

GlaxoWellcome

October 6, 2000

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Docket No. 97N-0023

Dear Docket Officer:

Please include this submission in the above docket and distribute to FDA staff reviewing comments in this docket. This letter is in regard to a December 6, 1999 letter addressed to Mr. Christopher C. Jennings, Deputy Assistant to the President for Health Policy Development, from the Generic Pharmaceutical Industry Association (GPIA) and the National Pharmaceutical Alliance (NPA). On February 4, 2000, this letter was accepted by the docket as part of the record (Doc. No. 97N-0023, C-9621) on FDA's rulemaking on the Use of Ozone-Depleting Substances; Essential Use Determinations.¹

The GPIA/NPA letter refers to proposed Decision XI/15, which was considered by the Montreal Protocol Parties during their Eleventh Meeting in December 1999. As discussed below, the GPIA/NPA letter contains many statements that are unsupported by law or fact. Most importantly, the GPIA/NPA position is contrary to the best interests of patients, and is incompatible with the U.S. commitment to phase out CFC use under the Montreal Protocol.

We would also note that this Decision was strongly endorsed by all major patient and physician groups, and the International Pharmaceutical Aerosol Consortium (IPAC), an association of leading companies involved in research, development, manufacturing and marketing of metered dose inhalers (MDIs) for the treatment of asthma and chronic obstructive pulmonary disease.² IPAC members are both research-based and generic, and include: AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Glaxo Wellcome, Medeva Americas, Inc., and Norton Healthcare Ltd.

¹ Use of Ozone-Depleting Substances; Essential Use Determinations, 64 Fed. Reg. 47719 (Sept. 1, 1999) (Notice of Proposed Rulemaking) ("NPR").

² See, e.g., Letter from Stakeholders to OEWG Co-Chairs Ibrahim Abdel Gelil and Jukka Uosukainen (September 21, 1999); Statement of IPAC on Metered Dose Inhaler Transition Issues at the 11th Meeting of the Parties (November 29 - December 3, 1999) (copies attached at Tab 3).

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At their upcoming Twelfth Meeting in December 2000, the Montreal Protocol Parties have the opportunity to consider a new decision on the MDI transition proposed by the European Union³. This decision includes provisions similar to Decision XI/15 (copy attached at Tab 2) and some additional measures that will facilitate the transition, and is once again supported by all major stakeholders including patient and physician groups and IPAC.⁴ Based on this broad base of stakeholder and industry support, together with the commitment by the U.S. to phase out CFCs, we urge the United States Government to support the EU decision and disregard the unfounded assertions made by GPIA/NPA. In the following sections, we have examined each part of the GPIA letter and provide comments and analysis for your benefit.

Decision XI/15 Would Not Have Discriminated Against Generic MDIs

The GPIA/NPA letter asserts that Decision XI/15 would have discriminated against generic MDIs. In fact, Decision XI/15 proposed deeming all new CFC MDI products non-essential -- with no distinction between generic and innovator products -- except those MDIs providing an unmet medical need. Thus, Decision XI/15 would not have discriminated against generic drugs, but rather would have encouraged the transition to CFC-free medicines. As with numerous other Montreal Protocol decisions addressing a wide range of products that contain chemicals that destroy the earth's ozone layer, this Decision would have helped to phase-out CFC use without regard to the origin of the product.

Similar to Decision XI/15, the EU decision would not necessarily halt product approvals, but would make all newly approved MDI products non-essential unless they are found to be necessary for health or safety as required by Protocol Decision IV/25.

Decision XI/15 Would Not Have Created a Pharmaceutical "Monopoly"

The GPIA/NPA letter implies that Decision XI/15 would have violated established anti-monopoly principles. As discussed below, these assertions are unfounded with respect to Decision XI/15 and the EU decision.

³ Decision XII/**: Measures to Facilitate the Transition to CFC-Free Metered-Dose Inhalers (MDIs), <http://www.unep.org/ozone/ec-proposal-mdi> (the "EU decision") (copy attached at Tab 1).

⁴ See, e.g., Comments of the U.S. Stakeholders Group on Metered Dose Inhalers, delivered by Pamela Wexler, American Lung Association, at the 20th OEWG Meeting (July 11-13, 2000); Statement of IPAC on Metered Dose Inhaler Transition Issues at the 20th Meeting of the Open-Ended Working Group of the Montreal Protocol (July 11-13, 2000) (copies attached at Tab 4).

- **Deeming Unnecessary New CFC MDIs Non-Essential Would Not Create an Unwarranted Monopoly in the Pharmaceutical Industry**

First, the GPIA/NPA letter makes the unsupported assertion that Decision XI/15 "is contrary to law because it provides an unwarranted monopoly within the pharmaceutical industry." But the letter does not identify which anti-monopoly laws are supposedly being violated. The United States, as well as many of the other major Protocol Parties, has strong antitrust laws to prevent illegal monopolies. Neither Decision XI/15 nor the EU decision contain any provision that would lead any country or entity to violate any of these laws.

Decision XI/15 would have made CFCs unavailable for new CFC MDIs that did not provide an otherwise unmet medical need. The EU decision would do the same unless the new CFC MDI product is "necessary for health and safety." These provisions would apply equally to new branded or generic CFC MDIs. Thus, no "artificially preserved marketplace for CFC-containing MDI drugs with little competition" would arise, as claimed by the GPIA/NPA letter. Moreover, GPIA/NPA's fear that the "artificial marketplace" would lead to inflated prices is unfounded. Strong competition already exists among many available MDI products. This competition is not just between branded and generic products, but also between branded products and across multiple delivery systems, including MDIs, dry powder inhalers (DPIs), nebulizers, oral tablets and solutions. Such competition will not be affected in any respect by the EU decision. In the face of this competition, there is no economic basis for the manufacturers of existing CFC MDIs to raise their prices.

- **Deeming New CFC MDIs Non-Essential Would Not Violate the Hatch-Waxman Act**

Second, the GPIA/NPA letter asserts that Decision XI/15 "is directly opposed to the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Act." However, the Hatch-Waxman Act⁵ does not abrogate FDA's responsibility under the Clean Air Act to manage the phase-out of CFCs in medical products in accordance with the Montreal Protocol.

The Hatch-Waxman Act was passed to address the serious decline in the development of both innovator and generic drugs following FDA's increased regulatory authority over new drug approvals beginning in 1962.⁶ Congress felt that the lag time between submission of a pioneer drug to FDA and approval of that drug

⁵ Pub. L. No. 98-417, 98 Stat. 1585 (1984).

⁶ H.R. Rep. No. 98-857, pt. 1 at 16-17 (1984) ("House Report"), reprinted in 1984 U.S.C.A.N. 2647, 2649-2650 (copy attached at Tab 5); see also Gerald J. Mossinghoff, Striking the Right Balance Between Innovation and Drug Price Competition: Understanding the Hatch-Waxman Act: Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process, 54 Food Drug L. J. 187, 187-188 (1999) (copy attached at Tab 6).

consumed too many years of the drug's patent, making research and investment in new drugs unprofitable for many pharmaceutical companies.⁷ Title II of the Act allows patent holders to restore some of the time lost in regulatory review to their patent term.⁸ To provide patients with greater access to generic drugs, Congress included provisions simplifying the generic drug approval process.⁹ Nothing in the Hatch-Waxman Act stipulates or implies that its provisions should take precedence over any of FDA's other statutory obligations.

FDA and EPA would implement any Protocol decision under Title VI of the Clean Air Act Amendments of 1990 (CAA).¹⁰ Under the CAA, CFCs produced for medical devices that FDA, in consultation with EPA, has deemed to be "essential"¹¹ are exempted from the ban on CFC production.¹² Moreover, EPA may only grant essential use authorizations of CFCs to those medical devices if FDA, in consultation with EPA, has deemed such authorizations to be necessary for use in those medical devices. These provisions do not conflict with the Hatch-Waxman Act; rather, they create an additional obligation for FDA. Nevertheless, even if there were a conflict, the CAA was enacted after the Hatch-Waxman Act, and thus would be controlling.¹³

The GPIA/NPA letter also incorrectly asserts that Decision XI/15 violated the Hatch-Waxman Act by requiring research and development into CFC-free technology. It is first worth noting that the EU decision does not include an "active pursuit" provision. In addition, looking back at Decision XI/15, this Decision would have set a condition of essentiality that the MDI manufacturer demonstrate that it is either "actively pursuing" R&D on CFC-free products or is discussing licensing with a company that is actively pursuing R&D. Regardless of whether Hatch-Waxman precludes FDA from requesting research data or information as a prerequisite for approval, under its CAA authority, FDA may request information on research activities for purposes of making essentiality determinations and has in fact done so on several occasions. Even now, any company requesting essential use CFC volumes must include a description of its research and development efforts when

⁷ House Report at 15, reprinted in 1984 U.S.C.C.A.N. 2647, 2648 ("The purpose of Title II of the bill is to create a new incentive for increased expenditures for research and development of certain products which are subject to premarket governmental approval.") (see Tab 5).

⁸ 35 U.S.C. §§ 155 and 155A; Pub. L. No. 98-417, 98 Stat. 1598 (copy attached at Tab 7).

⁹ 21 U.S.C. § 355(j)(1)-(2)(A); Pub. L. No. 98-417, § 101, 98 Stat. 1585-1586 (1984) (copy attached at Tab 8).

¹⁰ CAA § 601-618, 42 U.S.C. § 7671 *et. seq.*

¹¹ CAA § 601(8), 42 U.S.C. § 7671(8) (copy attached at Tab 9).

¹² CAA § 604(d)(2), 42 U.S.C. § 7671c(d)(2) (see Tab 9).

¹³ See, e.g., Watt v. Alaska, 451 U.S. 259, 266 (1981); see also 2B N. Singer, Sutherland on Statutes and Statutory Construction § 51.02 (5th Ed.) (copies attached at Tab 10).

submitting an essential use nomination request.¹⁴ Moreover, Decision XI/15 provided an alternative to showing active pursuit of R&D for CFC-free alternatives: "engaging in good faith legal negotiations with another company in order to obtain such alternatives."

Decision XI/15 Would Protect Patient Access to MDIs Throughout the Transition

The GPIA/NPA letter states that "Decision XI/15 will wield a double-blow to patients by limiting their medical treatment choices while also likely forcing them to pay exorbitant prices for the few choices they have remaining." This statement is without basis. Patients are already presented with a wide array of choices, including MDIs, DPIs, nebulizers and tablets from a wide-range of companies, and Decision XI/15 would not have affected these choices in any way. Decision XI/15 would have deemed non-essential only those new CFC MDIs that provided no new medical benefit. Similarly, the EU decision will deem non-essential only those CFC MDI products that are not necessary for health or safety. A new CFC MDI product that offers no new medical benefit -- or is not necessary for health or safety -- offers no new choice. Moreover, as noted above, given the competitive nature of this market, there is no objective evidence to suggest "exorbitant" prices would result.

In fact, contrary to the GPIA/NPA letter's assertion, Decision XI/15 would have ensured that adequate treatment options remained available throughout the transition -- as will the EU decision. Patient choice is more likely to be restricted by the decline in CFC supply and production capacity than by the theoretical availability of new, generic CFC MDIs for a few years before the final phase-out. Already the only CFC plant approved by FDA has announced plans to close by 2003. If new CFC MDIs are permitted to enter the market, they will compete for this already dwindling supply of CFCs, perhaps resulting in a shortage of CFCs -- and thus MDIs -- before the transition is complete.

Moreover, concerning prices, the experience in other countries where CFC-free MDIs have been approved and are on the market is that these products are marketed at comparable prices to branded CFC MDIs, which confirms that the competition in this market does not permit a price premium for a CFC-free replacement product. As FDA itself has noted, in the U.S. only one drug, albuterol, has a generic and branded CFC MDI on the market. Therefore, the issue of potential

¹⁴ See TEAP Handbook on Essential Use Nominations at Appendix D.II.C (August 1997) ("[E]ach Party should request each company applying for MDI essential use exemptions to report in detail to that Party how and to what extent resources are deployed and progress is being made on research and development and what license applications, if any, have been submitted to health authorities for non-CFC alternatives.") (copy attached at Tab 11).

price variations is limited to only albuterol MDIs.¹⁵ But Decision XI/15's provision on new CFC MDIs, and the analogous provision in the EU decision, would not affect any of the 15 generic albuterol products already on the market. Under the EU decision, only products approved after December 31, 2000 would be deemed non-essential -- and only if FDA finds those products to be not necessary for health or safety. Thus the price competition that currently exists in the albuterol market in the U.S. will be unaffected by Decision XI/15 and the EU decision.

Finally, the alleged harm to patients is belied by the fact that major physician and patient groups supported Decision XI/15 and support the EU decision.

Decision XI/15 Would Have Complemented a U.S. National Transition Strategy

The GPIA/NPA letter makes two claims regarding the impact of Decision XI/15 on a domestic transition strategy. As discussed below, these claims fail to recognize that Decision IX/15 would have complemented U.S. transition policy. This is also the case for the EU decision.

- **Decision XI/15 Would Have Facilitated FDA's Ability To Make Essentiality Determinations**

The GPIA/NPA letter asserts that "FDA's approach should not be supplanted by Directive XI/15." Congress clearly intended that Title VI of the CAA be implemented in concert with the Montreal Protocol -- not in isolation from it.¹⁶ Far from supplanting FDA's proposed policy for making essentiality determinations (as proposed in its NPR), Decision XI/15 would have complemented that proposed policy by providing a mechanism for denying essentiality designations for new CFC MDIs that provide no new health benefits. The EU decision would provide the same mechanism.

The NPR is primarily focused on designing the process and criteria for removing already approved CFC medical products from the market in compliance with the Montreal Protocol and Clean Air Act. On the other hand, Decision XI/15 and the EU decision address in relevant part the introduction of not-yet-approved CFC MDI products. Thus, Decisions XI/15 and the EU decision complement rather than supplant the NPR policy.

¹⁵ See Comments of Dr. Meyer at Hearing of Pulmonary and Allergy Drugs Advisory Committee of the Food and Drug Administration Center for Drug Evaluation and Research Hearing (November 22, 1999) ("PADAC Hearing"), Hearing Transcript at 79 (copy attached at Tab 12).

¹⁶ CAA § 614(b), 42 U.S.C. § 7671m(b) (The CAA is a "supplement to the terms and conditions of the Montreal Protocol ... and shall not be construed, interpreted, or applied to abrogate the responsibilities or obligations of the United States to implement fully the provisions of the Montreal Protocol.") (see Tab 9).

- **The Flexibility of Decision XI/15 Would Have Permitted the U.S. to Tailor Its Implementation To Meet Our Country's Unique Needs**

The GPIA/NPA letter also alleges that Decision XI/15 is a "one size fits all" transition strategy, and thus unacceptable. However, both Decision XI/15 and the EU decision include flexible terms that would allow each country to implement a national transition strategy suited to its individual needs. For example, both decisions would leave the ultimate determination of whether a new product is essential up to an individual Party's national health authority.

In addition, both decisions would leave it up to each Party to develop and implement its national or regional transition strategy in a manner that best suits its particular circumstances. Specifically, the EU decision would require that each non-Article (5) Party:

Develop a national or regional transition strategy based on alternatives or substitutes that are acceptable from the standpoint of health and that includes effective criteria and measures for determining when CFC MDI product(s) is/are no longer essential in its domestic market.¹⁷

Having a transition policy based on "acceptable" alternatives and which includes "effective" criteria for determining non-essentiality cannot in any way be construed as "one size fits all".

Decision XI/15 Would Not Have Unfairly Affected the Generic Drug Industry

The GPIA/NPA letter claims that implementing Decision XI/15 would "adversely affect members of the generic drug industry who have worked for years" to develop generic CFC MDIs. But all companies have been on notice for many years that U.S. and international law require the complete phase-out of CFCs to protect the earth's ozone layer. In fact, it has been over a decade since the Montreal Protocol and the CAA established a temporary exemption for CFCs for MDIs, and Protocol decisions for several years now have noted that a transition to CFC-free products is occurring.¹⁸ As EPA and FDA have consistently stated over many years, "the essential uses under the Montreal Protocol were never meant to be permanent exemptions"¹⁹ In 1997 and 1998, FDA stated emphatically in hearings before

¹⁷ EU decision ¶ 5.a (see Tab 1).

¹⁸ Decision VIII/11, UNEP/OzL.Pro.8/12; Decision VIII/12, Id.; Decision IX/19, UNEP/OzL.Pro.9/12 (copies attached at Tab 13).

¹⁹ Comments of Erin Birgfeld, Essential Use Manager, Stratospheric Protection Division, Office of Air and Radiation, EPA, at PADAC Hearing, Hearing Transcript at 27 (see Tab 12).

Congress that “[i]t must be recognized, however, that the Montreal Protocol and Clean Air Act mandate an eventual complete ban on the production of ODS and that the essential-use exemptions allowed under the Protocol are clearly not intended, or expected, to be permanent.”²⁰ Indeed, FDA effectively put companies on notice as far back as 1977 that essential use status is temporary.²¹ In the face of this, it was a questionable business decision for any company to have continued to pursue the development of CFC MDIs. The U.S. Government’s policy should not reverse over a decade of strong U.S. and international commitments to phase out CFCs by turning a temporary and conditional exemption for MDIs into a permanent one.

Decision XI/15 Would Have Protected Patient Choice

The GPIA/NPA letter also asserts that Decision XI/15 “would interfere with the practice of medicine by unreasonably limiting the MDI choices available to the physician.” In fact, Decision XI/15 would not have interfered with the practice of medicine at all, nor will the EU decision. Physicians currently have a broad range of medicines in MDIs and other delivery systems from which to choose the treatment that best serves their patients’ needs. Neither Decision XI/15 nor the EU decision would remove any existing product from the market. In other words, physicians and patients would still be able to choose from every MDI now available for the treatment of respiratory diseases. In addition, should a new MDI or other medicine in a CFC formulation offer a new choice for treatment, FDA would have the discretion to deem that medicine essential. In fact, the EU decision’s provision on new CFC MDIs is specifically limited to new products “approved for treatment of asthma and/or COPD.”²² Thus, a new CFC-containing treatment for, *e.g.*, diabetes would be unaffected by this decision.

Furthermore, both Decision XI/15 and the EU decision would protect patient choice by ensuring that the diminishing supply of pharmaceutical-grade CFCs is not further depleted by the proliferation of new, medically unnecessary CFC MDI products. The supply of pharmaceutical-grade CFCs continues to decrease as

²⁰ Statement of John Jenkins, M.D., Director, Division of Pulmonary Drug Products, Center for Drug Evaluation and Research, FDA, Hearing Before the Subcomm. on Health and Environment of the House Comm. on Commerce on Regulatory Efforts to Phaseout Chlorofluorocarbon-Based Metered-Dose Inhalers, 105th Cong. 2nd Sess. (May 6, 1998); see also Statement of Murray M. Lumpkin, Deputy Director for Review Management, Center for Drug Evaluation and Research, FDA, Hearing Before the Subcomm. on Health and Environment of the House Comm. on Commerce on Implementation of Title VI of the 1990 Clean Air Act Amendments and Plans for the Upcoming Meeting of the Parties to the Montreal Protocol in Montreal, 105th Cong., 1st Sess. 57 (July 30, 1997) (“July 1997 Hearing”), Hearing Report at 45 (copies attached at Tab 14).

²¹ Certain Fluorocarbons (Chlorofluorocarbons) in Food, Food Additive, Drug, Animal Food, Animal Drug, Cosmetic and Medical Device Products as Propellants in Self-Pressurized Containers, 42 Fed. Reg. 24536, 24537 (May 13, 1977) (Notice of Proposed Rulemaking) (copy attached at Tab 15).

²² EU decision ¶ 2 (see Tab 1).

demand decreases. The continued introduction of new CFC MDIs will only deplete that CFC supply more quickly. As noted above, the one remaining manufacturer of pharmaceutical-grade CFCs for the U.S. is planning to shut down its plant by 2003. If a CFC shortage results, patients will be denied treatment options.

The Impact of All CFCs on the Ozone Layer Must be Taken Into Account

The GPIA/NPA letter's statement that the use of CFCs for MDIs is "minimal" when compared to other uses of CFCs is contradicted by EPA's assessment that "[t]he residual use of CFCs in MDIs is a very significant use [I]t has a measurability and significant impact on the ozone layer if it were to continue for a long period of time."²³ FDA has also concluded that "the continued use of CFC's in medical products pose[s] an unreasonable risk of long-term biological and climatic impacts."²⁴

Moreover, the Montreal Protocol was designed to eliminate all uses of ozone-depleting substances, regardless of the relative volume of a particular use. Indeed, FDA has made it clear that "[t]hrough the Clean Air Act and the Montreal Protocol, the United States has committed to eliminate the use of all CFC's"²⁵ There is a sound scientific and policy basis for this position. As the State Department stated at the July 1997 House Commerce Committee hearing, "if you took every [CFC] use and tried to extrapolate its impact on the ozone layer, it might not be very large. So virtually, because there are so many uses, [we] have to add them up to see what the impact is on the ozone layer."²⁶ In addition, "there are thousands of uses, or hundreds of uses of CFCs. If we took them one by one, we would probably not have an ozone layer left."²⁷

FDA has endorsed the soundness of this position:

[T]he environmental impact of individual uses of nonessential CFC's must not be evaluated independently, but rather must be evaluated in the context of the overall use of CFC's. Cumulative impacts can result from individually minor but collectively significant actions taking place over a period of time. Significance cannot be avoided by

²³ Statement of Paul Stolpman, Director, Office of Atmospheric Programs, EPA, July 1997 Hearing, Hearing Report at 61; see also Statement of Paul Stolpman, Hearing Before the Senate Comm. on Labor and Human Resources on Chlorofluorocarbons in the Atmosphere, 105th Cong., 2d Sess. (April 2, 1998), Hearing Report at 18-19 (see Tab 14).

²⁴ NPR, 64 Fed. Reg. at 47734 (copy attached at Tab 16).

²⁵ Id. at 47724 (emphasis added) (see Tab 16).

²⁶ Statement of Rafe Pomerance, Deputy Assistant Secretary for Environmental and Development, Department of State, July 1997 Hearing, Hearing Report at 78 (see Tab 14).

²⁷ Id. at 72 (see Tab 14).

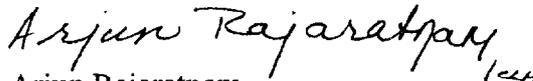
breaking an action down into small components. Although it may appear to some that CFC-MDI use is only a small part of total CFC use and therefore should be exempted, the elimination of CFC use in MDI's is only one of many steps that are part of the overall phaseout of CFC use. If each small step were provided an exemption, the cumulative effect would be to prevent environmental improvements.²⁸

Finally, as EPA eloquently stated in testimony at the July 1997 House hearing: "We must stay the course if we are to be successful in restoring the ozone layer."²⁹ Decision XI/15 would have provided the U.S. with a mechanism for doing so in a way that did not put patients at risk. The EU decision will provide the U.S. with another opportunity to do so.

* * * *

In sum, the GPIA/NPA letter provides no legal or factual basis for opposing the EU decision that in reality would be a tremendous benefit to patients and the environment. We urge the United States not to be influenced by the letter and instead to support adoption of the EU decision.

Sincerely,



Arjun Rajaratnam
Senior Counsel

cc: Robert J. Meyer, M.D.
Director, Pulmonary Drug Products Division
Food and Drug Administration
(with copies of footnoted texts)

Leanne Cusumano, Esq.
Center for Drug Evaluation and Research (HFD-1)
Food and Drug Administration
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²⁸ NPR, 64 Fed. Reg. at 47734 (CFR citations omitted) (see Tab 16).

²⁹ Statement of Paul Stolpman, July 1997 Hearing, Hearing Report at 57 (see Tab 14).



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September 21, 2000

Dockets Management Branch (HFA-305)
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Re: Proposed Change to MedWatch Form FDA 3500A [Docket number 96N-0393]

In response to the notice in the Federal Register of July 26, 2000, MDS Nordion would like to propose an addition to MedWatch Form FDA 3500A in the form of a tick box for a 30-day report under section G (All Manufacturers), sub-section 7 (Type of report).

Should you have any questions or require further information, please feel free to contact me by telephone at (613) 592-3400 ext. 2306 or by e-mail at jmilne@mds.nordion.com.

Sincerely,

A handwritten signature in cursive script that reads 'Janet Milne'.

Janet Milne
Regulatory Affairs Associate

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