Health Canada Santé Canada

QUALITY OVERALL SUMMARY - CHEMICAL ENTITIES
(New Drug Submissions/Abbreviated New Drug Submissions)
(QOS-CE (NDS/ANDS))

(version: 2004-04-01)

FOREWORD

The *Quality Overall Summary (QOS)* (Module 2.3) is a summary that follows the scope and the outline of the Quality Body of Data (Module 3.2). This *QOS-CE (NDS/ANDS)* template can be used by sponsors to summarize the Quality information for New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs) containing drug substances and their corresponding products of synthetic or semi-synthetic origin that are filed with Health Canada pursuant to Part C, Division 8 of the *Food and Drug Regulations*. This would exclude submissions for Biotechnological/Biological (Schedule D) and Radiopharmaceutical (Schedule C) drugs.

Complete those sections and fields that apply. It is understood that certain sections and fields may not apply and should be indicated as such by reporting "Not applicable" in the appropriate area with an *accompanying explanatory note*. The use of tables to summarize the information is encouraged, where possible. The tables included in this template may need to be expanded, as necessary. These tables are included as illustrative examples of how to summarize information. Other approaches to summarize the information can be used if they fulfill the same purpose. If scanned images are incorporated into the document (e.g., synthetic schemes, molecular structures), sponsors should ensure that a low resolution is used to avoid files that are excessively large. Sponsors should consult the relevant Health Canada guidance documents for further details (e.g., *Quality Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs) for Pharmaceuticals*).

Portions of the QOS-CE (NDS/ANDS) template can also be used to summarize the Quality information contained in submissions for post-approval changes. When filing a Supplement or a Notifiable Change (NC), the *relevant components of the template* should be completed. Those sections not affected by the change should be deleted.

When completing the QOS-CE (NDS/ANDS) template, this covering *Foreword* should be deleted.

MODULE 2.3: QUALITY OVERALL SUMMARY (QOS)

INTRODUCTION

(a) Summary of product information:

Proprietary (Brand) Name of Drug Product	
Non-proprietary or Common Name of Drug Product	
Non-proprietary or Common Name of Drug Substance (Medicinal Ingredient)	
Company (Manufacturer/Sponsor) Name	
Dosage Form(s)	
Strength(s)	
Route of Administration	
Proposed Indication(s)	

(b) Other Introductory information:

2.3.S DRUG SUBSTANCE (NAME, MANUFACTURER)

2.3.S.1 General Information (name, manufacturer)

2.3.S.1.1 Nomenclature (name, manufacturer)

(a) Recommended International Non-proprietary name (INN):

(b) Compendial name, if relevant:

(c) Chemical name(s):

(d) Company or laboratory code:

(e) Other non-proprietary name(s) (e.g., national name, USAN, BAN):

(f) Chemical Abstracts Service (CAS) registry number:

2.3.S.1.2 Structure (name, manufacturer)

(a) Structural formula, including relative and absolute stereochemistry:

(b) Molecular formula:

(c) Molecular mass:

2.3.S.1.3 General Properties (name, manufacturer)

(a) Physical description (e.g., appearance, colour, physical state):

(b) Physical form (e.g., polymorphic form, solvate, hydrate):

(c) Solubilities (e.g., in common solvents, aqueous/nonaqueous solubility profile):

(d) pH and pKa values:

(e) Other (e.g., partition coefficients, melting or boiling points, optical rotation, refractive index (for a liquid), hygroscopicity, UV absorption maxima and molar absorptivity):

2.3.S.2 Manufacture (name, manufacturer)

2.3.S.2.1 Manufacturer(s) (name, manufacturer)

(a) Name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing:

(b) List of referenced Drug Master Files (DMFs) and DMF Numbers (copies of DMF letters of access should be located in Module 1):

2.3.S.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer)

(a) Flow diagram of the synthetic process(es):

(b) Brief narrative description of the manufacturing process(es):

(c) Alternate processes and explanation of their use:

(d) Reprocessing steps and justification:

2.3.S.2.3 Control of Materials (name, manufacturer)

(a) Summary of the quality and controls of the materials (e.g., raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the drug substance:

(b) For drug substances or drug substance manufactured with reagents obtained from sources that are at risk of transmitting Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform Encephalopathy (TSE) agents (e.g., ruminant origin), a letter of attestation (with supporting documentation) should be provided confirming that the material is not from a BSE/TSE affected country/area. A copy of the letter may be found in:

2.3.S.2.4 Controls of Critical Steps and Intermediates (name, manufacturer)

(a) Summary of the controls performed at critical steps of the manufacturing process and on intermediates:

2.3.S.2.5 Process Validation and/or Evaluation (name, manufacturer)

(a) Description of process validation and/or evaluation studies (e.g., for aseptic processing and sterilization):

2.3.S.2.6 Manufacturing Process Development (name, manufacturer)

(a) Description and discussion of the significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing nonclinical, clinical, comparative, stability, scale-up, pilot, and, if available, production scale batches:

2.3.S.3 Characterisation (name, manufacturer)

2.3.S.3.1 Elucidation of Structure and other Characteristics (name, manufacturer)

(a) List of studies performed (e.g., IR, UV, NMR, MS, elemental analysis) and summary of the interpretation of evidence of structure:

(b) Discussion on the potential for isomerism and identification of stereochemistry (e.g., geometric isomerism, number of chiral centres and configurations):

(c) Summary of studies performed to identify potential polymorphic forms (including solvates):

(d) Summary of studies performed to identify the particle size distribution of the drug substance:

(e) Other characteristics:

2.3.S.3.2 Impurities (name, manufacturer)

(a) Identification of potential and actual impurities arising from the synthesis, manufacture and/or degradation:

(i) List of drug-related impurities (e.g., starting materials, by-products, intermediates, chiral impurities, degradation products), including chemical name, structure, and origin:

Drug-related Impurity (chemical name or descriptor)	Structure	Origin

Drug-related Impurity (chemical name or descriptor)	Structure	Origin

(ii) List of process-related impurities (e.g., residual solvents, reagents), including compound name and step used in synthesis:

(b) Basis for setting the acceptance criteria for impurities:

(i) Maximum daily dose (i.e., the amount of drug substance administered per day), ICH Reporting/Identification/Qualification Thresholds for drug-related impurities, and Concentration Limits (ppm) for process-related impurities (e.g., residual solvents):

(ii) Data on observed impurities for relevant batches (e.g., nonclinical, clinical, and comparative):

Impurity (drug-related and process-related)	Acceptance Criteria	Results (include batch number* and use) (e.g., nonclinical, clinical, comparative)		

*** include strength, if reporting impurity levels found in the drug product (e.g., for comparative studies)**

(iii) Justification of proposed acceptance criteria for impurities:

2.3.S.4 Control of the Drug Substance (name, manufacturer)

2.3.S.4.1 Specification (name, manufacturer)

(a) Specification for the drug substance:

Standard Claimed (e.g., Professed, House, USP, BP, Ph.Eur.)		
Specification Reference Number and/or Version		
Test	**Acceptance Criteria**	**Analytical Procedure (Type/Source/Version)**

2.3.S.4.2 Analytical Procedures (name, manufacturer)

(a) Summary of the analytical procedures (e.g., key method parameters, conditions, system suitability testing):

2.3.S.4.3 Validation of Analytical Procedures (name, manufacturer)

(a) Summary of the validation information (e.g., validation parameters and results):

2.3.S.4.4 Batch Analyses (name, manufacturer)

(a) Description of the batches:

Batch Number	Batch Size	Date and Site of Production	Use (e.g., nonclinical, clinical, comparative)

(b) Summary of results for relevant batches (e.g., nonclinical, clinical, comparative):

(c) Summary of analytical procedures and validation information for those procedures not previously summarized in 2.3.S.4.2 and 2.3.S.4.3 (e.g., historical analytical procedures):

2.3.S.4.5 Justification of Specification (name, manufacturer)

(a) Justification of the drug substance specification (e.g., evolution of tests, analytical procedures, and acceptance criteria, differences from compendial standard):

2.3.S.5 Reference Standards or Materials (name, manufacturer)

(a) Source of reference standards or reference materials (e.g., House, USP, BP, Ph.Eur.):

(b) Characterization and evaluation of non-official (e.g., non-compendial) reference standards or reference materials (e.g., method of manufacture, elucidation of structure, certificate of analysis, calibration against an official standard):

2.3.S.6 Container Closure System (name, manufacturer)

(a) Description of the container closure system(s) for the storage and shipment of the drug substance:

(b) Other information on the container closure system(s):

2.3.S.7 Stability (name, manufacturer)

2.3.S.7.1 Stability Summary and Conclusions (name, manufacturer)

(a) Summary of stress testing (e.g., heat, humidity, oxidation, photolysis, acid/base): and results:

(b) Summary of accelerated and long term testing (e.g., studies conducted, protocols used, results obtained):

(c) Proposed storage conditions and re-test period (or shelf life, as appropriate):

2.3.S.7.2 Post-approval Stability Protocol and Stability Commitment (name, manufacturer)

(a) Stability protocol for commitment batches (e.g., storage conditions (including tolerances), testing frequency, number of batches and batch sizes, container closure system(s), tests and acceptance criteria):

2.3.S.7.3 Stability Data (name, manufacturer)

(a) The actual stability results (i.e., raw data) should be provided in Module 3.

(b) Summary of analytical procedures and validation information for those procedures not previously summarized in 2.3.S.4 (e.g., analytical procedures used only for stability studies):

2.3.P DRUG PRODUCT (NAME, DOSAGE FORM)

2.3.P.1 Description and Composition of the Drug Product (name, dosage form)

(a) Description of the dosage form:

(b) Composition of the dosage form:

(i) Composition, i.e., list of all components of the dosage form, and their amounts on a per unit basis (including overages, if any):

Component and Quality Standard (and Grade, if applicable)	Function	Strength (label claim)			
		Quantity per unit	%	Quantity per unit	%
Total					

(ii) Composition of all *components that are mixtures* (e.g., colourants, coatings, capsule shells, imprinting inks):

(c) Description of accompanying reconstitution diluent(s), if applicable:

(d) Type of container closure system used for the dosage form and accompanying reconstitution diluent, if applicable:

2.3.P.2 Pharmaceutical Development (name, dosage form)

2.3.P.2.1 Components of the Drug Product (name, dosage form)

2.3.P.2.1.1 Drug Substance (name, dosage form)

(a) Discussion of the:

(i) compatibility of the drug substance with excipients listed in 2.3.P.1:

(ii) key physicochemical characteristics (e.g., water content, solubility, particle size distribution, polymorphic or solid state form) of the drug substance that can influence the performance of the drug product:

(iii) for combination products, compatibility of drug substances with each other:

2.3.P.2.1.2 Excipients (name, dosage form)

(a) Discussion of the choice of excipients listed in 2.3.P.1 (e.g., their

concentrations, their characteristics that can influence the drug product performance):

2.3.P.2.2 Drug Product (name, dosage form)

2.3.P.2.2.1 Formulation Development (name, dosage form)

(a) Summary describing the development of the drug product (e.g., route of administration, usage):

(b) Discussion of the differences in the formulations for the batches used the in the *in vivo* studies (e.g., pivotal clinical, comparative bioequivalence) and the formulation described in 2.3.P.1:

(c) Description of batches used in the comparative *in vitro* studies (e.g., dissolution) and in the *in vivo* studies (e.g., pivotal clinical, comparative bioequivalence), including strength, batch number, and type of study:

(d) Summary of results for comparative *in vitro* studies (e.g., dissolution) and comparative *in vivo* studies (e.g., bioequivalence):

(e) Summary of any information on *in vitro-in vivo* correlation (IVIVC) studies (with cross-reference to the studies in Module 5):

(f) For scored tablets, provide rationale/justification for scoring:

2.3.P.2.2.2 Overages (name, dosage form)

(a) Justification of overages in the formulation(s) described in 2.3.P.1:

2.3.P.2.2.3 Physicochemical and Biological Properties (name, dosage form)

(a) Discussion of the parameters relevant to the performance of the drug product (e.g., pH, ionic strength, dissolution, particle size distribution, polymorphism, rheological properties):

2.3.P.2.3 Manufacturing Process Development (name, dosage form)

(a) Discussion of the development of the manufacturing process of the drug product (e.g., optimization of the process, selection of the method of sterilization):

(b) Discussion of the differences in the manufacturing process(es) for the batches used the in the *in vivo* studies (pivotal clinical, comparative bioequivalence) and the process described in 2.3.P.3.3:

2.3.P.2.4 Container Closure System (name, dosage form)

(a) Discussion of the suitability of the container closure system (described in

2.3.P.7) used for the storage, transportation (shipping), and use of the drug product (e.g., choice of materials, protection from moisture and light, compatibility of the materials with the dosage form):

2.3.P.2.5 Microbiological Attributes (name, dosage form)

(a) Discussion of microbiological attributes of the dosage form (e.g., preservative effectiveness studies):

2.3.P.2.6 Compatibility (name, dosage form)

(a) Discussion of the compatibility of the drug product (e.g., with reconstitution diluent(s) or dosage devices, co-administered drugs):

2.3.P.3 Manufacture (name, dosage form)

2.3.P.3.1 Manufacturer(s) (name, dosage form)

(a) Name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing:

(b) List of referenced Drug Master Files (DMFs) and DMF Numbers (copies of DMF letters of access should be located in Module 1):

(c) Confirmation that all facilities involved in the production have a Good Manufacturing Practices (GMP) compliance rating and/or an Establishment License (EL) (GMP and/or EL information should be located in Module 1):

2.3.P.3.2 Batch Formula (name, dosage form)

(a) List of all components of the dosage form to be used in the manufacturing process, and their amounts on a per batch basis (including overages, if any):

Strength (label claim)		
Master Production Document Reference Number and/or Version		
Batch Size(s) (number of dosage units)		
Component and Quality Standard (and Grade, if applicable)	**Quantity per batch**	**Quantity per batch**

Strength (label claim)		
Master Production Document Reference Number and/or Version		
Batch Size(s) (number of dosage units)		
Component and Quality Standard (and Grade, if applicable)	**Quantity per batch**	**Quantity per batch**
Total		

2.3.P.3.3 Description of Manufacturing Process and Process Controls (name, dosage form)

(a) Flow diagram of the manufacturing process:

(b) Narrative description of the manufacturing process, including equipment type and working capacity, process parameters:

(c) Justification of reprocessing of materials:

2.3.P.3.4 Controls of Critical Steps and Intermediates (name, dosage form)

(a) Summary of controls performed at the critical steps of the manufacturing process and on isolated intermediates:

2.3.P.3.5 Process Validation and/or Evaluation (name, dosage form)

(a) Summary of the process validation and/or evaluation studies conducted or a summary of the proposed validation protocol for the critical steps or critical assays used in the manufacturing process (e.g., protocol number, parameters, results):

2.3.P.4 Control of Excipients (name, dosage form)

2.3.P.4.1 Specifications (name, dosage form)

(a) Summary of the specifications for non-compendial excipients and for compendial excipients which include supplementary tests not included in the monograph(s):

(b) Confirmation that none of the excipients which appear in the drug product are prohibited for use in drugs by the Canadian *Food and Drug Regulations*:

(c) List of referenced Drug Master Files (DMFs) and DMF Numbers (copies of DMF letters of access should be located in Module 1):

2.3.P.4.2 Analytical Procedures (name, dosage form)

(a) Summary of the non-compendial analytical procedures:

2.3.P.4.3 Validation of Analytical Procedures (name, dosage form)

(a) Summary of the validation information for the non-compendial analytical procedures:

2.3.P.4.4 Justification of Specifications (name, dosage form)

(a) Justification of the specifications (e.g., evolution of tests, analytical procedures, and acceptance criteria, exclusion of certain tests, differences from compendial standard):

2.3.P.4.5 Excipients of Human or Animal Origin (name, dosage form)

(a) List of excipients that are of human or animal origin (including country of origin):

(b) Summary of the information (e.g., sources, specifications, description of the testing performed, viral safety data) regarding adventitious agents for excipients of human or animal origin:

(c) For excipients obtained from sources that are at risk of transmitting Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform Encephalopathy (TSE) agents (e.g., ruminant origin), a letter of attestation (with supporting documentation) should be provided confirming that the material is not from a BSE/TSE affected country/area. A copy of the letter may be found in:

2.3.P.4.6 Novel Excipients (name, dosage form)

(a) Summary of the details on the manufacture, characterization, and controls, with cross references to supporting safety data (nonclinical and/or clinical) on novel excipients (i.e., those used for the first time in a drug product or by a new route of administration):

2.3.P.5 Control of Drug Product (name, dosage form)

2.3.P.5.1 Specification(s) (name, dosage form)

(a) Specification(s) for the drug product:

Standard Claimed (e.g., Professed, House, USP, BP)		
Specification Reference Number and/or Version		
Test	**Acceptance Criteria (release and stability)**	**Analytical Procedure (Type/Source/Version)**

Standard Claimed (e.g., Professed, House, USP, BP)		
Specification Reference Number and/or Version		
Test	**Acceptance Criteria (release and stability)**	**Analytical Procedure (Type/Source/Version)**

2.3.P.5.2 Analytical Procedures (name, dosage form)

(a) Summary of the analytical procedures (e.g., key method parameters, conditions, system suitability testing):

2.3.P.5.3 Validation of Analytical Procedures (name, dosage form)

(a) Summary of the validation information (e.g., validation parameters and results):

2.3.P.5.4 Batch Analyses (name, dosage form)

(a) Description of the batches:

Strength and Batch Number	Batch Size	Date and Site of Production	Use (e.g., nonclinical, clinical, comparative)

(b) Summary of results for relevant batches (e.g., nonclinical, clinical, comparative):

(c) Summary of analytical procedures and validation information for those procedures not previously summarized in 2.3.P.5.2 and 2.3.P.5.3 (e.g., historical analytical procedures):

2.3.P.5.5 Characterisation of Impurities (name, dosage form)

(a) Information on the characterization of impurities, not previously provided in 2.3.S.3.2 (e.g., summary of actual and potential degradation products, basis for setting the acceptance criteria):

2.3.P.5.6 Justification of Specification(s) (name, dosage form)

(a) Justification of the drug product specification(s) (e.g., evolution of tests, analytical procedures, and acceptance criteria, differences from compendial standard):

2.3.P.6 Reference Standards or Materials (name, dosage form)

(a) Source of reference standards or reference materials (e.g., House, USP, BP, Ph.Eur.):

(b) Characterization and evaluation of non-official (e.g., non-compendial) reference standards or reference materials (e.g., method of manufacture, elucidation of structure, certificate of analysis, calibration against an official standard):

2.3.P.7 Container Closure System (name, dosage form)

(a) Description of the container closure systems, including unit count or fill size, container size or volume:

(b) Materials of construction of each primary packaging component:

(c) Summary of specifications of each primary and functional secondary (e.g., foil pouches) packaging components:

(d) List of referenced Drug Master Files (DMFs) and DMF Numbers (copies of DMF letters of access should be located in Module 1):

2.3.P.8 Stability (name, dosage form)

2.3.P.8.1 Stability Summary and Conclusions (name, dosage form)

(a) Summary of stress testing and results (e.g., photostability studies, cyclic studies for semi-solids, freeze-thaw studies):

(b) Summary of accelerated and long term testing (e.g., studies conducted, protocols used, results obtained):

(i) Description of stability study details:

Storage Conditions (˚C, % RH, light)	Strength and Batch Number	Batch Size	Container Closure System	Completed (and Proposed) Test Intervals

(ii) Summary and discussion of stability study results:

(c) Proposed storage conditions and shelf life (and in-use storage conditions and in-use period, if applicable):

2.3.P.8.2 Post-approval Stability Protocol and Stability Commitment (name, dosage form)

(a) Stability protocol for commitment batches:

Protocol Parameter	Description
Storage conditions (including tolerances)	
Testing frequency	
Number of batches per strength and batch sizes	
Container closure system(s)	
Tests and acceptance criteria	
Other	

(b) Stability protocol for continuing (i.e., ongoing) batches:

Protocol Parameter	Description
Storage conditions (including tolerances)	
Testing frequency	
Number of batches per strength and batch sizes	
Container closure system(s)	
Tests and acceptance criteria	
Other	

2.3.P.8.3 Stability Data (name, dosage form)

(a) The actual stability results (i.e., raw data) should be provided in Module 3.

(b) Summary of analytical procedures and validation information for those procedures not previously summarized in 2.3.P.5 (e.g., analytical procedures used only for stability studies):

(c) Bracketing and matrixing design and justification for commitment and/or continuing (i.e., ongoing) batches, if applicable:

2.3.A APPENDICES

2.3.A.1 Facilities and Equipment (name, manufacturer)

(a) Summary of information on facilities and equipment, in addition to the

information provided in other sections of the submission:

2.3.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)

(a) Summary of the information assessing the risk with respect to potential contamination with adventitious agents:

2.3.A.3 Excipients

(a) Summary of the details of manufacture, characterization, and controls, with cross references to supporting safety data (nonclinical and/or clinical) for the novel excipients:

(b) Summary of significant amount of data for noncompendial, nonnovel excipients:

2.3.R REGIONAL INFORMATION

2.3.R.1 Production Documentation (name, dosage form)

2.3.R.1.1 Executed Production Documents (name, dosage form)

(a) List of batches (including strengths) for which executed production documents have been provided (e.g., pivotal clinical and comparative bioequivalence batches):

2.3.R.1.2 Master Production Documents (name, dosage form)

(a) The blank master production documents for each strength, proposed batch size, and manufacturing facility should be provided in Module 3.

2.3.R.2 Medical Devices (name, dosage form)

(a) Summary of the description and details on medical devices used to deliver the dosage form that are external to the drug product (e.g., eye droppers, plastic applicators):