Health Canada Santé Canada

DRAFT GUIDANCE DOCUMENT

ADDENDUM - Quality (Chemistry and Manufacturing) Guidance: Questions and Answers

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Published by authority of the
Minister of Health

Draft Date	2016/08/31

Health Products and Food Branch

Canada

Our mission is to help the people of Canada maintain and improve their health. Health Canada	The Health Products and Food Branch's mandate is to take an integrated approach to the management of the risks and benefits to health related products and food by: • minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and, • promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health. Health Products and Food Branch

Également disponible en français sous le titre : *Ébauche de la Ligne directrice : Addenda - Qualité (chimie et fabrication) : Questions et réponses*

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 guidance documents.

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ADDENDUM - Quality (Chemistry and Manufacturing) Guidance - Questions and Answers

Questions and answers are published from time to time to provide additional clarity and interpretation of guidance. These Questions and Answers as published will be open for comment at the time they are published in the Question and Answer format. During updates to guidance, the interpretation is either incorporated into updated guidance or will be published in this addendum in the Question and Answer format.

This order of the questions in this section is listed in CTD format for ease of access.

3.2.S Drug Substance

3.2.S.4 Control of Drug Substance

Q): When qualifying a limit for an impurity in a generic product based on levels found in the Canadian Reference Product (CRP), what evidence should be submitted to show that it is the same impurity that is being analysed?

A): Generally, having the same retention time in an HPLC run using a single method, would not be considered sufficient to show the same impurity is being analysed. As such, it is recommended that samples of both the test and reference materials be spiked with the same impurity reference standard to show increased concentrations. For unidentified impurities, confirmation by another technique should be utilised, for example (e.g.), retention time comparison using a different chromatographic method, diode array spectroscopic detection.

3.2.S.5 Reference Standards or Materials

Q): What information should be submitted to validate primary and secondary reference standards?

A): A primary reference standard other than a compendial standard should be highly purified and fully characterized. All data supporting structure elucidation, strength and purity should be submitted. A certificate of analysis should also be submitted with purity assigned based on mass balance.

Secondary reference standards [working standards, house standards] should be prepared similarly to the primary reference material and standardized against the compendial reference standard or primary reference standard. Secondary reference standard should be fully characterized as to identity (IR and UV spectra should be submitted for both the primary and secondary reference standards run concomitantly) and purity, and copies of CofA should be provided.

In all cases, all purification steps used to further purify samples taken from a pilot or commercial batch for the purpose of generating a reference standard should be described.

3.2.P Drug Product

3.2.P.2 Pharmaceutical Development

Q): What is the significance of f2 while comparing dissolution test results?

A): Calculation of similarity factor, f2, is recommended to compare dissolution profiles from solid dosage forms (e.g., tablets, capsules) to establish in vitro similarity between different test samples of the same product. This comparison could be used to support a request for waiver of performing bioequivalence study.

An f2 value between 50 and 100 suggests the two dissolution profiles are considered similar. If the f2 values are below 50, an investigation should be initiated to determine the cause of apparent dissimilarity. Scientific explanation and alternative data may be considered on a case by case basis.

3.2.P.3 Manufacture

Q): Is it necessary for analytical testing facilities to meet GMP requirements?

A): Yes. Analytical tests performed by any facility must be compliant with Good Manufacturing Practices (GMP) requirements of Division 2 under the *Food and Drug Regulations*. This requirement is applicable to all Canadian distributors and importers engaged in the sale of a drug (as described in C.02.003) who either have their own testing facility or rely upon the services of another testing facility for evaluation of raw material (C.02.009), packaging material (C.02.016) finished product (C.02.018), and stability (C.02.028).

Q): What is the requirement in the pre-approval stage, in the way of data to support transportation of drug product intermediates and bulk dosage forms from one facility to another for final processing and/or packaging in the market container?

A): It should be noted that the HPFB Inspectorate's *GMP Guideline* and *Guidelines for Temperature Control of Drug Products during Storage and Transportation* provides guidance for transportation requirements for drug product in its final market container. However, at the pre-approval stage an assessment is needed of the transportation conditions of drug product intermediates (e.g., granules, coated pellets) and bulk dosage forms (e.g., bulk tablets, bulk solutions), which are transported from one manufacturing facility to another for additional processing and/or packaging in the final market containers.

Data required to support transportation of finished product intermediates and bulk dosage forms will vary, depending on the nature of the intermediate or bulk product and the mode of transportation. Transportation studies should consider conditions likely to be encountered during transportation, including exposure to elevated and depressed temperature and humidity, and reduced atmospheric pressure (such as might be encountered during air transportation), and physical stresses associated with vibration and impact. The pre-market submission should include results of, or a detailed protocol for, transportation studies, and may include tests conducted on actual shipped samples, or on samples subjected to simulated transportation conditions. Product characteristics which should be considered include, but are not limited to the following:

- assay and degradation products (all intermediates and bulk drug products)
- precipitation of dissolved solutes for solutions
- phase separation of multi-phase (disperse) systems
- settling of fines in powders and granules
- friability of tablets or granules
- container/closure integrity (e.g., liquid preparations subjected to reduced pressure).
- any other stability/performance indicating test specific to the particular drug product type

The transportation studies should be adequate to support conclusions regarding selection of appropriate bulk packaging materials, mode(s) of transportation, necessary controls on shipping conditions, and maximum hold times.

Document Change Log

Version	ADDENDUM Quality (Chemistry and Manufacturing) Guidance: Questions and Answers	**Replaces**	Not Applicable. New Guidance
Date	August 31, 2016	**Date**	