involve risk management, nor has the potential to increase exposure level of the drug) but for which prior approval by Health Canada is required. It is neither a Level I, Level II (90 day), Level III or Level IV change. This new category was developed to allow more urgent Level II (90 day) Notifiable Changes to be given priority in the processing queue.

#### **2.1.8 Examples**

Examples of Level II (120 day) related changes include but are not limited to the following:

Any changes to the text related to OVERDOSE with the exception of those changes listed in the Level II (90 day) examples.

Any changes to the text related to the Pharmacokinetics section of the ACTION AND CLINICAL PHARMACOLOGY (CLINICAL PHARMACOLOGY for veterinary drugs) section of the Product Monograph/ Package Insert that does not alter the conditions of use in any way.

Any changes made to the text of the PHARMACOLOGY, MICROBIOLOGY, TOXICOLOGY (SAFETY AND EFFICACY STUDY INFORMATION for veterinary drugs) sections of the Product Monograph/Package Insert that does not alter the conditions of use in any way.

A change to the CLINICAL TRIAL section which does not alter the conditions of use in any way.

A new drug interaction or pharmacokinetic study has been added, or an existing drug interaction has been better characterized, that does not alter the conditions of use of the drug in any way.

A change solely to a percentage (observed or reported) appearing in an ADVERSE EVENTS table, where there is no associated change to cautionary text in the Product Monograph/Package Insert (e.g., no explicit conditions of use to be affected). This includes both decreases and increases to the value.

The addition of data or modification of text, other than Level II (90 day) or Level III changes, which does not result in any other changes to the information provided to the Health Care Professional or consumer/client.

Any addition to the REFERENCE section of the Product Monograph/Package Insert that does not affect any other text in the label or that does not alter the conditions of use of the drug in any way.

### **2.1.9 Submission Filing**

The changes included in this reporting category should be filed, along with the recommended supporting data, to Health Canada as a Level II (120 day) change.

### **2.1.10 Level III - Annual Notifications**

#### **Criteria**

A Level III change is defined as any change to the label that is not expected to impact the safety, efficacy, and/or effective use of the drug. The changes included in this reporting category may be implemented by the sponsor without the prior review by Health Canada of the data supporting such a change.

#### **2.1.11 Examples**

Examples of a Level III related change include but are not limited to the following:

Any change to the layout of the label that does not represent a change to the labelling requirement of Sections C.01.004 and A.01.016 of the *Food and Drug Regulations* (e.g., contrast, artwork, font, position) or the terms of market authorization.

Changing a publication in the REFERENCE section of the Product Monograph/Package Insert listed as “in press” to a published listing.

The existing text of the labels (for human drugs) have been revised to add clarity as it relates to maintaining consistency with common label phrase standards (e.g., change from “Product Monograph available on request” to “Product Monograph

available to health care professional on request”, change from “Not recommended for children to “Not for use in children” etc.).

Revisions to Part III, Consumer Information section of the Product Monograph (for human drugs) to standardize text in each of the following sections: Overdose, Missed Dose, How to Store It or Reporting Suspected Side Effects.

Any change in spelling of the text of the label (e.g. ,“adition” is replaced by “addition”).

Sponsor contact information (e.g., customer service number, website addresses, etc.).

### **2.1.12 Submission Filing**

The changes included in this reporting category should be filed to Health Canada as a Level III change. A copy of the most recent revised label(s) (inner and outer) should be submitted to Health Canada as part of the Annual Drug Notification if Level III changes have been implemented from the time of the last approved label to the time of Annual Drug Notification. The Product Monograph/Package Insert should be annotated when filing the next submission to Health Canada to indicate those Level III changes that have been implemented. Supporting data for the Level III changes recommended in this guidance documents should *not* be submitted; however, the data should be available to Health Canada within thirty (30) calendar days of a request.

## **2.2 Pre-Submission Enquiries**

Prior to filing a submission, sponsors are advised to contact Health Canada if:

- i) any of the conditions (a-g) listed below apply to the proposed change.
  - (a) For Level 1 changes, only one clinical trial/study<sup>6</sup> is available or the data package is comprised solely of publications.
  - (b) The clinical trial/study makes use of an end point or statistical method that is new or not validated.
  - (c) The clinical trial/study does not reach statistical significance for the primary endpoint or the endpoint used to support the change.

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<sup>6</sup> Not applicable to drugs for Veterinary use.

- (d) The clinical trial/study made use of a comparator authorized but not available on the Canadian market.
- (e) For Subsequent Entry Products where the Canadian Reference Product (CRP) is no longer marketed<sup>7</sup>.
- (f) For Subsequent Entry Products where approval of a strength outside of the CRP dosing range is sought.
- (g) For subsequent entry products where the clinical trial/study or publication makes use of a non-Canadian reference product as a comparator<sup>8</sup>, or;
  - ii) where existing guidances/policies are unclear or do not cover specific situations or ;
  - iii) if the sponsor wishes to discuss product specific data requirements.

Depending on the issue/concern, a pre-submission meeting may be arranged to allow more in depth discussion between the sponsor and Health Canada. Contact information and procedures are provided in the Health Canada documents, *Guidance for Industry: Management of Drug Submissions* for drugs intended for human use and *Guidance for Industry: Management of Regulatory Submissions* for drugs intended for use in animals.

### 3. DOCUMENTATION

Health Canada has the mandated responsibility to perform a thorough and rigorous assessment on a drug submission received for a change to a new drug and render an evidence and context-based decision within a specified time frame.

The intent of this section is to highlight the range in categories of data and contextual information that may be relevant to the evaluation of a particular submission. Regulatory decision-making is optimal when contextualized via a variety of information beyond solely the data which could include: characterization of the patient or treated population in question, regional clinical practice standards, the availability of alternative therapies, the sponsor's interpretation of the data, as well as the interpretation by other major international agencies (e.g., as per labels approved by that jurisdiction). If no other major agency has rendered an opinion at the time of the evaluation or if discussions are currently underway, that fact is then considered important contextual information.

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<sup>7</sup> Refer to the “*Canadian Reference Product Policy*” (1995).

<sup>8</sup> Ibid

The presence of an information category in these lists does not mean those data are necessarily required, but rather it's anticipated that the sponsor will either provide the information, or a rationale as to the absence. This will help to minimize delays that can result when a submission is silent on a relevant topic. As stated in the Foreword of this document, alternate approaches to the principles and practices described in this document **may be** acceptable to Health Canada provided they are supported by adequate justification.

The associated guidance document *Post-Notice of Compliance (NOC) Changes: Framework* should be consulted for details regarding the filing of submissions and annual notifications to Health Canada. Documentation recommended in Section 2.2.3.3 of the aforementioned guidance should be included with a Level I, Level II (90 day) or Level II (120 day) filing and documentation in Section 2.2.4 should be included with the corresponding Annual Notification.

The following recommended data to support safety and efficacy changes should be included or commented on, where applicable, in the submission package for Level I, Level II (90 day), and Level II (120 day) changes below.

### **3.1 Supporting Data - Level I and Level II Changes**

All data required to support the change should be provided with the submission. For Human Drug Submissions, where applicable, the data should be provided in the format defined by the *International Conference on Harmonization (ICH) Common Technical Document (CTD)*. A *Comprehensive Summary: Bioequivalence (CS:BE)* should also be completed and provided where applicable. For Veterinary Drug Submissions, data should be provided in the format of the *Guidance for Industry: Preparation of Veterinary New Drug Submissions*. Refer to existing Health Canada guidance documents for further detail regarding individual product requirements.

#### **3.1.1 Supporting Data Common to Level I and Level II Changes**

The following should be included, where applicable, in the submission package for Level I and Level II changes:

An annotated and non-annotated electronic and an annotated hard copy of the Product Monograph, prescribing information, consumer information, package inserts, package labels or any other labels. Additions to the text should be highlighted, deletions should be indicated by strikeout and references provided to the specific location of the information within the submission.

#### **Supporting Data:**

- a) Clinical and/or non-clinical trial/study data relevant to the submission. This may include but is not limited to: clinical trials (whether focussed on

efficacy or safety), bioequivalence trials, pharmacokinetic studies, pharmacodynamic studies, epidemiological data/study results, pharmacovigilance studies, Periodic Safety Update Report (PSUR) data, review reports/analysis of specific safety concerns, risk management plans/pharmacovigilance plans or patient registry data.

- (b) Other data which may be relevant to the submission. This may include, but is not limited to: rationales, real world information regarding drug use, declarations/attestations, opinion papers, conference presentations, publications in peer-reviewed scientific journals and drug utilization information.

**Contextual Information:**

- (a) A submission involving safety and efficacy updates to the Product Monograph should include a copy of the most recent company core data safety sheet<sup>9</sup>.
- (b) Copies of the most recent labels authorized in other major International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use/ International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (ICH/VICH) regulatory jurisdictions (including Food and Drug Administration (FDA), European Union (EU), Therapeutic Goods Administration (TGA), Australian Pesticides Veterinary Medicines Authority (APVMA).
- (c) Correspondence or communications from other major ICH /VICH regulatory jurisdictions (including FDA, EU, TGA, APVMA) which may be relevant to the submission or a statement confirming that such communications have not been required by any authorities.
- (d) For subsequent entry products, the revision date and control number of the Product Monograph (Package Insert for veterinary drugs) of the Canadian Reference Product used in preparation of the sponsor's Product Monograph/Package Insert.

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<sup>9</sup> Not applicable to drugs for Veterinary use.

**3.1.2 Additional Contextual Information specific to Level I Changes, where applicable:**

- (a) The current status, with respect to other major ICH/VICH regulatory jurisdictions (including FDA, EU, TGA, APVMA) (e.g., currently under review, approved, rejected, or not submitted) at the time of submitting the proposed change to Health Canada.
- (b) Where the review has been completed by other major ICH/VICH regulatory jurisdictions (including FDA, EU, TGA, APVMA), a summary of any significant issues raised, how they were addressed and resolved or; a statement confirming that there were no significant issues identified by those authorities. Where available, copies of any foreign review reports, correspondence or communications (including Questions and Answers) which may be relevant to the submission.
- (c) Where the review has not yet been completed by other major ICH/VICH regulatory jurisdictions (including FDA, EU, TGA, APVMA), a summary of any significant issues being raised.

**3.1.3 Additional Contextual Information specific to Level II (90 day) Changes:**

- (a) Wording of any related instructions or communications (translated into English or French) to Health Care Professionals that may have been or is currently required in other major ICH/VICH regulatory jurisdictions (including FDA, EU, TGA, APVMA) or a statement confirming that such instructions or communications have not been required by any authorities.
- (b) The most recent electronic or hard copy of the Periodic Safety Update Reports (PSURs). These can be cross-referenced if previously provided to Health Canada.
- (c) The Company Core Data Safety Sheet<sup>10</sup>.

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<sup>10</sup> Not applicable to drugs for Veterinary use.

### **3.2 Supporting Data - Level III Changes**

Any data that may have been generated by the sponsor in support of a Level III change should *not* be submitted but should be available to Health Canada within thirty (30) calendar days of a request.

## **4. GLOSSARY**

### **Adverse Event (AE):**

Any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug product, whether or not considered related to the drug product.

### **Company Core Safety Sheet:**

A corporate document maintained by the drug sponsor that contains relevant safety information regarding a drug for human use.

### **Efficacy Claim:**

A claim that can be a word, a sentence, a picture, a symbol, or a paragraph on product labels, package inserts or advertisements where the representation for sale is capable of being understood as the capacity of producing a desired result or effect.

### **Explicit Claim:**

A claim that can be a word, a sentence, a picture, a symbol or a paragraph on product labels, package inserts or advertisements where the representation for sale is fully revealed or expressed without vagueness or ambiguity leaving no question as to meaning or intent.

### **Implicit Claim:**

A claim that can be a word, a sentence, a picture, a symbol or a paragraph on product labels, package inserts or advertisements where the representation for sale is capable of being misunderstood or misinterpreted so as to imply or suggest something in addition to what is explicit.

### **Label:**

Label includes any legend, word or mark attached to, included in, belonging to or accompanying any food, drug, cosmetic, device or package (*Food and Drugs Act*) (e.g., product monograph, package insert, inner and outer labels etc.)

### **Package:**

Package includes any thing in which any food, drug, cosmetic or device is wholly or partly contained, placed or packed (*Food and Drugs Act*).

**Package Insert (Human Drugs):**

The factual, scientific document for a human drug product that is devoid of promotional material, describes the properties, claims, indications, and conditions of use for the drug, and that contains any other information that may be required for optimal, safe, and effective use of the drug. This information is provided with the drug at point of sale.

**Package Insert (Veterinary Drugs):**

The factual, scientific document for a veterinary drug product that, devoid of promotional material, describes the properties, claims, indications, and conditions of use for the drug, and that contains any other information that may be required for optimal, safe, and effective use of the drug (i.e., equivalent to the Product Monograph for human drugs).

**Patient Registries:**

An organized collection of data on humans within a particular disease group or other special group (e.g., cancer, pregnancy, birth-defect, organ transplant, and serious skin disease registries).

**Pharmacovigilance Studies:**

Studies involving the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.

**Safety Claim:**

A claim that can be a word, a sentence, a picture, a symbol or a paragraph on product labels, package inserts or advertisements where the representation for sale is capable of being understood as being safe or comparatively safer from undergoing or causing undue hurt, injury or loss.

**Withdrawal Period/Withholding Period:**

The length of time between the last administration of a drug to an animal and the time when tissues or products collected from the treated animal for consumption as food contain a level of residue of the drug would not likely cause injury to human health. (C.01.001(1) of the *Food and Drug Regulations*).