Health Canada Santé Canada

GUIDANCE DOCUMENT

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

Published by authority of the
Minister of Health

Date Adopted	2017/10/30
Effective Date	2018/01/30

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 : *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.

Document Change Log

Version	ADDENDUM Quality (Chemistry and Manufacturing) Guidance: Questions and Answers	**Replaces**	Draft Guidance
Date	January 31, 2017	**Date**	August 31, 2016
Change	August 31, 2016		
Nature of and/or Reason for Change	Guidance finalized 1. Addition of information on Quality by Design previously provided as an appendix to the 2014 Consultation.		

Table of Contents

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 high risk API, 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 sterile APIs, 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. sterile products, 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.

Q): What is <u>Health Canada's rationale for requesting specified NORs when PARs are proposed</u>?

A):

Objective

The purpose of this appendix is to provide background discussion on Health Canada's rationale for requesting that Normal Operating Ranges (NORs), which are considered to be synonymous with target operating ranges, be provided when a Proven Acceptable Range (PAR) (or multiple PARs) are proposed.

Considerations:

The following is a summary of specific issues raised frequently:

- Issue 1: NORs are maintained in batch records and in site quality management systems. NORs should not be required for registration when PARs are filed
- Issue 2: Registration of NORs are not an expectation under ICH nor for any other jurisdiction.

- Issue 3: The ICH Q8(R2) definition of PAR should be incorporated, which does not use the term NOR.

ICH Quality Guidance Documents

> *ICH Q8 (R2) Glossary Definition of a Proven Acceptable Range:*
> "A characterised range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria."

However, limited further discussion is currently provided in ICH documentation regarding PARs. In Health Canada's current experience, the primary point of confusion in ICH definition of a PAR appears to be the phrase 'while keeping **other** parameters **constant**'. The ICH documentation does not specify if the definition implies that **all** other parameters (*i.e.* both critical and non-critical) need to remain constant when a single parameter is varied. It also does not specify if 'constant' should be interpreted to be synonymous with 'target setting' or should be interpreted as meaning 'at a constant value' with this value being implied to reside within the normal operating range (NOR) for each other respective process parameter when a single parameter is varied.

Current Review Practices and Rationale

Health Canada considers NORs to represent a range around a target operational setting that contains common manufacturing variability (i.e. the range in which **unintentional** variation is reasonably anticipated during operation for a process parameter when it is set at its target value). While review practices are constantly evolving with guidance development, scientific advancement and review experience so far with QbD submissions, Health Canada currently consider requests or claims to intentionally operate two or more process parameters away from target settings simultaneously as a request/claim for a design space. The request to intentionally operate a single process parameter (at a time) off target while all other (non-critical and critical) process parameters are set at their targets (and potentially unintentionally vary within their respective NORs) is considered to be a request/claim for a PAR. Multiple PARs can be requested for the same unit operation, so long as the Applicant is clear on their intent to, at any one time, only operate a single parameter at a setting within the PAR but not on target while all others remain at their target setting (*i.e.* with potential unintentional variation within their respective NORs). As a consequence, indicating NORs clearly in QbD submissions and their associated CPIDs is considered to be necessary.

To clarify, this does not imply that process parameter targets and NORs are fixed and require regulatory approval to change. Post-approval changes to targets and NORs should be performed as per the sponsors' internal Quality Management System (ICH Q10) and filed as necessary

according to Health Canada's Post-NOC Changes: Quality Document (2013) Appendix 1 sections 3.2.S.2 change #4 and 3.2.P.3 change #25.

Based on Health Canada's current review experience, generally the supporting studies provided for PARs are developmental univariate (One variable at a time – OVAT) studies where all other parameters (critical and non-critical) are held at target settings; a simplified example is provided in Table 1 below. These OVAT studies are scientifically considered to support the PAR for the parameter in question while all other parameters are held constant at target values (*e.g.* 10 rpm and 15 min in Table 1 below). However, in combination with risk assessments and analysis as per ICH Q9, these OVAT studies are generally considered to support the proposed PAR while all other (critical and non-critical) parameters are set at their target values, but unintentionally vary within their NOR (as opposed to remaining strictly at their target setting evaluated in the study) (*e.g.* 8 – 12 rpm and 13 – 17 min in Table 1 example below) in order to account for common manufacturing variability.

Table 1: Simplified example of OVAT study process parameters

Unit Operation: Blending of excipients – proposed target settings, NORs, PARs and supporting OVAT study run process parameter settings			
Process Parameter	**Blending Speed**	**Blending Duration**	**Bin % Fill**
Proposed Target setting	10 rpm	15 min	65 %
Proposed NOR	8 - 12 rpm	13 - 17 min	65 % ± 3%
Proposed PAR	5 - 15 rpm	10 - 20 min	None
OVAT run 1	5 rpm	15 min	65 %
OVAT run 2	10 rpm	15 min	65 %
OVAT run 3	15 rpm	15 min	65 %
OVAT run 4	10 rpm	10 min	65 %
OVAT run 5	10 rpm	20 min	65 %

Providing multivariate studies to support proposed PAR(s) is also acceptable, and provides additional information beyond OVAT studies regarding the interactions between process parameters. However, when multiple PARs are proposed and an Applicant requests intentional variations of two or more PARs simultaneously away from target settings (*e.g.* 5 rpm blending speed and 10 min blend duration based on the simplified example in Table 1 above), this is considered a request for a design space and is reviewed as such.