Guidance on post-notice of compliance changes:Overall quality document for biologic and Schedule C drugs for human use

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Ligne directrice sur les changements survenus après l’avis de conformité : Document de synthèse sur la qualité pour les médicaments biologiques et les médicaments de l'Annexe C destinés à l'usage humain

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Document change log

Date	Nature of and reason for change	Location
May 15, 2026	• Initial implementation of International Council for Harmonisation (ICH) Q12 for drugs regulated by the Biologic and Radiopharmaceutical Drugs Directorate (BRDD) • Removal of references to human pharmaceutical drugs • Introduction of Level III immediate notification	• Overall quality document (for biologics and Schedule C drugs for human use) • Framework document (for biologics and Schedule C drugs for human use)

Table of Contents

Introduction

Objectives

1. To assist with the classification of quality changes made to a new drug that has received a notice of compliance (NOC).
2. To provide sponsors with recommendations on the data to support a change which would be considered sufficient to allow a determination of the impact of the change on the quality of the new drug as it relates to safety, efficacy and/or effective use of the new drug.

Scope and application

This guidance document applies to sponsors intending to make changes to drugs that have received a NOC pursuant to Section C.08.004 of the Food and Drug Regulations, that are biologics and Schedule C drugs (radiopharmaceuticals and cold kits) for human use including those submissions for which a NOC has been recommended but the issuance of the NOC has been placed on hold.

The previous *Post-Notice of Compliance (NOC) Changes: Quality Document* with the four appendices has been separated into an overall quality document and two companion guidance documents according to product lines (for biologic and Schedule C drugs). Guidance for human pharmaceuticals continues to use the previous *Post-Notice of Compliance (NOC) Changes: Quality Document* and the guidance for veterinary drugs is now in a separate document and is entitled: *Post-Notice of Compliance (NOC) Changes: Guidance for quality of veterinary drugs: Overview*. Each companion guidance document for biologic and Schedule C drugs contains detailed information on the reporting category for changes and data requirements to support each change. Therefore, this document should be read in conjunction with the following:

- Guidance on post-notice of compliance changes: Quality for biologics
- Guidance on post-notice of compliance changes: Quality for Schedule C drugs

This guidance document should also be read in conjunction with the associated Health Canada guidance documents entitled *Guidance on Post-Notice of Compliance Changes:*

Framework for Biologic and Schedule C Drugs for Human Use and *Post-Notice of Compliance (NOC) Changes: Safety and Efficacy Document* as well as other related Health Canada guidance documents. Information regarding general submission requirements and target performance standards may be found in the *Guidance on management of drug submissions and applications*.

Background

The first version of Health Canada's *Post-Notice of Compliance Changes – Quality Document* was finalized in 2009. The document was periodically updated and maintained an emphasis on applying a science-based and risk-based approach to the quality assessment of biologic and Schedule C drugs. The new suite of guidance documents will be regularly updated in an equivalent manner to support the process for introducing quality changes to marketed drugs. Sponsors are advised to consult the associated *Guidance on Post-Notice of Compliance Changes: Framework for Biologic and Schedule C Drugs for Human Use* for further background information, including a list of policies and guidance documents.

Guidance has also been updated to incorporate applicability of some of the regulatory tools and enablers in the International Council for Harmonisation (ICH) Q12 guideline entitled "Technical and regulatory considerations for pharmaceutical product lifecycle management", for example, the use of post-approval change management protocols (PACMPs) and the product lifecycle management (PLCM) document. Note that if a product is authorized under specialized "terms and conditions", ICH-Q12-based regulatory flexibility may not apply. Contact Health Canada for guidance.

Guidance on post-notice of compliance changes: Framework for biologic and Schedule C drugs for human use

Guidance for change classification – Categories

The change classification categories used by Health Canada are analogous to those used by other major regulatory agencies and fully capture the flexibility encouraged by ICH Q12. The conditions to be met for each change are meant to provide guidance with respect to the assessment of the potential risk and determination of the change classification category for a quality-related change. Specific change examples based on the application of these conditions are provided in each of the companion guidance documents. For assistance in classifying a change, sponsors are encouraged to contact Health Canada. Contact information is provided in *Guidance on Management of Drug Submissions and Applications*. Reporting categories authorized via PACMPs take precedence over what is indicated in the companion guidance documents and should be clearly identified and referenced in submission documentation, including the cover letter.

The implementation date for a quality change is important, particularly for changes introduced without prior approval, and is defined as the date the change is recorded in the company's change management system (which is typically when the first batch made after incorporating the change is released for marketing within a regulatory jurisdiction, anywhere in the world).

Sponsors are advised to exercise caution in classifying a series of changes for the same drug product intended to be implemented simultaneously or to be phased-in sequentially (that is, "bundling"), whenever those changes invoke communication, that is, involve a reporting category. Although the individual changes may be classified at a particular reporting category, collectively the changes may warrant a higher risk reporting category. Sponsors are advised to contact Health Canada for specific guidance regarding filing requirements in such cases.

Level I - Supplements (major changes)

Level I - Supplements communicate changes to information previously provided for an approved drug that are "significantly different" as they relate to the matters specified in C.08.003 (2) of the Food and Drug Regulations and have the potential to impact the safety, efficacy, quality and/or effective use of the drug.

In general, a Level I - Supplements involves the provision of extensive information to support the change and necessitates a comprehensive assessment of the primary information and any additional supporting documentation (such as where a change is supported by *in vivo* studies). This is to allow Health Canada the opportunity to fully

evaluate the proposed change and how the principles of risk management were applied, the potential for adverse effects on quality, including the identity, strength, purity or potency of the drug product as these factors may have an impact on the safety or effectiveness of the drug product, and to consider any potential effect upon market availability.

The changes included in this reporting category should be filed, along with the recommended supporting data, to Health Canada as a supplement to a new drug submission (SNDS), a supplement to an abbreviated new drug submission (SANDS), a supplement to an extraordinary use new drug submission (EUSNDS) or a supplement to an abbreviated extraordinary use new drug submission (EUSANDS). The change may not be implemented by the sponsor until a NOC has been issued.

Level II - Notifiable changes (moderate changes)

Level II - Notifiable changes communicate changes that have a moderate potential to have an adverse effect on quality, including the identity, strength, purity or potency of the drug product – factors which may have an impact on the safety or effectiveness of the drug product.

The changes included in this reporting category are applicable to biologic and Schedule C drugs only and should be filed, along with the recommended supporting data, to Health Canada as a notifiable change. Level II changes should not be implemented by the sponsor until a no objection letter (NOL) has been issued.

Level III - Notifications (minor changes)

Level III - Notifications communicate changes that have low potential to have an adverse effect on the quality, including the identity, strength, purity or potency of the drug product – factors which may have an impact on the safety or effectiveness of the drug product. The changes included in this reporting category may be implemented by the sponsor without prior review of the supporting data by Health Canada. While the risk of a significant effect on the drug product is low for these changes, Health Canada needs to be notified of these changes either immediately after implementation, or on an annual basis, as explained below.

All Level III – Notifications should be submitted using the Post-Notice of Compliance Changes: Notices of Change (Level III) Form.

Immediate notifications

In the case of immediate notifications, the changes are such that timely awareness is necessary and Health Canada should be notified within the time window extending from 21 days before and 14 days after the implementation date (see Guidance for change classification – Categories above).

This reporting category includes the majority of major and moderate changes that have been downgraded to minor quality changes as a result of the execution of a PACMP.

Annual notifications

In the case of annual notifications, sponsors are to notify Health Canada of the change during the annual drug notification period in accordance with C.01.014.5 of the Food and Drug Regulations. A communication can contain notification of multiple changes with different implementation dates (see "Guidance for change classification – Categories" above).

A Level III change should be submitted at the time the change is implemented or submitted during the annual drug notification period depending on the type of drug and the type of change (quality or safety and efficacy).

Note: Section C.01.014.5 of the Food and Drug Regulations states: Every manufacturer of a drug shall, annually before the first day of October and in a form authorized by the Director, furnish the Director with a notification signed by the manufacturer or by a person authorized to sign on his behalf, confirming that all the information previously supplied by the manufacturer with respect to that drug is correct.

Level IV – Changes not reported (quality changes with no impact)

Level IV - Changes not reported are changes not expected to have an adverse effect on the quality, including the identity, strength, quality or potency of the drug product and so not expected to have an impact on safety or effectiveness. They may be implemented without any communication with Health Canada. The changes should be managed within the relevant pharmaceutical quality system (PQS) and comply with good manufacturing practices (GMP) requirements of Division 2 of the Food and Drug Regulations. Examples of Level IV changes or general guidance on changes that are not reportable are provided in the companion guidance documents.

Guidance for implementation

General information

The associated *Guidance on Post-Notice of Compliance Changes: Framework for Biologic and Schedule C Drugs for Human Use* should be consulted for details regarding the filing of change requests and notifications to Health Canada. Documentation recommended in "Submission filing for Level I - Supplements, Level II - Supplements (Safety) and Notifiable Changes" of the aforementioned guidance should be included as part of a supplement or notifiable change (NC) filing and documentation in Level III – Immediate and Annual Notifications (minor quality changes) should be generated prior to making the changes but does not need to be submitted as part of the corresponding notification (immediate or annual – see more details under "Supporting data - Level III changes").

The change examples presented in the companion guidance documents are intended to assist with the classification of changes made to the product quality information. However, reporting categories and data provisions authorized via a PACMP take precedence over the general guidance. For convenience, the change examples are organized according to the structure of the common technical document (CTD). The information summarized in the tables provides recommendations for:

a. the conditions to be fulfilled for a given change to be classified as a Level I, II or III change. If any of the conditions outlined for a given change are not fulfilled, the change is automatically considered the next higher level of change. For example, if any of the conditions recommended for a Level II - Notifiable change are not fulfilled, the change should be reported as a Level I - Supplement.
b. the supporting data for a given change, either to be submitted to Health Canada or, where indicated, maintained on file by the sponsor and made available to Health Canada upon request within 30 days. Where applicable, the corresponding modules of the CTD for the supporting data have been identified in brackets. An adequate rationale is required when supporting data cannot be provided.
c. the change reporting category (supplement, notifiable change, immediate notification or annual notification).

As previously mentioned, it is important to note that Health Canada reserves the right to request additional information or material as deemed appropriate, or to define conditions not specifically described in this document. Sponsors should contact Health Canada when a change that may have the potential to impact product quality is not found in the tables.

Pharmaceutical product lifecycle management – Regulatory tools and enablers

Use of the following harmonized regulatory tools and enablers with associated guiding principles (as fully described in the ICH Q12 guideline), is voluntary. However, their use will enhance the management of post-approval changes and facilitate transparency between industry and Health Canada.

Established conditions

Established conditions for all products regulated by the Biologic and Radiopharmaceutical Drugs Directorate (BRDD) are outside the scope of Health Canada's initial implementation of ICH Q12. This guidance document will be revised once ICH Q12 is fully implemented.

Post-approval change management protocol

A post-approval change management protocol (PACMP), as described in ICH Q12, establishes a framework for a well-defined plan for future implementation of a quality change. This will include the tests to be done and acceptable limits to be achieved when assessing the effect of specific changes on the quality, safety or efficacy of a product. For some changes, the routine quality tests performed to release the drug substance or drug product are not considered sufficient for assessing the impact of the change and additional in-process tests and characterization tests may be needed. Note that a PACMP is not suitable whenever supportive efficacy, safety (clinical or non-clinical) or human PK or PD data is required to evaluate the effect of the change.

The purpose of a PACMP, which can be designed to be used repeatedly, is to provide transparency in the data requirements for changes and to increase the predictability of the effects of changes. This two-step process allows for the more expedient distribution of a product by permitting the sponsor to submit a protocol for a change which, if approved, may justify a reduced reporting category for the change when the supporting data are obtained and the change is implemented. However, if an On-Site Evaluation is warranted, a reduced reporting category for Step 2 cannot be granted.

Any change in reporting category and details of the supporting data to be generated will be captured in the authorized version of the PACMP. Typically, for a minor quality change that results from the execution of a PACMP, the change should be notified immediately after implementation.

For changes potentially applicable to multiple products or multiple facilities, a broader protocol can be proposed where the risks are similar and the same risk mitigation strategies are applicable, a pre-submission meeting may be appropriate. The scope of a broader PACMP should be clear and include a list of all products to which it applies. The dossier on file for each product identified in a broader PACMP should capture the information regarding its applicability. A submission can be co-filed for all impacted products or cross-referencing may be appropriate after approval of the parent submission. Contact Health Canada for specific guidance.

The use of an authorized PACMP is not obligatory but, when used, should be clearly referenced in submission documents, including the cover letter. It should be captured in the Level III form by selecting ‘PACMP’ in ‘Section B.8’ under ‘Change’. Identification of the authorized PACMP and reference to the parent control number should be provided in the free text box. Updating the dossier on file each time a PACMP is used will be accomplished through the reporting mechanism prescribed at step 2 of the protocol.

A PACMP can be provided in the original new drug submission. Otherwise, a new protocol or a change to an existing one requires submission of a supplement and issuance of a NOC. PACMPs should be captured in the certified product information document (CPID) via a hyperlink to the PLCM document or in their entirety if there is no PLCM document. For mechanisms to deal with already existing protocol-like arrangements that have been permitted in specific situations, please consult the appropriate companion guidance document or contact Health Canada.

Product lifecycle management document

As defined in ICH Q12, once authorized, the product lifecycle management (PLCM) document serves as a central repository in the dossier for negotiated established conditions (ECs) and their associated reporting categories, PACMPs and post-approval CMC commitments. It includes the key elements described below and references to the related information located elsewhere in the application. Providing the PLCM document as part of the submission is critical when the sponsor proposes ECs.

The elements of the PLCM document are summarized below. Because these elements are subject to review and negotiation, the document may contain region-specific differences.

When filed with a new submission, the PLCM document remains a draft until the submission review is complete and the PLCM document becomes authorized:

- ECs (elements not yet implemented by Health Canada):
    - The ECs for the product should be listed in the PLCM document. The identification and justification of initially proposed ECs are located in the relevant sections of the CTD.
- Reporting categories for making changes to approved ECs:
    - The reporting category associated with making a change to each EC should be listed in the PLCM document. The detailed justification of the initially proposed reporting categories is located in the relevant sections of the CTD.
- PACMPs:
    - PACMPs that are submitted to prospectively manage and implement one or more post-approval changes should be listed.
- Post-approval CMC commitments:
    - Specified CMC development activities, agreed-to by the sponsor and Health Canada at the time of authorization, (such as specific process monitoring, additional testing, process validation) that will be performed either prior to or during the commercial phase should be listed in the PLCM document.

An updated PLCM document should be included in post-approval submissions for CMC changes, as applicable.

The PLCM document should be placed in ‘Module 3, Section 3.2.R.8.’ and should be listed in the CPID via a hyperlink to the PLCM document.

Pharmaceutical development and quality by design

The ICH has developed two guidelines, Q11: Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) and Q8: Pharmaceutical Development that are relevant to generating the content expected for sections 3.2.S.2.2 to 3.2.S.2.6 and for 3.2.P.2, respectively, of a regulatory submission in the CTD format.

The pharmaceutical development section is intended to provide a comprehensive understanding of the product and manufacturing process for reviewers and inspectors.

The aim of pharmaceutical development is to design a quality product and to design its manufacturing process to consistently deliver the intended performance of the product. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of design space, specifications and manufacturing controls.

Design space is proposed by the applicant in an NDS or supplement and is subject to regulatory assessment and approval. Introducing a change while working within the design space is not considered a change that would require regulatory communication but should be documented with the requisite change controls where necessary. Movement outside of the design space is considered to be a change and would normally initiate a regulatory post-approval change process.

If approved, the details of the design space should be recorded in the CPID. Sponsors are encouraged to discuss with Health Canada when considering the establishment of a design space.

Implementation timelines of changes

The implementation date for a manufacturing change is defined as the date the change is recorded in the company's change management system (which is typically when the first batch made after incorporating the change is released for marketing within a regulatory jurisdiction, anywhere in the world).

Regardless of whether changes classified as annual notifications or immediate notifications are submitted in a supplement, the *Post-Notice of Compliance Changes - Notices of Change: Level III Form* should be submitted.

Specific details about when to file the Level III changes are provided in "Level III – Notifications (minor quality changes)" of the *Guidance on Post-Notice of Compliance Changes: Framework for Biologic and Schedule C Drugs for Human Use*.

Quality changes that result in changes to labelling

Many quality changes may affect the labelling of the product. Where the product monograph should be updated to support a change, it may be necessary to submit the labelling changes as a supplement even when the quality change is classified as a notification. For information on the requirements for reporting labelling changes, including product monograph changes, consult Health Canada's guidance documents *Questions and Answers: Plain Language Labelling Regulations for Prescription Drugs* or *Questions*

and Answers: Plain Language Labelling Regulations for Non-Prescription Drugs. These documents help clarify, differentiate or categorize which labelling changes (such as design or contents) to mock-ups (such as inner or outer labels, package insert, instructions for use (IFUs), wallet or dosing cards) warrant filing a supplement or a notification. Each guidance should be read as a stand-alone document to identify reporting categories. Where both the quality change and the labelling change require submission of a supplement, these changes may be submitted in the same supplement.

Supporting data - Level I and Level II changes

All data recommended to support the change should be provided with the submission as described in the companion guidance documents or as agreed in an approved PACMP. Where applicable, these data should be provided in the format defined by the ICH CTD. A quality overall summary (QOS) should also be completed and provided, where applicable. Refer to existing Health Canada guidance documents for further detail regarding individual product recommendations.

When recommended supporting data cannot be submitted, a detailed rationale should be provided. If the supporting data requested in a companion guidance document influences the acceptable reporting category but cannot be submitted, pre-submission advice is advisable.

Supporting data common to Level I and Level II changes

The following should be included, where applicable, in the submission package for Level I and Level II quality changes:

a. a covering letter that includes a brief narrative description and rationale of the change(s)
b. a list of changes in ‘Module 1.0.7 Note to Reviewer’ describing each in sufficient detail to allow for a quick assessment as to whether the appropriate reporting category has been used along with a table outlining the currently approved and the proposed information
c. an annotated and non-annotated electronic copy of:
    i. the relevant CPID (that is, CPID-B or CPID-R)
    ii. the product monograph or package insert and
    iii. a sample of the inner and outer labels (Level I changes require label mock-ups while Level II changes require written text in place of mock-ups) to reflect any proposed changes and

d. an annotated and non-annotated electronic copy of the relevant Health Canada quality overall summary (QOS) template or the revised sections of the QOS is preferred. However, a document clearly detailing the proposed changes may be submitted in lieu of an annotated QOS in Module 2.3.

In addition to the common information above, and as listed in “Submission filing for Level I - Supplements, Level II - Supplements (Safety) and NCs” of the *Guidance on Post-Notice of Compliance Changes: Framework for Biologic and Schedule C Drugs for Human Use*, recommendations are included in the companion guidance documents outlining the specific information to support the various quality changes.

When cross-references are made to previously submitted information, details on the cross-referenced information should be indicated in the covering letter (such as brand name of the drug product, manufacturer's or sponsor's name, submission type, control number, date approved).

Certificate of suitability

For biologics (Schedule D drugs), the use of transmissible spongiform encephalopathy (TSE) certificates of suitability to the monographs of the European Pharmacopoeia (CEPs) issued by the European Directorate for the Quality of Medicines and Healthcare of the Council of Europe (EDQM) may be provided to support raw materials, auxiliary materials and reagents at risk of transmitting BSE or TSE agents. However, they are not accepted to support changes to the drug substance used in biologics (Schedule D drugs) nor Schedule C drugs (radiopharmaceuticals and cold kits). However, sponsors are encouraged to contact Health Canada for further guidance.

Supporting data - Level III changes

Immediate notifications

The supporting data to be generated with Level III – Immediate notifications are described in the companion guidance documents or as authorized as part of a PACMPs. Supporting data not submitted with the notification should be available to Health Canada within 30 calendar days if requested at any time. Unrequested supporting data forming part of a multi-jurisdiction filing does not need to be removed.

Supporting data should only be submitted at the same time as the Level III notification form when it is indicated in companion guidance documents or when submitting an internationally harmonized CTD dossier.

Annual notifications

Data generated by the sponsor in support of a change being reported in an annual notification should not be part of the submission but should be available to Health Canada within 30 calendar days, if requested.

An annotated copy of the revised product monograph or package insert and/or CPID or other data (with the dates of implementation clearly identified) should only be submitted for a notification when identified as necessary in the companion guidance documents or, in most situations, with the filing of the next Level I – Supplement or Level II – Notifiable change that also necessitates the filing of the same type of affected document.

General guidance about what information to file for Level III changes is provided in “Level III – Immediate and Annual Notifications (minor quality changes)” of the *Guidance on Post-Notice of Compliance Changes: Framework for Biologic and Schedule C Drugs for Human Use*.

Supporting data - Level IV changes

Data to support a Level IV – Changes not reported should be managed within the relevant PQS, comply with GMP requirements of Division 2 of the Food and Drug Regulations and be available for routine GMP inspection.

Annotated versions of any affected documents (such as product monograph, package insert or CPID) should be filed with the next Level I – Supplement or Level II – Notifiable change that also necessitates the filing of the same type of affected document.

Comparative studies

Comparative in vivo studies

A number of changes outlined in the companion guidance documents include recommendations for supporting comparative *in vivo* studies (such as bridging clinical studies for biologics).

Sponsors should consult the ICH Q5E guideline and applicable Health Canada guidance documents when conducting comparative *in vivo* studies.

Comparative in vitro studies

A number of changes outlined in the companion guidance documents include recommendations for supporting comparative *in vitro* studies (such as comparative dissolution studies). Where an *in vitro* comparison is recommended to support a post-NOC change, the comparison should be made to the product manufactured according to the same formulation and the same or representative manufacturing process used in the pivotal clinical and/or comparative bioavailability studies approved for the original drug submission (such as including batch formula, manufacturing process). This is referred to as the "approved product" in the appendices.

Alternative approaches to this recommendation may be acceptable, if scientifically justified. For example, a comparison to a sponsor's marketed product (rather than the product used in the pivotal clinical and/or comparative bioavailability studies) could be justified if a significant body of information has been established for the marketed drug product.

Sponsors should refer to the general chapters available in the current Schedule B pharmacopoeia for general dissolution and drug release specifications [for example, United States Pharmacopeia (USP) <711>, USP <724>, European Pharmacopeia (Ph.Eur.) 2.9.3].

Stability testing

If stability studies are recommended to support a post-approval change, these studies should be conducted in accordance with applicable ICH and Health Canada guidance documents.

In these circumstances, the purpose of stability studies is to confirm the previously approved shelf-life and storage conditions. The scope and design of such stability studies are informed by the knowledge and experience of the drug product and drug substance acquired since authorization. For PACMPs, additional design considerations as outlined in ICH Q12, Chapter 9 may be applied.

Other potentially relevant ICH guidance documents include:

a. Stability testing of new drug substances and products [Q1A)
b. Stability testing: Photostability testing of new drug substances and products (Q1B)
c. Stability testing: Requirements for new dosage forms (Q1C)
d. Bracketing and matrixing designs for stability testing of new drug substances and products (Q1D)
e. Evaluation of stability data (Q1E)
f. Stability testing of biotechnological/biological products (Q5C)

In the case where accelerated stability studies are not routinely performed due to the nature of the product, a rationale should be provided unless previously authorized via a PACMP.

Acronyms

ASMF
active substance master file

ANDS
abbreviated new drug submission

BRDD
Biologic and Radiopharmaceutical Drugs Directorate

BSE
bovine spongiform encephalopathy

CMC
chemistry, manufacturing and controls

CPSFI
changes in product-specific facility information

CQA
critical quality attribute

CTD
common technical document

DMF
drug master file

DPIF
drug product information form

EDQM
European Directorate for the Quality of Medicines of the Council of Europe

EL
establishment licence

GMP
good manufacturing practices

HC
Health Canada

HVAC
heating, ventilation, air conditioning

ICH
International Council for Harmonisation

INN
International Non-proprietary Name

IVIVC
in-vitro, in-vivo correlation

NC
notifiable change

NDS
new drug submission

NOC
notice of compliance

PQS
pharmaceutical quality system

QC
quality control

Q1A
ICH guideline entitled “Stability testing of new drug substances and products”

Q1B
ICH guideline entitled “Stability testing: Photostability testing of new drug substances and products”

Q1C
ICH guideline entitled “Stability testing: Requirements for new dosage forms”

Q1D
ICH guideline entitled “Bracketing and matrixing designs for stability testing of new drug substance and drug product”

Q1E
ICH guideline entitled “Evaluation of stability data”

Q4b
ICH guideline entitled “Evaluation and recommendation of pharmacopoeial texts for use in the ICH regions”

Q5A
ICH guideline entitled “Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin”

Q5B
ICH guideline entitled “Analysis of the expression construct in cells used for production of r-DNA derived protein products”

Q5C
ICH guideline entitled “Stability testing of biotechnological/biological products”

Q5D
ICH guideline entitled “Derivation and characterisation of cell substrates used for production of biotechnological/biological products”

Q5E
ICH guideline entitled “Comparability of biotechnological/biological products”

Q8(R2)
ICH guideline entitled “Pharmaceutical development”

Q11
ICH guideline entitled “Development and manufacture of drug substances (chemical entities and biotechnological/biological entities)”

Q12
ICH guidelines entitled “Technical and regulatory considerations for pharmaceutical product lifecycle management”

SANDS
supplement to an abbreviated new drug submission

SNDS
supplement to a new drug submission

TSE
transmissible spongiform encephalopathy

WFI
water for injection

WHO
World Health Organization

Definitions

Adjuvant:
Component that potentiates the immune responses to an antigen and/or modulates it towards the desired immune responses. Adjuvant may be of pharmaceutical origin (chemical or synthetic adjuvant) or of biological origin (biological adjuvant).

Batch:
A quantity of drug in dosage form, a raw material or a packaging material, homogeneous within specified limits, produced according to a single production order and as attested by the signatories to the order. In the case of continuous manufacture, a batch corresponds to a defined fraction of the production that is characterized by its intended homogeneity. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch.

Biological auxiliary material:
Raw material from a biological source which is intended to be used as a processing aid in the fabrication of the drug. It may be absent from the drug or may remain as an impurity in the drug at the end of the manufacturing process (for example, biological additives used to supplement cell culture medium in production fermenter, human antithrombin III used to complex and remove human thrombin).

Biological starting material:
Raw material from a biological source which is intended to be used in the fabrication of a drug and from which the active ingredient is derived either directly (such as plasma derivatives, ascitic fluid, bovine lung, etc.) or indirectly (such as cell substrate, host or vector production cells, eggs, viral strains, etc.).

Certificate of suitability (CEP):
A certificate of compliance of a substance with the relevant requirements of the European Pharmacopoeia monographs for use in medicinal products issued by the European Directorate for the Quality of Medicine of the Council of Europe (EDQM).

Container closure system:
The sum of packaging components that together, contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product. A packaging system is equivalent to a container closure system.

Control strategy:
A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications and the associated methods and frequency of monitoring and control.

Change-over procedure:
A logical series of validated steps that ensures the proper cleaning of suites and equipment before the processing of a different product begins.

Closed process or closed system:
Process equipment or process step in which the product is not exposed to the external environment. A closed system requires that the quality of materials entering or leaving the system and the manner in which these materials are added or removed from the system is carefully controlled.

Critical manufacturing step:
A manufacturing process or step that may result in a potential change in the purity or impurity profile or that may do so because of the nature of the starting materials or the resulting product or intermediate, requires containment within a specially designed manufacturing area or production facility. This includes, for example, the development and preparation of cell banks and seed lots, initial propagation, scale-up, blood and plasma pooling and fractionation, fermentation, harvesting, inactivation, purification, addition of adjuvants or preservatives and the conjugation and pooling of bulk concentrates. It also includes the final preparation of the drug product, including concentration or diafiltration, formulation, sterile filtration, filling and lyophilization.

Critical process parameter:
A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

Critical quality attribute:
A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality.

Delayed release:
Release of a drug (or drugs) at a time other than immediately following oral administration.

Design space:
The multidimensional combination and interaction of input variables (such as material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.

Different host or media-type:
Mammalian cells or any micro-organisms involved in the manufacture of a drug substance which are different from the existing hosts in the facility or use a cell culture or fermentation medium with significantly differing composition.

Discrete chemical entity:
A single molecular entity with a known chemical structure.

Dosage form:
A drug product that has been processed to the point where it is now in a form in which it may be administered in individual doses.

Drug product:
The dosage form in the final immediate packaging intended for marketing.

Drug substance:
The unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form.

Equivalency of method:
The proposed analytical method has been validated and demonstrated to be equivalent to the approved method in term of suitability for its intended use.

Equivalent equipment:
Equipment with similar design and same operating principle and fabricated with product-contact material of same or higher grade quality. Equivalent equipment should give a product of same quality as the one processed by the previous equipment.

Excipient:
Anything other than the drug substance in the dosage form.

Extended release:
Extended release products are formulated to make the drug available over an extended

period after ingestion. This allows a reduction in dosing frequency compared to a drug presented as a conventional dosage form (for example, as a solution or an immediate release dosage form).

Facility:
A building in which a specific manufacturing operation or multiple operations take place.

Fermentation train:
Equipment and conditions involved in the stepwise expansion of the cell culture process.

Functional secondary packaging:
Packaging material not in direct contact with the product that provide additional protection or serve to deliver the product.

HVAC (heating, ventilation and air conditioning):
Industry term for the systems and technology responsible for the heating, ventilation and air conditioning in buildings. HVAC systems regulate comfort (temperature and humidity), energy efficiency and air quality.

Immediate release dosage forms:
Dosage forms that allow the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug.

In-process control:
Check performed during production in order to monitor and, if necessary, to adjust the process to ensure that the finished product conforms to its specifications. The control of the production environment or equipment may also be regarded as part of in-process control.

Interchangeable:
Where such status is indicated, any of the official texts from JP, EP or USP can be substituted one for the other (appropriately referenced) in the ICH regions for purposes of the pharmaceutical registration or approval process. Using any of the interchangeable methods, an analyst will reach the same accept or reject decisions irrespective of which PDG pharmacopeia is used.

Modified release dosage forms:
Dosage forms whose drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate release dosage form. Modified release solid oral dosage forms include both delayed and extended release drug products.

Multi-product facility:
A facility where more than one product of the same type or products from different classes are fabricated (such as pharmaceutical and biological drugs).

Non-critical area:
Area that does not encompass process steps.

Non-critical excipient:
Excipient with no active function, for example, solution used to adjust pH.

Non-critical manufacturing step:
A manufacturing process or step that has no impact upon purity and impurity profile or requires no specific facility considerations, for example, buffer and media preparation, storage of intermediates and packaging (note that some biological drugs may require critical temperature and/or light control during packaging).

Open system:
Any steps in a manufacturing process where in-process materials or components are exposed to the external environment.

Pilot scale:
A batch of a drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. For solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is the larger.

Presentation:
Container that contains the drug product. The container may be used directly or indirectly in the administration of the drug (such as vials, pre-filled syringes, pre-filled pens).

Primary container closure component:
Packaging material in direct contact with the product.

Proposed drug substance or drug product:
Drug substance and/or drug product manufactured using a process incorporating the proposed change(s).

QC approved documents:
“QC approved” means approved by the person in charge of the quality control department.

Reprocessing:
Subjecting all or part of a batch or lot of an in-process drug, a bulk process intermediate (final biological bulk intermediate) or a bulk drug of a single batch or lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications.

Schedule B pharmacopoeia:
Pharmacopoeia listed in Schedule B of the Food and Drugs Act (such as United States Pharmacopeia, European Pharmacopoeia).

Shelf-life (also referred to as expiration period):
The time period during which a drug product is expected to remain within the approved shelf-life specification, provided that it is stored under the conditions defined on the container label.

Strength:
Quantity of medicinal ingredient in a particular dosage form. For solution, concentration of the active pharmaceutical ingredient multiplied by the fill volume.

Release controlling excipient (or agent):
An excipient in the final dosage form whose primary function is to modify the duration of release of the active drug substance from the dosage form.

Unexpected events:
“Unexpected events arising during manufacture or because of stability concerns” refers to unexpected events resulting in a failure to meet specifications.

Validation:
The documented act of demonstrating that any procedure, process and activity will consistently lead to the expected results. Includes the qualification of systems and equipment.

Note about guidance documents in general

Guidance documents provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. They also provide assistance to Health Canada staff on how mandates and objectives should be met fairly, consistently and effectively.

Guidance documents are administrative, not legal, instruments. This means that Health Canada may consider alternative approaches to meeting the regulatory requirements that stakeholders may propose. However, to be acceptable, alternative approaches to the principles and practices described in this document must be supported by adequate justification. Stakeholders should discuss their proposals with the relevant program area in advance so that Health Canada can determine whether the applicable statutory or regulatory requirements can be met.

Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, to help us adequately assess the safety, efficacy or quality of a therapeutic product. We are committed to ensuring that such requests are justifiable and decisions are clearly documented.