Health Canada Santé Canada

Therapeutic Products Directorate
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97-023722

July 21, 1997

Letter to Main Trade Associations

Dear Sir or Madame:

Subject: Reduction in the Use of Dichloromethane in Tablet Coating Operations

Subsequent to the passage of the Canadian Environmental Protection Act (CEPA) in 1993, Environment Canada, Health Canada, industry representatives and stakeholders have been working collaboratively in a Strategic Options Process to develop a program to reduce environmental releases of dichloromethane (DCM) in Canada. Recent statistics identify the continued use of DCM in tablet coating processes as a significant point source of DCM emissions.

The Therapeutic Products Directorate supports efforts to reduce workplace exposure and environmental releases of DCM. The principle focus in the pharmaceutical sector has been the conversion from DCM-based to aqueous coating processes. In order to assist pharmaceutical companies in this endeavour, a summary of the current Directorate information and filing requirements associated with a change in tablet coatings has been prepared and is appended to this letter.

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If you have any questions related to the attachment, please do not hesitate to contact the Division of Pharmaceutical Quality, Bureau of Pharmaceutical Assessment, Therapeutic Products Directorate at (613) 941-3184 (Fax: (613) 941-0571). Questions pertaining to the Strategic Option Process should be directed to Mr. Stephen MacDonald, Toxic Substances Section, Environmental Health Directorate at 957-0382 (Fax: (613) 941-4546).

Original Signed By
Barb Benning

(for)Dann M. Michols
Director General

Enclosure

Change in Tablet Coating : Information and Filing Requirements Pursuant to the Food and Drugs Act and Regulations

This guidance addresses data and filing requirements related to changes in the tablet coating formulation/procedure/equipment that result from a switch from an organic to an aqueous coating process. For guidance on additive requirements for changes to the formulation of the tablet core that are necessitated by a conversion to an aqueous coating, please consult the Drugs Directorate Policies entitled *Bioequivalence of Proportional Formulations - Solid Oral Dosage Forms* and *Stability Requirements for Changes to Marketed New Drugs* (available under Policies on the Therapeutic Products Website at **http://www.hc-sc.gc.ca/hpb-dgps/therapeut**).

1. New Drugs

1.1 Conventional Release Solid Oral Dosage Forms:

Covers immediate release products where the coating does not play a role in the release of the drug from the drug product.

1.1.1 Test Documentation

- scientific justification for waiver of bioequivalence testing. Comparative dissolution profiles must also be an integral part of any justification. Individual and mean dissolution profile values must be provided on at least one batch produced according to the current and the proposed formulations.

- master documents for a typical production size batch for the current and the proposed formulations. All differences should be highlighted.

- certificates of analysis for at least one batch produced according to the current and the proposed formulations.

- stability data:[1]

  i) pre-market: the amount of pre-market stability data necessary to support a change from an organic-based to an aqueous coating process will depend on a number of factors, including the moisture and light sensitivity of the drug substance and the drug product.

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[1] Adapted from the Drugs Directorate Policy entitled *Stability Requirements for Changes to Marketed New Drugs.*

Where a drug is known to be stable, no pre-market data stability data may be necessary. In the case of a less stable drug, however, some accelerated data (e.g. a minimum of 3 months at 40^0C/75% RH on two batches of drug product) should be available prior to submission filing. Long term data developed at recommended storage conditions (e.g. 25^0C/60% RH for recommended storage at 15^0-30^0C) should also be provided, if available.

ii) post-market: first two production batches should be tested in accordance with the approved stability protocol.

- in accordance with GMP principles, validation/re-validation of the manufacturing process. Studies may be conducted on initial commercial batches.

Note: While pre-approval by the Directorate is required for a change in the coating material and/or coating procedure for a new drug, as described below, companies planning to convert to an aqueous-based coating for multiple products are encouraged to consult with the Directorate to discuss the possibility of developing a matrix testing plan that might lessen overall product testing while still providing adequate assurance of product equivalence for all products covered by the matrix design.

1.1.2 Filing Level

Notifiable change, provided the above information establishes the equivalence of drug product characteristics.

Note: In accordance with the Drugs Directorate Policy entitled *Sufficient Time* (also available on the Therapeutic Products (TP) Website), companies are not required to file notifiable changes with the Directorate once sufficient experience has been acquired with a specific drug product. "Sufficient time", according to the policy, represents a minimum of seven years from the initial date of marketing in Canada (drug notification). However, if "significant changes" are contemplated after the seven year period that alter or may be expected to alter the safety and effectiveness of the drug product, e.g. changes that require supporting clinical or bioequivalence data, the filing of a supplement is required and the product returns to new drug status for an additional three years.

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It is also important to note that, irrespective of whether or not pre-approval by the Therapeutic Products Directorate is required for a proposed change to a drug product, all manufacturer/distributors or importers are expected to have adequate supporting data, as described above, prior to the implementation of the change.

1.2 Modified-Release Dosage Forms

The requirements stated in section 1.1 above also apply to modified release products, with the exception of products where the coating affects drug release.

In the case of delayed-release or other modified-release preparations whose coatings affect drug release, the following conditions apply:

1.2.1 Test Documentation

As described in section 1.1.1, with the exception that bioequivalence studies must additionally be undertaken to demonstrate product equivalence.

1.2.2 Filing Level

Supplement required.

2. Drugs not in New Drug Status

Covers drugs that are subject to the filing requirements of the Drugs Directorate Guideline on the *Preparation of Drug Identification Number Submissions* (available on TP Website under Guides).

2.1 Test Documentation

As described above for New Drugs, subject to the exemptions on the conduct of bioequivalence studies, as discussed in Sections VII and VIII of the above mentioned Guideline.

2.2 Filing Level

Manufacturers are expected to have on hand adequate supporting data prior to the implementation of a proposed change, and to update the information previously provided to the Directorate, as specified in section C.01.014.4 of the Regulations to the Food and Drugs Act.

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