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Bureau of Pharmaceutical Sciences
Therapeutic Products Directorate
Health Canada
Address Locator 0201D
101 Tunney's Pasture Driveway
Ottawa, Ontario K1A 0K9

**Reference:** Health Canada Quality (Chemistry and Manufacturing) Draft Guidance Document: *New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs)*

Dear Sir/Madam,

PDA appreciates the opportunity to comment on this draft guidance which is intended to update and consolidate existing guidance documents as well as to clarify information provided in Module 3 of the CTD. PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts on behalf of our Regulatory Affairs and Quality Advisory Board and Board of Directors.

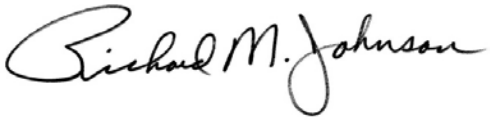
PDA recommends that discussion of GMP requirements should be left out of this guidance and included in HC Good Manufacturing Practices Guidelines GUI-0001 to avoid misunderstanding between the contents of a submission to support licensure and the requirements for routine manufacture at a site. In some sections of this guidance, especially in the manufacturing and controls section P.3, the level of detail seems to require inclusion of GMP information in the submission dossier. Specific examples are noted in the attached comments.

PDA additionally suggests using ICH standard terminology throughout the document. For example, use the Q7 term Active Pharmaceutical Ingredient (API) consistently instead of active ingredient, active substance or active moiety. PDA believes following internationally accepted standards is clearer to applicants and avoids misunderstandings or misinterpretation. In those instances where adoption of international terminology is not feasible, we

recommend that the rationale for using alternate terminology be provided to ensure that any difference in meaning can be fully understood by the reader.

If there are any questions, please do not hesitate to contact me.

Sincerely,



Richard M. Johnson
President, PDA

| General Comments | Rationale |
|---|---|
| To improve clarity and provide the most specific information to readers of this guidance, PDA recommends that all information regarding content of the QOS should be consolidated into a single section. PDA also suggests adding a reference to the QOS template on the Health Canada website. For your convenience, PDA has made note below of those areas throughout section 3.2.S which reference content of the QOS and could be consolidated.<br><br>• Lines 850-853: The QOS should include a list of the studies performed, a brief summary of results, and a conclusion from the studies (e.g. if the results support the proposed structure). The drug submission should include copies of the spectra, peak assignments, and a detailed interpretation<br>• Lines 1142: Summary of specifications in the QOS:<br>The specification can be summarized according to the table recommended in Health Canada's QOS-CE (NDS/ANDS) template including the Tests, Method Types, Sources, and Code Number/Version/Date. (…).<br>• Lines 1056-1068: Summarization of data in the QOS<br>• Lines 1142-1150: Summary of Specifications in the QOS<br>• Line 1198: The summary of the analytical procedures in the QOS should provide a sufficient level of detail to be accurate and concise. (…).<br>• Line 1250: It should be ensured that the summary of the validation reports for the analytical procedures included in the QOS provides a sufficient level of detail (…).<br>• Line 1433: The table in Health Canada's QOS-CE (NDS/ANDS) template can be used to summarize the results from the stress testing. (…).<br>• Line 2362: For purposes of summarizing analytical methods and validation in the QOS, tables in electronic format are available from Health Canada (…). | Having all the information in a single section is most convenient for applicants and readers of this guidance. |

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| PDA similarly recommends that all information regarding content for the DMF should be consolidated into a single section such as 'Drug Master Files (DMF)', from line 403 and has indicated below those sections:<br><br>• Line 560:<br>If a DMF is filed with Health Canada and cross-referenced for certain proprietary information (e.g. sections Modules S 2.2, S 2.3, S 2.4, and S 2.6), the DMF number assigned by Health Canada should be provided.<br><br>• Line 1997:<br>If a Drug Master File (DMF) is filed with Health Canada and cross-referenced for certain proprietary information, provide the DMF number assigned by Health Canada.<br><br>• Line 2561:<br>• If a Drug Master File (DMF) is filed with Health Canada and cross-referenced for certain proprietary information (e.g. composition), provide the DMF number assigned by Health Canada.<br>In addition, and in order to avoid any misunderstandings, the need to provide the DMF number as assigned by HC should be clearly stated in the general DMF section. | Again, having all the related information in a single section is most convenient for applicants and readers of this guidance. |
| PDA suggests using ICH standard terminology throughout the document. For example use API per ICH Q7 instead of the following: active ingredient – lines 1567, 1568, 1598, 2028; active substance – lines 184, 185, 200; or active moiety – lines 399, 1566, 2028. | Following internationally accepted standards is clearer to applicants and avoids any misunderstandings or misinterpretation. In those instances where adoption of international terminology is not feasible, we recommend that the rationale for using alternate terminology be provided to ensure that any difference in meaning can be fully understood by the reader. |

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| In some sections (especially in the manufacturing and controls section P.3) the level of details seems to include the requirement to include GMP requirements and information in the submission dossier. Some examples PDA recommends deleting from this document are:<br>• Lines 1835-36 discussing environmental controls<br>• Lines 1896-1905 discussing containment and prevention of cross contamination<br>• Lines 2346 requesting copies of house analytical procedures | PDA recommends that discussion of GMP requirements should be left out of this guidance and included in HC Good Manufacturing Practices Guidelines GUI-0001 to avoid misunderstanding between contents of a submission to support licensure and the requirements for routine manufacture at a site. |
| PDA recommends that HC add clear references to dossier section numbers throughout the guidance. For example:<br><br>In line 731 the text is: *The specifications for the materials (…) should be provided in the drug submission*<br>PDA recommends the reference **section S.2.2 Control of Materials – Raw Materials** be added to the end of the sentence. | More specific references will make the guidance easier to follow and provide clarity for applicants. |



**Specific Comments:**
Please note: Suggested text ~~deletions~~ are indicated with strikethrough text while **additions** are highlighted in bold text.

| Line No. | Current Text | Proposed Change | Rationale |
|---|---|---|---|
| 611, 618, 620 | Starting material | **API** Starting Material | PDA recommends use of the wording from ICH Q7 to avoid confusion and promote harmonization. |
| 730-731 | The specifications for the materials used in the synthesis, fermentation, | The specifications for the **critical and novel** materials used… | PDA recommends that specifications be provided for those materials that have |

| Line No. | Current Text | Proposed Change | Rationale |
|---|---|---|---|
| | extraction, isolation, and purification steps should be provided in the drug submission. | | potential to impact quality of API. Providing specifications for all reagents and other materials would be overly burdensome for companies and reviewers. |
| 746-748 | a letter of attestation (with supporting documentation) should be provided confirming that the material is not from a BSE/TSE affected country/area, …. | PDA requests that Health Canada provide an example of a list of affected countries and where this information could be obtained such as the BSE Portal at the World Organization for Animal Health. PDA also suggests that Health Canada consider adopting the format used in EC *Notes for Guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via medicinal products* for any needed supporting data. | To promote harmonization and use of existing tools and given that HC currently accepts TSE CEPs. |
| 750-752 | References:<br>ICH Q6A, Q11<br>Stereochemical Issues in Chiral Drug Development | PDA suggests adding the following additional references:<br>• HC's DMF guidance<br>• EDQM website for TSE certification requirements. www.edqm.eu; http://www.edqm.eu/en/Search-EDQM-website-519.html?bStat=1&sChaineRecherchee=TSE<br>• *EU: Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3); (2011/C 73/01)* | Because Health Canada already accepts TSE CEPS, a reference to the EDQM website and the EU Note for Guidance provide helpful information for applicants.<br>The DMF guidance provides an example of BSE/TSE letter (in appendix E) |

| Line No. | Current Text | Proposed Change | Rationale |
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| 1275 – 1276 | Analytical results from a GMP compliant laboratory should be provided for at least two batches from each proposed manufacturing site of the drug substance. | **Of the batches included**, analytical results from a GMP compliant laboratory… | Please clarify that this sentence refers to the same analytical data in lines 1270-1276. |
| 1659-1660 | For combination products, the compatibility of drug substances with each other should be discussed. | For ~~combination~~ products **that are a combination of multiple APIs** the compatibility…. | PDA recommends clarification by changing wording to avoid confusion with line 2837 where combination products are discussed as either medical devices or drugs according to the principal mechanism of action. |
| 1665-1666 | An API may be converted to a different chemical or physical form (e.g. in situ conversion of free base to salt, change of polymorphic form) during the drug product manufacturing process | An API may be converted to a different chemical**, stereoisomer** or physical form (e.g. in situ conversion of free base to salt, change of **stereoisomer, or** polymorphic form) during the drug product manufacturing process | Conversion to different stereoisomers needs also to be considered as noted in ICH Q7. |
| 1797 | No text | PDA recommends adding a reference section for Health Canada's Policy: Bioequivalency of Proportional Formulations | PDA appreciate the inclusion of references in various sections and encourages Health Canada to do this consistently throughout the guidance document. |
| 1800-1801 | The selection and optimization of the manufacturing process described in P3.3, in particular its critical aspects, should be explained. | The selection and optimization of the manufacturing process described in P3.3, in particular its ~~critical aspects~~ **critical control points**, should be explained. | This terminology from ICHQ9 is more precise and commonly understood. |
| 1811-1812 | The scientific rationale using the principles of risk management for the choice of the manufacturing, filling, and packaging processes that | The scientific rationale using the principles of risk management for the choice of the manufacturing, filling, and packaging processes **and storage** | PDA recommends this clarification to ensure that scientific rationale is also applied to the choice storage conditions as part of the manufacturing process. |

| Line No. | Current Text | Proposed Change | Rationale |
|---|---|---|---|
| | can influence drug product quality and performance… | **conditions** that can influence drug product quality and performance… | |
| 1815-1817 | Developmental work conducted to establish appropriate controls to avoid deterioration during the manufacturing process should be discussed (e.g. protection from heat, light or moisture, controls during wet granulation). | Developmental work conducted to establish appropriate controls to avoid deterioration during the manufacturing process **and storage** should be discussed (e.g. protection from heat, light or moisture, controls during wet granulation). | Also for clarification as above, that storage is part of the manufacturing process. |
| 1926 | Name, physical description, dimensions (e.g. thickness) | Name, physical description, dimensions (e.g. thickness, **volume, diameter)** | PDA suggests providing these additional examples as headspace on differing bottle dimensions can have impact on stability data. |
| 2007-2008 | This includes the facilities involved in the fabrication, packaging, labeling, testing, importing and distribution of the drug product. | The term "fabrication" is unique statutory language used in Canada. PDA recommends defining "fabrication" by using, or comparing it to, common international terminology (such as the definition of Manufacture provided in ICH Q7) to ensure its meaning is fully understood. | Following internationally accepted standards is clearer to applicants and avoids any misunderstandings or misinterpretation. In those instances where adoption of international terminology is not feasible, we recommend that the rationale for using alternate terminology be provided to ensure that any difference in meaning can be fully understood by the reader. |
| 2027 | The table should include all components used in the manufacturing process, regardless if they appear in the final drug product (e.g. solvents, nitrogen, silicon for stoppers). | PDA recommends that Health Canada specify the applicant provide details of drug product components either here or in section P.1. as described in lines 1564, but not both. | PDA believes that providing duplicate information is overly burdensome and leads to potential error. |
| 2072 | All routine in-process controls | All routine in-process controls should be | PDA suggests Health Canada follow |

| Line No. | Current Text | Proposed Change | Rationale |
|---|---|---|---|
| | should be listed in this section, whether critical or. If an in-process control is not critical, it is acceptable to state that it is just monitored. | listed in this section. ~~whether critical or. If an in-process control is not critical, it is acceptable to state that it is just monitored.~~. | generally accepted industry terminology where an in-process control is on its own neither critical or non-critical but is linked to a process step which is either critical or non-critical. Details about the monitoring of non-critical process steps are generally described in the GMP documentation and are not part of the CMC dossier. |