Health Canada Santé Canada

Section 12 Notice **Additional Information Required as a Post-Market Requirement**

Product Name: ***Pyroxasulfone Technical***
Registration Number: ***30573***
Application Number: ***2021-1932***
PMRA #: ***3305360***

During the registration period which has been granted to December 31, 2025, the following information is to be generated and must be provided to the Pest Management Regulatory Agency by November 23, 2024 and should indicate the DACO numbers specified. A partial response to the outlined data requirements will not be accepted.

Part 0 Index

DACO: **0**
Title: **Index**

Details: Please submit an electronic index of the data package submitted in response to this letter. Please refer to Regulatory Directive 2006-05, *Requirements for Submitting Data Index, Documents and Forms*, for additional information.

Part 2 Chemistry requirements for the registration of a technical grade of active ingredient or an integrated system product (ISP)

DACO: **2.11.1**
Title: **Manufacturing Summary**

Details: Provide a brief overview of the manufacturing process outlining the major steps and reactants, summarizing the more comprehensive description required under DACO 2.11.3. This is to include a general characterization of the process, for example, batch or continuous, and the typical quantity of product produced per batch (or per unit time, if continuous).

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DACO: **2.11.2**
Title: **Description of Starting Materials**

Details: The following information is to be provided for each starting material used to produce the technical grade of active ingredient or integrated system product (ISP):
(i) each brand name, trade name, common name, chemical name, Chemical Abstracts Service Registry number, or other commercial designation;
(ii) the name and address of the companies that produce the starting materials or, if that information is not known to the applicant, the name and address of the companies that supply the starting materials;
and
(iii) all information concerning the composition of each starting material, including a copy of all specifications or other documents describing it.

It should be emphasized that an applicant is not required to perform chemical analysis of starting materials to meet the above criteria, but only provide information to which the applicant has, or should have, access. The information required for formulants, if applicable to an ISP, is consistent with the three requirements identified above for starting materials.

If multiple suppliers are used for starting materials/formulants, specifications for all suppliers should be provided. Changes in suppliers once a product is registered are subject to the requirements of Regulatory Directive DIR2016-02, *Notification/Non-Notification,* or subsequent revisions.

DACO: **2.11.3**
Title: **Detailed Production Process Description**

Details: An applicant must submit information on the manufacturing process used to produce the technical grade active ingredient or ISP at each stage of production resulting in a separately isolated substance, as follows:
(i) a flow chart of the chemical reactions, including structures, at each step of the process and of the major unit operations, including separation steps;
(ii) the identities of the reactants, solvents and catalysts used to produce the product, their quantities and the order in which they are added;
(iii) a description of the equipment used that may influence the composition of the substance produced;
(iv) a description of the conditions, for example, reaction time, temperature, pressure, pH, humidity – that are controlled during each step of the process to affect the composition of the substance produced
(in particular to minimize the formation of impurities), and the corresponding limits that are maintained;
(v) a description of the purification steps, including those used to recover or recycle starting materials/solvents, intermediates or the substance produced; and
(vi) a description of the procedures used to assure consistent composition of the substance produced, for example, calibration of equipment, sampling regimens and other quality control measures such as tests used to monitor reaction completion.

Additional requirements are applicable to the manufacturing of stereoisomeric active ingredients. Three types of products may form during the manufacturing of such actives:
(i) a racemic mixture;
(ii) a single stereoisomer (enantiomer or diastereomer that, by definition, includes geometric [cis/trans or Z/E] isomers); or
(iii) a stereoselectively enhanced isomeric mixture.
For (ii) and (iii), a full description of the stereoselective manufacturing process is to be provided. Stereospecific identity and purity is to be identified for starting materials.

DACO: **2.11.4**
Title: **Discussion of Formation of Impurities**

Details: The applicant must provide a discussion of the impurities that may be found in the product and why they may be present. The discussion should be based on established chemical theory and on what the applicant knows about the starting materials and the production process. The thoroughness of the theoretical discussion can be evaluated in parallel with the batch analysis data under DACO 2.13, to assess whether potential impurities would be comprehensively identified by the methods used. If the applicant has reason to believe that an impurity the PMRA would consider to be toxicologically significant may be present, the discussion must include an expanded description of the possible formation of the impurity. The following potential sources of impurity formation must be discussed, as applicable:
(i) each impurity that was found to be present in any analysis of samples produced according to the process identified under DACO 2.11.3 conducted by or for the applicant; and
(ii) each other impurity that the applicant has reason to believe **may be present** in a product at any time before use at a level $\geq 0.1\%$ by weight, based upon what is known about:
a) the composition (or composition range) of each starting material used to produce the product;
b) the impurities that are known to be present (or believed likely to be present) in the starting materials, and the known or presumed level (or range of levels) of these impurities;
c) the intended reactions and side reactions that may occur in the production of the product, and the relative amounts of byproduct impurities produced by such reactions;
d) the possible degradation of the ingredients in the product after its production but prior to its use;
e) the potential postproduction reactions between the ingredients in the product;
f) the possible migration of components of packaging materials into the pest control product;
g) the potential carryover of contaminants from use of production equipment previously used to manufacture other products or substances; and
h) the process control, purification and quality control measures used to produce the product that may preclude the presence of potential impurities.
On a case-by-case basis, the PMRA may require an expanded discussion of potential impurity formation resulting from other potential chemical reactions, involving other ingredients, or at additional points in the production process.

DACO: **2.13.3**
Title: **Batch Data**

Details: The composition of a minimum of five batches of the product must be provided to support the specifications. The batches must be manufactured at the site proposed for registration (DACO 2.2), using the specified manufacturing process (DACO 2.11.3), and characterized using the methods described (DACO 2.13.1). Date of manufacture, scale of production (pilot vs. commercial), and site of production for each batch must be included, and the oldest of the five batches must not exceed 10 years in age at the time of submission. For a continuous process, lots produced on different days should be submitted.

Corresponding raw data to be submitted include representative quantitative chromatograms of: (1) standards; (2) blanks, and (3) the five batches of the technical grade active ingredient or ISP that were used to support the specifications. Chromatograms must be clearly labelled to identify all analytical parameters and peaks, including those that may represent compounds quantitated by other methods included in the submission.

These batches may initially represent pilot plant production from the proposed site; however, once commercial production commences (either at the same location or at a different facility), data from an additional five batches that correspond to the commercial-scale location/process will be required under a separate application to support the specifications. If multiple manufacturing sites are proposed at once, batch data are required for each site except in the case of a new active ingredient where commercial production has not been initiated – see PMRA Memorandum to Registrants: *Use of Pilot-Scale Data to Register Multiple Sites for New Active Ingredients* (2017) for details. The results of the five-batch analysis should be reported with appropriate uncertainty and significant figures, and material closure of at least 98.5% must be obtained. Registrants will be required to submit batch data, not older than 10 years, to support postmarket reviews.

DACO: **2.13.4**
Title: **Impurities of Toxicological Concern (Impurities of Human Health and Environmental Concern)**

Details: Analysis for these impurities is required when they are used as, or may occur in, starting materials or they may form during the manufacture of the technical grade active ingredient.

For example, nitrosamine analysis is required when appropriate amines and an identifiable nitrosating agent (including nitrites and nitrates) are present due to the raw materials or manufacturing process utilized. These analyses, when required, should reflect the lowest practical LOQ, which will vary according to the sample and chemical. Upper certified limits are required for impurities of toxicological significance present at detectable levels.

Any waiver request for not providing such data must be supported by a scientific rationale as to why the presence of such impurities can be excluded and will be assessed based upon the nature of the raw materials, chemistry of the active ingredient and the specific manufacturing process. Applicants should employ best available technology (BAT) when manufacturing technical grade active ingredients to reduce such impurities

to the lowest level possible, and when conducting the corresponding analyses.
As per DACO 2.13.3, the lots analyzed must be less than 10 years old.
Impurities of toxicological concern include, but are not limited to:
• Dichlorodiphenyltrichloroethane (DDT) and other chlorinated diphenyl ethanes and ethylenes, such as analogs and isomers of DDT, dichlorodiphenyldichloroethane (DDD), dichlorodiphenylethane (DDE) and extrachloro-dichlorodiphenyltrichloroethane (Cl-DDT)
• Polychlorinated dibenzodioxins/dibenzofurans
• Hexachlorobenzene, pentachlorobenzene and tetrachlorobenzenes
• Polychlorinated biphenyls (PCBs)
• Polynuclear aromatics, also referred to as polynuclear aromatic hydrocarbons
• 3,3′,4,4′-tetrachloroazobenzene (TCAB) and 3,3′,4,4′-tetrachloroazoxybenzene (TCAOB)
• Aniline and substituted anilines
• Ethylene thiourea
• Hydrazines
• Nitrosamines
• Oxygen analogs of organophosphates
• Sulfoxides and sulfones of organophosphates and carbamates
• Tetraethyl dithiopyrophosphate (sulfotep) and tetraethyl pyrophosphate (TEPP)
• Metals such as antimony, arsenic, cadmium, chromium, cobalt, nickel, lead and mercury
• Aflatoxins
• Methyl eugenol (typically seen only in non-conventional products, for example, essential oils)
• Dimethyl sulfate
• Ethyl methanesulfonate and isobutyl methanesulfonate
• Formaldehyde
• Cyanides such as hydrogen cyanide, potassium cyanide and sodium cyanide
• Pentachlorobenzonitrile
• 1,2,4-triazole
• Residual solvents that should be avoided, such as carbon tetrachloride, benzene and 1,2-dichloroethane
• Residual solvents that should be minimized, such as toluene, chloroform, cyclohexane, dichloromethane, hexane, *N*,*N*-dimethylformamide and xylene
Impurities having characteristics of potential toxicological significance may include:
(i) any impurity that is a structurally related analog of the parent compound of toxicological significance;
(ii) any impurity that is also an active ingredient; or
(iii) any impurity that is identified by an international regulatory body, by a Canadian government policy/risk management strategy, or in standard toxicology data bases, such as Toxline or the Registry of Toxic Effects of Chemical Substances, as having oncogenic, neurotoxic, genotoxic, developmental or endocrine effects, etc. If a product has been analyzed for any of these compounds, the analytical method, validation data including recovery and LOD/LOQ for the impurity, or reasonable surrogate if appropriate, and batch data as per DACO 2.13.3, are to be provided. Since detection and quantitation limits may vary from case to case, consultation with the PMRA is recommended. Note that the impurities that meet the criteria in the federal

Toxic Substances Management Policy (TSMP) for virtual elimination are identified in the *Pest Control Products Act* List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern. Applicants should contact the PMRA if there is a question about the status of any specific impurity not listed.