This is the 1st affidavit of Eric Ormsby
of Ottawa, Ontario, in this case and was
made on January 15, 2015

Court File No: T-2030-13

FEDERAL COURT

BETWEEN:

NEIL ALLARD
TANYA BEEMISH
DAVID HEBERT
SHAWN DAVEY

Plaintiffs

and

HER MAJESTY THE QUEEN IN RIGHT OF CANADA

Defendant

AFFIDAVIT # 1 OF ERIC ORMBSY

I, Eric Ormsby, public servant, of the City of Winchester, in the Province of Ontario AFFIRM THAT:

1. I am employed by Health Canada as Manager, Office of Science, Bureau of Policy, Science and International Programs, Therapeutic Products Directorate, Health Products and Food Branch, Health Canada, a role I have filled since October 2000. I have worked for Health Canada in the therapeutic products area for 33 years.

2. As the Manager, I report to Patrice Lemyre, Director, Bureau of Policy, Science and International Programs. The Therapeutic Products Directorate is part of the Health Products and Food Branch of Health Canada, headed by Anil Arora, Assistant Deputy Minister.

3. My responsibilities comprise the supervision of the Office of Science. The role of the Office of Science includes the management of scientific advisory committees, the management of dispute resolution processes and the development of science-related policies and regulations. It is also responsible to recommend therapeutic product classifications in order that the appropriate regulatory framework is applied to therapeutic products before being sold in Canada. As such, I have personal knowledge of the evidence sworn to in this affidavit, save and except where any of the following information is stated to be based on information and belief, in which case I state the source of the information and verily believe that information to be true.

I. INTRODUCTION

4. As in all developed countries around the world, prescription and non-prescription drugs are subject to government regulatory pre-market assessment and monitoring processes. In Canada, this oversight is a federal responsibility, enabled by the *Food and Drugs Act* (FDA) and *Food and Drug Regulations* (FDR). Attached hereto, and marked as **Exhibit "A"** to my affidavit, is a copy of a publication entitled "Safe, Effective, High Quality Pharmaceuticals," published by the Therapeutic Products Directorate and dated February 2006, which is a document that accurately summarizes answers to common questions regarding our mandate with respect to drugs.

5. The science-based drug regulatory assessment and monitoring processes are safeguards aimed to protect Canadians from drugs that are not safe. The current FDR help to ensure that drugs will not be available for sale if the product, throughout its life cycle, cannot demonstrate three fundamental characteristics. First, the drugs must provide a demonstrable benefit, as shown through clinical studies of diseased patients. Second, the drugs' safety issues must be capable of being mitigated through labelling and, when appropriate, limits on patient access by requiring medical prescriptions, as demonstrated through clinical studies and post-market monitoring. Third, the drugs must be of high quality and manufactured under Good Manufacturing Practices (GMP) to help to ensure that a consistently safe product is sold throughout their life cycle. The regulatory monitoring process allows the regulator to remove drugs from the market should new information on unacceptable safety concerns be identified. In these ways, regulatory oversight increases the probability that drugs on the market will be safe, effective and of the highest quality when used as recommended.

6. The FDA and the *Controlled Drugs and Substances Act* (CDSA) are distinct statutory regimes. If a drug falls under both regimes, any activity involving that drug must comply with both regimes.

7. The FDA and its regulations set out a framework for the authorization for sale of drugs in Canada. It is designed to ensure that no drug will cause major safety issues when used according to approved labelling or accompanying documentation. The CDSA and its regulations provide for additional control on substances that can alter mental processes and that may produce harm to public health and public safety when diverted or misused.

8. Cannabis is both a drug under the FDA and a controlled substance scheduled under the CDSA.

II. HISTORY AND OVERVIEW OF THE DRUG ACCESS REGULATORY FRAMEWORK IN CANADA

9. The history and evolution of the FDA and its regulations demonstrate an intentional movement toward strengthening patient/consumer health and safety through a comprehensive framework.

10. Food and drug legislation was first contained in provisions of the *Inland Revenue Act of 1874*. These provisions were replaced by the *Adulteration Act of 1885*. Then in 1920 the government repealed the earlier legislation and promulgated the FDA. Major enhancements to the FDA were passed in 1920, 1927, 1934, 1939, 1949, 1954, 1963, as well as continuous enhancements to the FDR. The FDA is legislation that was enacted in large measure to protect vulnerable populations from false claims and adulterated and ineffective drugs.

11. In 1947, the FDA and its regulations were reworked significantly, laying the foundation for the current regulations. By 1951, manufacturers were required to file new drug submissions prior to marketing their drugs under Division 1. However, the reworked regulations did not prevent the thalidomide tragedy of the early 1960s that resulted in serious birth malformations and infant deaths. This tragedy led to the modern new drug regulations in 1963.

12. The FDA first defines what a drug is. Section 2 of the FDA sets out that "drug" includes any substance or mixture of substances manufactured, sold, or represented for use in

(a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals,

(b) restoring, correcting or modifying organic functions in human beings or animals, or

(c) disinfection in premises in which food is manufactured, prepared or kept.

13. The FDA outlines a number of prohibitions on the sale of drugs in Canada. For example, Section 8 states:

> No person shall sell any drug that
>
> (a) was manufactured, prepared, preserved, packaged or stored under unsanitary conditions; or
>
> (b) is adulterated.

Section 9 states:

> (1) No person shall label, package, treat, process, sell or advertise any drug in a manner that is false, misleading or deceptive or is likely to create an erroneous impression regarding its character, value, quantity, composition, merit or safety.
>
> (2) A drug that is not labelled or packaged as required by, or is labelled or packaged contrary to, the regulations shall be deemed to be labelled contrary to subsection (1).

Section 11 states:

> No person shall manufacture, prepare, preserve, package or store for sale any drug under unsanitary conditions.

14. Under the FDR, there are three ways in which a new drug in dosage form can be authorized for sale:

    a) upon issuance of a Notice of Compliance (NOC) and a Drug identification number (a DIN);

    b) in the context of a clinical trial to which the Minister has not objected; or

    c) pursuant to a Letter of Authorization under the Special Access Program (SAP).

15. The FDA applies to all food, drugs, cosmetics, natural health products and devices sold in Canada, whether manufactured in Canada or imported. By governing their sale and advertisement, the FDA and its regulations prevent deception and work to ensure the safety of foods, drugs, cosmetics, natural health products and medical devices. The regime allows for reporting of adverse events and product recalls where information comes to light to show a product poses disproportional risks to health and safety.

16. The general prohibition in the FDA and its regulations on the sale of drugs without authorization is founded on a precautionary approach, where all drugs are presumed to pose risk and a drug may not be sold until there is sufficient evidence establishing the safety and effectiveness of the drug for the proposed condition of use. The current regulatory scheme is based on the recognition that there is extensive uncertainty regarding the effects of drugs under development and that promising treatments do not always work out.

III. MARIJUANA EXEMPTION FROM THE FDA

17. Marijuana meets the definition of a "drug" under the FDA and it is also a controlled substance listed in schedule II of the CDSA. The CDSA framework prohibits the possession, trafficking, production, importation and exportation of controlled substances, such as marijuana, except where authorized by regulation or through an exemption issued under Section 56 of the CDSA.

18. In response to the 2000 Ontario Court of Appeal decision in *R. v. Parker*, the Government of Canada made access to dried marijuana for medical purposes available to seriously ill Canadians who had the support of a medical practitioner; first by means of the *Marihuana Medical Access Regulations* (MMAR), which came into force in 2001, and then, as of June 7, 2013, the *Marihuana for Medical Purposes Regulations* (MMPR).

19. In 2003, the Ontario Court of Appeal *Hitzig* decision found the MMAR constitutionally defective because they did not provide for a reasonable access to a legal source of supply of marijuana for medical purposes. Therefore in 2003, the Government of Canada undertook to sell dried marijuana and entered into a contract with Prairie Plant Systems (PPS) by which PPS could produce dried marijuana for Health Canada's sale to those persons authorized to possess it for medical purposes pursuant to the MMAR, and who could not, or preferred not to produce it for themselves or to designate someone else to grow it for them.

20. Because the Government of Canada was now selling dried marijuana, it needed to be exempt from the FDA/FDR regime, and so the Government developed the *Marihuana Exemption Regulations* (MER) in 2003. The

MER only exempted dried marihuana produced under contract in right to her Majesty however.

21. Under the now repealed MMAR, and currently under the MMPR, a person seeking to use dried marijuana for medical purposes requires only the support of a medical practitioner to purchase dried marijuana. This process of access is significantly different than that which applies to drugs regulated under the FDA and its regulations. Such drugs would require a prescription in order for a patient to purchase the drug.

22. Under the amended 2014 MER, the FDA now applies to marijuana produced by licensed producers in accordance with the MMPR. Under the MMPR, licensed producers are prohibited from selling dried marihuana that has not been produced under sanitary conditions or that has been adulterated. Licensed producers under the MMPR are also subject to Good Production Practices as set out in the MMPR (similar to Good Manufacturing Practises as set out in the FDR).

23. Dried marijuana manipulated into other dosage forms (such as oils, tinctures or creams) would be considered new drugs in a final dosage form. Like all other drugs, they would be subject to the FDA and the FDR. Regulation of the sale of these derived products ensures that, if approved:

- the products will have the benefits claimed for specific therapeutic uses and that those benefits outweigh their risks;

- the products will be consistent in terms of quality and content;

- product labelling and monographs will contain an assessment of safety and efficacy data that can be made available to guide patients and medical practitioners in determining appropriate therapeutic treatments to specific disorders;

- the products are unadulterated and made in accordance with Good Manufacturing Practices (GMP); and

- mechanisms exist for adverse event reporting and recall in the event of unexpected negative events.

IV. AUTHORIZATION PROCESS FOR THE SALE OF PRODUCTS DERIVED FROM CANNABIS IN CANADA

24. The MMPR allow for the sale of dried marijuana only. Any other drug product made from cannabis should be accessed by Canadians through the three processes mentioned in paragraph 14 above: 1) through a Letter of Authorization issued under the SAP; 2) through a clinical trial to which the Minister has not objected; or 3) through the authorization for sale of a drug by way of a NOC and a DIN.

SPECIAL ACCESS PROGRAMME (SAP)

25. The regulatory authority to permit the sale of unauthorized drugs for emergency purposes was established in 1966 through an amendment to the FDR. In the late 1980s, all related functions were centralized under a single operational unit known at the time as the Emergency Drug Release Programme. In 1996, as part of broad organizational changes within Health Canada, the name of the Emergency Drug Release Programme was changed

to the "Special Access Programme" (SAP) as part of a decision to further consolidate all related functions within a single operational unit. Prior to this change, separate programmes had operated for biologic, pharmaceutical and non-prescription drugs.

26. The SAP is governed by sections C.08.010 and C.08.011 of the FDR. These provisions empower the Director, the Assistant Deputy Minister, Health Products and Food Branch, Health Canada with discretionary authority to issue SAP authorizations in response to requests from individual practitioners. The Director may authorize the sale of a specified quantity of drug or deny access to a drug based on the data supplied by the practitioner and other information it may have in its possession. A guidance document for industry and practitioners relating to the SAP that was adopted in 2008 and updated in 2013 is attached as Exhibit "B" to this Affidavit.

27. A practitioner is responsible for initiating a request on behalf of a patient and ensuring that the decision to prescribe the drug for a specific indication is supported by credible evidence available in the medical literature or provided by the manufacturer. The practitioner is also responsible for ensuring Health Canada receives all materials necessary for the SAP assessment. On occasion, SAP officials may ask for further information from the practitioner. Officials may also seek and review other documentation on the subject matter.

28. During a SAP assessment, the Director determines, based on the information before her or him:

    a) if the condition is a medical emergency;

b) whether all other marketed therapies have been tried and failed, considered and deemed unsuitable or are otherwise unavailable; and

c) there is credible data supporting the use, safety and efficacy of the drug for the medical emergency at issue.

29. If a SAP Letter of Authorization is issued, the Letter is transmitted to a specified manufacturer and a copy is provided to the applicant practitioner. SAP authorization permits the specified manufacturer to sell a specific quantity of the drug to a specific practitioner for a specific patient. An authorization does not compel a manufacturer to sell a drug; authorizations simply permit the sale of a drug provided the manufacturer is willing and able to supply the drug. The sale of the specified quantity of the drug under SAP is exempt from both the FDA and FDR.

30. Requests that do not satisfy the SAP requirements are denied and notice of such denial is transmitted to the applicant practitioner.

31. Although there have been requests made under SAP for products containing cannabidiol, they have been denied because they did not meet one or more of the requirements set out at paragraph 28 above.

CLINICAL TRIAL APPLICATIONS **(CTA)**

32. Drug development typically begins with a screening process in which promising molecules are identified, synthesized and tested. Molecules that pass this initial screening process are subjected to laboratory and animal

studies that characterize their basic pharmacologic properties and assess their toxicities and potential benefits.

33. Animal studies establish a number of facts including how a drug is absorbed, distributed, metabolized and excreted. Information is sought about the most effective route of administration, and the potential for drug and food interactions. Animal studies include assessment of different doses that could cause toxicity (adverse events, including organ damage and death), carcinogenicity (propensity to cause cancer), teratogenicity (propensity to cause birth defects), as well as impairment of reproduction and fertility. Information gained from animal studies is used to decide whether to proceed with clinical trials in humans.

34. If a sponsor of a new drug has developed a promising drug and now wishes to test the drug on Canadians, they must submit a Clinical Trial Application (CTA). This application is assessed mainly to ensure that the subjects/patients recruited into the study will not be placed under undue risks and that they know the potential risks of the drug. There are generally many CTAs for each drug during development, with each clinical trial providing an important part of the puzzle to characterise the risk/benefit profile of the drug.

35. The purpose of a clinical trial is to formally and systematically gather information on the safety and efficacy of a drug in humans. Clinical trials also verify the claims made by a sponsor and address the uncertainty regarding the harms or benefits of drugs in humans. Clinical trials are conducted by physicians, scientists and other health care professionals in controlled settings using internationally recognized good clinical practices.

36. Scientific and regulatory support for the broad use of a new drug can only be gained through well-designed clinical trials which compare a new drug with a placebo or an established standard of care. Such trials must be conducted within internationally accepted research methods to ensure the credibility and value of data collected which, in turn, is used to assess the balance of risks and benefits.

37. Human trials are usually performed in three phases. Phase I trials are the "first in human" trials in which an experimental drug is usually given to a small number of healthy volunteers. The goal of a Phase I trial is to determine how the drug is absorbed, distributed in the body, metabolized and excreted, as well as to estimate the initial safety and tolerability of the drug at different dosages.

38. Phase II trials are the initial trials to assess efficacy in patients for a specific indication. Due to their preliminary nature, they are also called "therapeutic exploratory studies". Some of the information gained in Phase II trials includes the best dose and frequency of the drug, the target population (e.g. those with mild or severe disease) and the best outcome measures (or study endpoints) to assess efficacy.

39. The objective of Phase III trials, also called "therapeutic confirmatory studies", is to demonstrate the safety and efficacy of the drug in the intended patient population under the intended conditions of use. Phase III trials typically enrol hundreds if not thousands of patients over the course of many months or years. The results from these trials will determine whether or not a sponsor or manufacturer will seek market authorization from regulatory authorities.

40. The provisions governing the sale of a drug for use in clinical trials are contained in Division 5 of Part C of the FDR. The use of a drug in clinical trials must also comply with the provisions of the CDSA and its regulations if the drug is listed on a Schedule of the CDSA.

41. If the benefits of a drug are not scientifically substantiated through the clinical trial data, patients may be led to believe that a product being marketed as a drug has greater benefit than it actually has. This, in turn, could possibly lead patients, to their detriment, to forego a therapy with demonstrated benefit.

42. Without a careful, progressive assessment of a drug that can systematically take all these factors into account with a minimal amount of bias, an accurate and reliable risk/benefit assessment cannot be achieved. As a result, clinical trials have developed as the standard by which objective, scientific evaluation of the risks and benefits of a drug take place.

43. The clinical trial process is intended to substantiate a drug's safety and efficacy before being marketed to reduce to the extent possible unexpected adverse effects occurring in patients who use the drug. The adverse effects of a treatment can, at times, be difficult to distinguish from the complications of the disease being treated. Clinical trial data is used to help identify the cause of such events.

44. There have been 29 approved clinical trials in Canada since 1992 for various forms of cannabis, from isolated cannabidiols to the smoking of dried cannabis.

MARKET AUTHORIZATION PROCESS

45. Under section C.01.014 of the FDR, no manufacturer shall sell a drug in dosage form, whether or not it is a new drug, unless a Drug Identification Number (DIN) has been assigned to the drug. A DIN is an 8 digit numerical code following the acronym "DIN" that identifies drug product characteristics including manufacturer, brand name, medicinal ingredient, strength of the medicinal ingredient, pharmaceutical form, and route of administration. The DIN is a unique identifier used by industry, the health care system, and the regulator to track the sale of a drug and to monitor the use of the drug in the marketplace.

46. In addition, with respect to a "new drug" under section C.08.002 of the FDR, a manufacturer cannot sell a "new drug" in Canada unless the Minister has issued a Notice of Compliance (NOC) relating to the drug manufacturer. To obtain this NOC, the manufacturer must file a "New Drug Submission" (NDS) with Health Canada. In the case of a new drug, a NDS also serves as an application for a DIN.

47. Once the manufacturer has obtained what they feel is the appropriate data for a new drug they must file a NDS with Health Canada. Health Canada assesses this information according to the regulations of Division 8 of the FDR.

48. Section C.08.002(2) of the FDR sets out the required contents of a NDS. An NDS must include:

- a description of the drug;

- the claimed benefits;

- any adverse reactions experienced;

- the identification of the manufacturer; and

- all relevant data relating to the chemistry, manufacturing and specifications of the drug.

In addition, information must be provided about the drug manufacturing facility and production machinery so as to ensure to the extent possible consistent quality of the drug once it is marketed. Finally the submission must include the animal and human trial data to establish the safety and effectiveness of a specified use of the drug for a specified patient population at a specified dose.

49. To obtain a NOC for a new drug pursuant to a NDS, the manufacturer must provide sufficient information to the Minister to enable an assessment of the safety and effectiveness of the new drug. Section C.08.002(2)(g) and (h) of the FDR provide:

"A new drug submission shall contain sufficient information and material to enable the Minister to assess the safety and effectiveness of the new drug including the following:

...

(g) detailed reports of the tests made to establish the safety of the new drug for the purpose and under the conditions of use recommended; and

(h) substantial evidence of the clinical effectiveness of the new drug for the purpose and under the conditions of use recommended.

50. The quality of a drug is determined by assessment of the chemistry and manufacturing processes used to produce it, and by tests that document the consistent potency, purity and stability of the drug during its shelf life. Review of the quality of the drug ensures it does not contain any other substances that may cause harm to patients. The following two guidelines summarize the national and international practices in this regard: (1) "Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs)" dated July 18, 2001 is attached hereto, and marked as **Exhibit "C"** to my affidavit; (2) "Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients ICH Topic Q7 A" dated October 3, 2002 is attached hereto, and marked as **Exhibit "D"** to this my affidavit. The sponsor of the submission must also provide evidence that the test batches were manufactured under GMP.

51. To ensure that sites continue to be GMP compliant, regular inspections of manufacturing sites are done by Health Canada inspectors or through co-operation agreements with other regulators.

52. The NOC is issued only after a product monograph is finalized. The product monograph is the definitive and approved summary of the conditions of use of the drug. It identifies the name of the drug, its pharmacology, its indications of use, when it should not be used, warnings, precautions,

adverse effects, dosages, formats and a listing of all non-medicinal ingredients. The product monograph is widely published and used by health care professionals in the prescribing, dispensing and use of the drug.

53. Even if a particular form of a drug has received a NOC and a DIN, any change to its uses or new dosage forms each require a filing of a new drug submission or supplemental new drug submission.

54. The source of a drug can vary. While currently drugs are typically associated with synthetic chemical manufacturing processes, the first drugs approved in the early years were plant specific. An example of this is digitalis extracted from the foxglove family of plants. Drugs can also be derived from other biologic material such as microbes, human or animal tissue.

55. Three non-dried cannabis products have been authorized for sale in Canada under the FDR, two of which continue to be sold today. The first is Sativex®, a buccal spray containing extracts of cannabis with standardized concentrations of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), which is authorized to treat certain symptoms associated with multiple sclerosis. It is also conditionally authorized for pain relief in adults with advanced cancer. The second is Cesamet®, a capsule containing nabilone, a synthetic cannabinoid authorized for the management of nausea and vomiting associated with cancer therapy. The Monographs for Sativex® and Cesamet® are attached to this my affidavit at **Exhibit "E"**. The third was Marinol®, a capsule containing synthetic THC. It was authorized for AIDS-related anorexia, as well as nausea and vomiting due to cancer chemotherapy; however, the manufacturer discontinued its sale in Canada.

POST-MARKET MONITORING OF DRUGS

56. Drugs may have rare, but important adverse effects that may only be revealed after its widespread use in the general population, followed by careful examination of post-market reported adverse event information. If further data is obtained that demonstrates that a drug's harms outweigh its benefits, authorization for its sale in Canada may be withdrawn. The Marketed Health Products Directorate of the Health Products and Food Branch carries out Health Canada's responsibilities regarding the post-market surveillance of drug use in terms of both safety and efficacy.

57. Often, as a result of a post-market review, Health Canada recommends to the sponsor that the Product Monograph be updated to notify patients and health care professionals of the new information.

58. If the risk/benefit profile of the drug has shifted where the risk now outweighs the benefit, the sponsor is warned that Health Canada will proceed with actions to remove the drug from the market. If the sponsor does not voluntarily remove the drug, Health Canada proceeds with action under C.01.013 which is the first step towards removing the drug's DINs and thus its market authorization.

59. In the absence of a drug regulation regime, such as the one set in place by the FDA/CDSA, which sets out standards and provides for compliance and enforcement capacity, consumers would not be effectively protected from the potential harms of products that purport to be therapeutic.

V. CONCLUSION

60. In summary, the regulatory approval process ensures that the manufacturer develops a drug that is well characterized, and that the production of the drug results in consistent pharmacologic properties. The process involves systematic assessment and reporting of extensive information on the drug and its effects. Furthermore, it restricts the claims a manufacturer can make about a drug, limiting claims to those areas for which there is sufficient scientific evidence.

61. The regulatory oversight provided by the FDA and its regulations is necessary to ensure that only safe and effective drugs are made available to Canadians and to protect vulnerable populations from false claims and ineffective or harmful substances being marketed as therapeutic products, dangerous practices that could cause individuals to forego established therapies in favour of untested and potentially ineffective ones.

62. By requiring drugs to undergo independent clinical evaluation, and a subsequent assessment process, both of which rely largely on internationally adopted standards, the risks associated with a drug's use and its potential benefits can be clearly identified. In this way, patients and their physicians are provided with the information necessary to make fully informed choices about whether the use of a drug is appropriate in any given circumstance.

AFFIRMED BEFORE ME)
At the city of Ottawa,)
in the Province of Ontario,)
on the 15th day of January, 2015)

Commissioner for Taking Affidavits)

ERIC ORMSBY

Sherri Laureen Szabados, a Commissioner, etc.,
Province of Ontario, for the Government of Canada,
Department of Health.
Expires December 2, 2015

This is **Exhibit "A"** referred to in the Affidavit of **ERIC ORMSBY** Affirmed before me at the City of Ottawa, in the Province of Ontario, this 15th day of January 2015.

A Commissioner for Taking Affidavits

Sherri Laureen Szabados, a Commissioner, etc.,
Province of Ontario, for the Government of Canada,
Department of Health.
Expires December 2, 2015

Safe, Effective, High Quality Pharmaceuticals

From non-prescription health products such as acetaminophen to highly potent drugs prescribed for cancer therapy, pharmaceuticals play an important role in Canadians' health and in Canada's health care system. They can save lives, prevent the spread of disease, improve our quality of life, and control pain and suffering. Health Canada believes the role of pharmaceuticals is likely to grow in the future as technological advances result in drugs that offer new treatment options.

The Health Products and Food Branch (HPFB) of Health Canada is the federal authority that regulates all pharmaceuticals meant for human use in Canada.

Pharmaceuticals: prescription and non-prescription drugs

Pharmaceuticals are mostly synthetic products made from chemicals for therapeutic use. HPFB's Therapeutic Products Directorate (TPD) is responsible for the regulation and evaluation of prescription and non-prescription pharmaceuticals in Canada.

All pharmaceuticals for use by humans in Canada are subject to the Food and Drugs Act and its regulations.

Minimizing risk, maximizing safety

New pharmaceuticals are carefully reviewed by TPD before being authorized for sale in Canada. Pharmaceutical manufacturers must submit substantive scientific evidence of a product's safety, efficacy, and quality. HPFB scientists review this evidence to determine whether the potential risks from the new pharmaceuticals are acceptable when balanced against the positive effects.

HPFB's Special Access Programme (SAP) allows health care professionals to gain limited access to pharmaceutical products that have not yet been approved for sale in Canada. Special access can be requested for emergency use or if conventional therapies have failed, are unavailable or are unsuitable to treat a patient. SAP can also respond to specific health crises, such as an outbreak of a communicable disease.

Post-Market Surveillance

TPD's commitment to public safety continues after a pharmaceutical is introduced into the health care system. TPD works closely with the HPFB Inspectorate and Marketed Health Products Directorate to monitor approved pharmaceuticals for compliance with manufacturing regulations and guidelines, advertising regulations and expected and unexpected health risks such as adverse reactions.

TPD also works with other partners and stakeholders to monitor the on-going benefits and risks of approved pharmaceuticals. These include other groups within Health Canada, scientific advisory committees, independent experts, patient and consumer groups, health professionals, other regulatory agencies, professional associations, and other levels of government.

Meeting global standards

Concern for human health transcends borders. Health Canada is recognized around the world for its product safety standards and risk management approach. HPFB participates in international regulatory cooperation work, sharing resources and knowledge with other governments around the world. TPD is a significant contributor to international harmonization efforts, especially through the creation and implementation of technical guidance and standards for the development, registration and control of pharmaceuticals.

Working smarter

Recent advances in technology and health research are contributing to an unprecedented increase in the number of new pharmaceuticals. Health Canada is working to streamline and improve its regulatory framework with the goal of giving Canadians faster access to more new pharmaceuticals while continuing to focus on public safety.

Health Canada
Health Products and Food Branch
250 Lamark Avenue
Graham Spry Building
Address Locator: 2005A
Ottawa ON K1A 0K9
Telephone: (613) 957-1806
Fax: (613) 954-3957
Email: hpfb-dgpsa@hc-sc.gc.ca
Website:
www.healthcanada.gc.ca/hpfb

Therapeutic Products Directorate
Building 2, Tunney's Pasture
Address Locator: 0701A1
Ottawa, ON K1A 0B9
Phone: (613) 941-0827
Fax: (613) 941-0825
Email: SIPDMail@hc-sc.gc.ca
Website: www.healthcanada.gc.ca/drugproducts

Canada

This is **Exhibit "B"** referred to in
the Affidavit of **ERIC ORMSBY**
Affirmed before me at the City of
Ottawa, in the Province of Ontario,
this 15th day of January 2015.

A Commissioner for Taking Affidavits

Sherri Laureen Szabados, a Commissioner, etc.,
Province of Ontario, for the Government of Canada,
Department of Health.
Expires December 2, 2015

Health Canada / Santé Canada

December 20, 2013

NOTICE

Our file number: 13-119188-196

Final Special Access Programme (SAP) for drugs Guidance Document

This document provides guidance on access to unauthorized drugs through the SAP and clarifies the mandate, intent and scope of the Programme. It outlines the process to be followed when requesting a drug through the SAP, as well as the information required to comply with Sections C.08.010 and C.08.011 of the *Food and Drug Regulations*.

This document has been updated as a result of amendments to the *Food and Drug Regulations* published in Canada Gazette Part II on June 19, 2013. The *Regulations Amending Certain Regulations concerning Prescription Drugs* (Repeal of Schedule F to the *Food and Drug Regulations*) provides for the repeal of Schedule F and incorporation by reference of a list of prescription drugs. This regulatory amendment comes into effect on December 19, 2013.

As a result of this amendment, a number of existing Guidance Documents have been identified that make reference to Schedule F and the regulatory process for assigning prescription status. Due to the replacement of Schedule F with the Prescription Drug List and the replacement of a regulatory process with an administrative process, the identified Guidance Documents required updating.

The Document Change Log has been added to reflect the changes.

Questions or concerns related to the *Guidance Document for Industry and Practitioners - Special Access Programme for Drugs* should be directed to:

Bureau of Policy, Science and International Programs
Therapeutic Products Directorate
Holland Cross, Tower B
Address Locator 3102C5
1600 Scott Street
Ottawa, Ontario
K1A 0K9

Tel.: 613-941-2108
Fax: 613-941-3194
E-mail: sapdrugs@hc-sc.gc.ca

Canada

Health Canada Santé Canada

GUIDANCE DOCUMENT FOR INDUSTRY AND PRACTITIONERS

Special Access Programme for Drugs

Published by authority of the
Minister of Health

Date Adopted	2008/01/14
Effective Date	2013/12/19

Health Products and Food Branch

Canada

Our mission is to help the people of Canada maintain and improve their health. *Health Canada*	HPFB's Mandate is to take an integrated approach to managing the health-related risks and benefits of health related to health 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 : Programme d'accès spécial - médicaments

FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with the policies and governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada's 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 scientific 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	Guidance for Industry: Special Access Program for Drugs	**Replaces**	Guidance for Industry: Special Access Program for Drugs
Date	December 19, 2013	**Date**	January 28, 2008

Change	Nature of and/or Reason for Change
December 19, 2013 Revision in Appendix A	Changes were made to the document to reflect an amendment to the *Food and Drug Regulations* that replaced Schedule F with Prescription Drug List.

TABLE OF CONTENTS

1 INTRODUCTION

1.1 Policy Objectives

To ensure that requests for special access to unauthorized[1] drugs are received, processed and decided upon effectively, consistently, and in accordance with sections C.08.010 and C.08.011 of the *Food and Drugs Regulations*.

1.2 Policy Statements

Health Canada is authorized under the *Food and Drugs Act* to regulate the safety, efficacy and quality of therapeutic products, including drugs (pharmaceuticals, radiopharmaceuticals, biologics and genetic therapies), natural health products andmedical devices. Prior to market authorization of a drug, access is usually limited to clinical trials sponsored by a manufacturer or research organization, and authorized by Health Canada through a clinical trial application. On those occasions when a drug is not available through enrollment in a clinical trial, Health Canada may allow an exemption from the *Food and Drugs Act* and its *Regulations* to permit the sale[2] of an unauthorized drug for a medical emergency.

Special access by Canadian health practitioners to unauthorized drugs is intended for serious or life-threatening conditions where conventional therapies have failed, are unsuitable, or are unavailable either as marketed products or through enrollment in clinical trials. Emergency access should be exceptional and where possible, open label or compassionate access trials should be incorporated into drug development plans to meet the needs of patients not eligible for enrollment in other pivotal trials.

The Special Access Programme (SAP) considers requests from practitioners for access to unauthorized drugs for treatment, diagnosis, or prevention of serious or life-threatening conditions when conventional therapies have been considered and ruled out, have failed, are unsuitable or unavailable. The regulatory authority supporting the Programme is discretionary and a decision to authorize or deny a request is made on a case-by-case basis by taking into consideration the nature of the medical emergency, the availability of marketed alternatives and the information provided in support of the request regarding the use, safety and efficacy of the drug. If access is granted, the practitioner agrees to report on the use of the drug including any adverse events encountered with such use and, upon request, account for all quantities received.

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1 The term "unauthorized" used throughout the document implies that sale of the drug has not commenced, pursuant to C.01.014 or that the product has been discontinued or removed from the market pursuant to C.01.014.6 and C.08.006 of the *Food and Drug Regulations*.

2 According to the *Food and Drugs Act*, "sell" includes offer for sale, expose for sale, have in possession for sale and distribute, whether or not the distribution is made for consideration.

The SAP is neither a mechanism to encourage the early use of drugs nor is it meant to circumvent clinical development of a drug or regulatory review of a submission for marketing. Access to any drug through the SAP should be limited in duration and quantity to meet emergency needs only. In the event that a drug submission is under regulatory review, access should be limited until that review is complete. Manufacturers should anticipate exceptional demand for a drug and, where possible, incorporate open-label or compassionate access clinical trials into their development plans to meet the needs of patients who might be ineligible for enrollment in other pivotal trials. Drugs accessed through the SAP do not undergo the scrutiny of a benefit-risk assessment provided within the regulatory framework applied to new drug submissions or clinical trial applications. Accordingly, authorization through SAP does not constitute an opinion that a drug is safe, efficacious or of high quality. Furthermore, an authorization through the SAP does not compel a manufacturer to sell a drug.

1.3 Scope and Application

This guidance document is intended to clarify the mandate, intent and scope of the SAP and outline:

- the process to be followed to access a drug that cannot otherwise be sold or distributed in Canada;
- the responsibilities of the practitioners, manufacturers, and Health Canada in that process;
- the information required to comply with Sections C.08.010 and C.08.011 of the *Food and Drug Regulations*.

For the purposes of this guidance document, "drugs" include pharmaceuticals, radiopharmaceuticals, biologics and natural health products[3]. It excludes medical devices[4], veterinary drugs[5] and active pharmaceutical ingredients (APIs)[6].

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3 The Natural Health Products (NHPs) finds its authority under the *Natural Health Products Regulations*, however an amendment to the regulations permits sections C.08.010 and C.08.011 of the *Food and Drug Regulations* to apply to NHPs (*Regulations Amending the Natural Health Product Regulations (Special Access)*, SOR/2004-119, May 11, 2004).

4 The Medical Device Bureau administers its own Special Access Programme and has its own Special Access Regulations contained in the *Medical Devices Regulations*. Information on how to access a medical device through the Programme is available on the Health Canada website (http://www.hc-sc.gc.ca/dhp-mps/acces/md-im/index-eng.php)

5 The Veterinary Drugs Directorate finds its authority under sections C.08.010 and C.08.011 of the *Food and Drug Regulations* and administers a similar programme called Emergency Drug Release (EDR). Information on the Veterinary EDR is available on the Veterinary Drugs Directorate website (http://www.hc-sc.gc.ca/dhp-mps/vet/edr-dmu/index-eng.php).

6 Active Pharmaceutical Ingredients (APIs) for pharmaceutical compounding are subject to the requirements of the *Food and Drug Regulations*, Division 1A - Establishment Licensing and Division 2 - Good Manufacturing Practices (GMP).

1.4 Background

The regulatory authority to permit the sale of unauthorized drugs for a medical emergency was established in 1966 through an amendment to the *Food and Drug Regulations*. For many years, this authority was initially administered by the Emergency Drug Release Programme (EDRP) within Health Canada's former Health Protection Branch. The original purpose of the EDRP was to provide access to unauthorized drugs for medical emergencies on a case-by-case basis. In the 1990's, an internal evaluation of the EDRP found that the program was increasingly being used as a means to obtain broad access to drugs that were inthe later phases of clinical trials or in the new drug submission review process. Consequently, the Programme's interpretation of the term "medical emergency" was expanded to include serious or life-threatening conditions and the EDRP was renamed as the Special Access Programme (SAP).

2 ROLES AND RESPONSIBILITIES

2.1 SAP

Requests are received by the SAP from practitioners seeking authorization for the sale of an unauthorized drug for their patient(s). Following careful consideration of the request, the SAP may either authorize a manufacturer to sell a drug to a practitioner, request additional information from the practitioner or deny the request.

The SAP undertakes the following risk management activities:

- emphasizing that marketed alternatives should always be considered and/or tried before considering the use of unauthorized drugs;
- recommending alternative mechanisms, such as clinical trials, to provide emergency access to unauthorized drugs;
- encouraging the exchange of information about drugs released through the SAP between manufacturers, practitioners and the SAP;
- monitoring issues and concerns pertaining to drugs available through the SAP;
- coordinating the dissemination of drug advisories, developed in conjunction with the manufacturer, for Healthcare Professionals respecting new information regarding drugs available through the SAP;
- reviewing documentation supporting emergency use of a nonmarketed drug prior to its first release through the SAP;
- working with the manufacturer to gather and document information about a drug, its development and regulatory status; and
- ensuring practitioners have access to current and relevant information respecting a drug available through the programme.

Information pertaining to the management of individual requests is outlined in Section 4.

The SAP reviews and tracks all Adverse Drug Reaction (ADR) reports submitted by either the practitioner or the manufacturer. In the case of a serious and unexpected ADR, the SAP will contact the manufacturer and recommend that information available on the drug be updated accordingly. The SAP may also contact the practitioner in the event of serious and unexpected ADRs.

2.2 Practitioners

The practitioner initiates a request and ensures that the decision to prescribe the drug is supported by credible evidence. Such evidence is usually found in an investigator's brochure, prescribing information from another jurisdiction, or publications in the medical literature.

It is recommended that practitioners provide their patients with information about the drug's potential risks and/or benefits as well as alternative therapies available. It is also recommended that practitioners seek informed consent from their patients.

The practitioner is responsible for reporting to both the manufacturer and the Director on the results of the use of the drug in the medical emergency, including any adverse drug reactions encountered. The practitioner must also, upon request, provide an accounting for all drug supplies received.

2.3 Manufacturers

Following authorization of a request by the SAP, the manufacturer is responsible for deciding whether or not to sell the drug. A manufacturer is under no obligation to sell an unauthorized drug and the SAP cannot compel a manufacturer to do so. A decision to invoice for a product authorized by the SAP rests with the manufacturer. Manufacturers are responsible for determining price, if any, and may consult the Patented Medicines and Pricing Review Board (PMPRB) in this regard if necessary.

The manufacturer may impose conditions on the sale of a drug to ensure that it is used in accordance with the latest information available. For instance, the manufacturer may restrict the amount of the drug sold, request further patient information, or offer a protocol for the use of the drug. Manufacturers are also responsible for providing all relevant information, such as an Investigator's Brochure, to requesting practitioners.

Foreign manufacturers are responsible for ensuring that they meet the regulatory requirements of their own country with respect to the export of drugs to Canada, especially in the case of a controlled drug. In addition, Health Canada's Office of Controlled Substances must issue an Import Permit to the manufacturer. This permit allows the drug supplies to be shipped without incident into Canada and ensures that all appropriate authorities are so notified.

Manufacturers should clearly display the SAP Letter of Authorization with other related documents, such as export permits, to facilitate clearance by the Canada Border Services Agency (CBSA).

Manufacturers are expected to ensure that significant new information respecting the safety, efficacy and quality of drugs released under the SAP is made available to practitioners and the SAP expeditiously. Should new information about a drug become available in other jurisdictions, this information should be vetted through the SAP prior to communication with practitioners.

3 INITIATING A SPECIAL ACCESS REQUEST

To initiate a Special Access Request, practitioners must complete one of the following Special Access Request (SAR) Forms.

3.1 Special Access Request- Form A

The Special Access Request (SAR) Form, Form A, should be used when the practitioner is requesting patient specific access to a drug for one or multiple patient(s) when required for immediate use or in anticipation of use in the short term.

3.2 Special Access Request for Future Use- Form B

The SAR Form for Future Use, Form B, should be used to request access to a drug is required on hand in anticipation of patients presenting with a medical emergency. The practitioner should include a clinical rationale as to why it is required on hand as opposed to requesting it for specific patients.

Both forms and their associated instructions may be accessed and downloaded from the Health Canada website.

Completed forms should be faxed, or sent by mail to:

Special Access Programme
Health Canada, Tunney's Pasture
Address Locator 3105A
K1A 0K9

Telephone: 613-941-2108
Fax: 613-941-3194
E-mail: SAPdrugs@hc-sc.gc.ca

A cover sheet is not required for forms sent by facsimile. Telephone requests should be reserved for life-threatening situations requiring immediate attention. By telephone, practitioners should be prepared to provide all of the required information using the form as a guide.

3.3 After Hours Requests

To place a request outside of the SAP regular office hours (please refer to Section 5), the On Call officer should be contacted.

The On Call officer can be reached by calling the regular business line (613-941-2108) and pressing 0. The officer will either answer directlyor return the phone call within 20 minutes. The officer will determine and discuss how the request will be processed. If authorization is granted, the officer will endeavour to contact the manufacturer immediately or before the next business day. While many manufacturers have on-call services, not all are equally accessible. In circumstances where a manufacturer does not offer an On Call service, processing of the request may be delayed until the next business day.

Practitioners should submit a completed *SAR Form* to the SAP the following day.

4 SPECIAL ACCESS REQUEST (SAR) FORM PROCESSING

4.1 Screening

Most requests are processed within 24 hours of receipt. However, given the mandate of the programme and the volume of requests received, requests are triaged to ensure that urgent matters take precedence over less urgent matters. For example, requests for blood products and certain antibiotics are given priority. Screening includes ensuring that: all sections of the form are complete; the information provided is legible; a quantity of 6 months or less is requested; the practitioner has provided their license number, and the request is signed and dated. Once a request is screened, it is forwarded to an officer for review.

4.2 Consideration

Consideration is the process by which the SAP decides whether authorization is appropriate and justified. Each request represents a unique set of circumstances and is supported to varying degrees by information provided by the practitioner. Consideration takes into account and balances the following factors (Figure 1. Request Consideration Matrix) to ensure that an emergency exists and there is credible data to support the request:

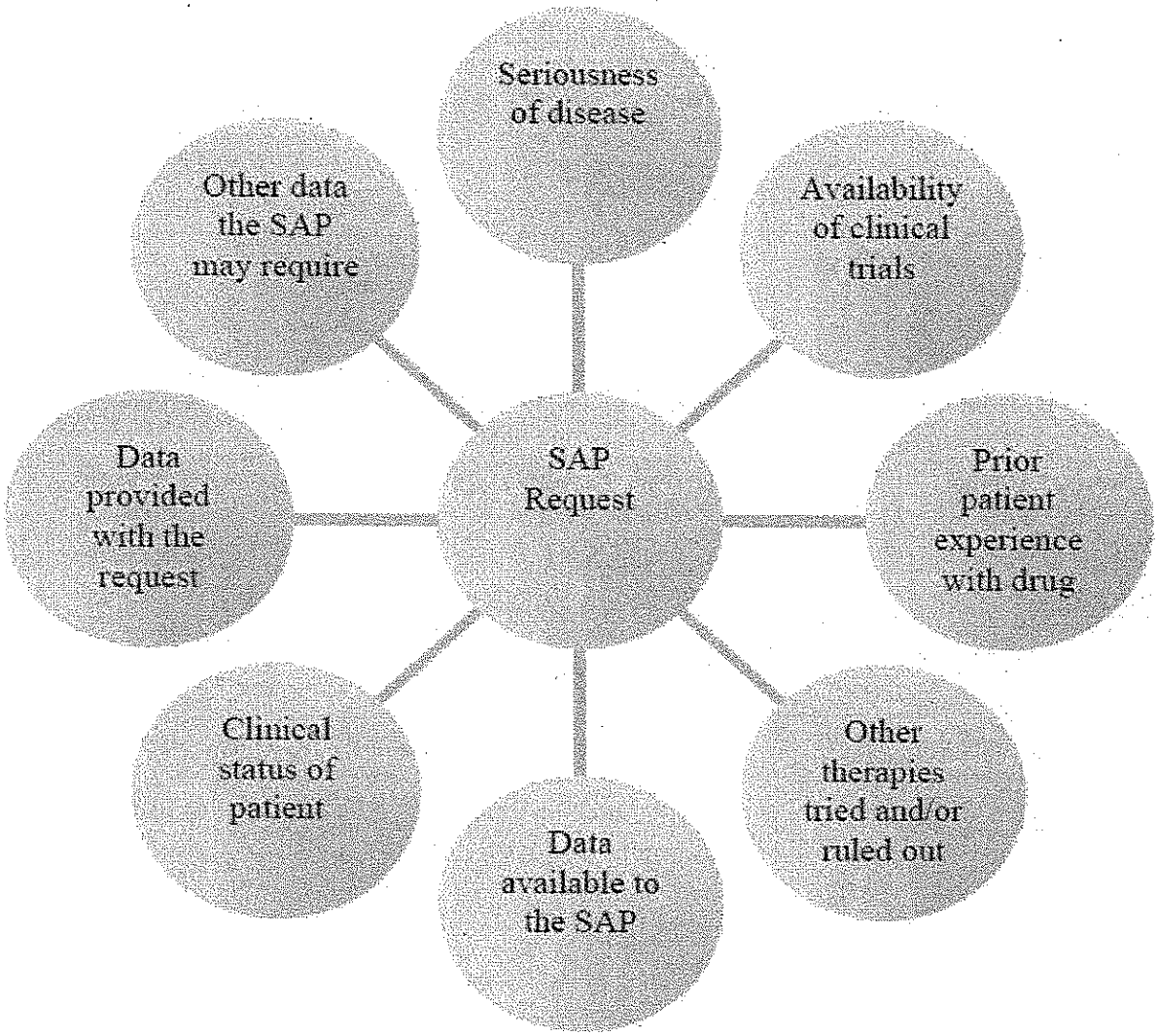

Figure 1. Request Consideration Matrix

Seriousness of disease	• description of the medical emergency for which the drug is requested
Clinical status of patient	• description of current clinical status of the patient, including prognosis
Other therapies tried and/or ruled out	• summary of marketed therapies that have failed, have been considered, ruled out or are unavailable
Prior patient experience with the drug	• summary of a patient's past experience with the drug, including evidence of efficacy and adverse drug reactions
Data provided with request	• quality and relevance of data to the medical emergency • a hierarchy of available evidence may range from: • prescribing information/package insert from the jurisdiction where the drug may be marketed • data from the literature outlining the results of randomised controlled trials • data from the literature outlining the results of non-randomised trials • case series and individual case reports from the literature **and/or;** • unpublished reports
Other data the SAP may require	• additional information from the practitioner respecting the drug or the clinical rationale
Data available to the SAP	• medical literature, treatment guidelines, investigator's brochures, information obtained from the manufacturer, clinical trial reports, consultations with Health Canada experts, etc. • consultations with expert reviewers in the Therapeutic Products Directorate and the Biologics and Genetic Therapies Directorate • confirmation of the Canadian and international development /regulatory status of the drug
Availability of clinical trials	• determine if enrollment in clinical trials is an option for an individual patient.

4.3 Special Considerations

4.3.1 Drugs that have received a negative regulatory response

The SAP will consider requests for drugs that have received a negative decision [that is (i.e.), NOD/W or NON/W] following the review of a drug submission by Health Canada or another regulatory jurisdiction provided that:

- the manufacturer agrees to disclose the concerns raised by the relevant regulator to the requesting practitioner(s).
- the manufacturer drafts a letter to requesting practitioners that includes the main concerns from the withdrawal letter.
- the relevant review bureau at Health Canada verifies that the concerns are well described.

These steps ensure that requesting practitioners and their patients are aware of all relevant information respecting the drug required to make an informed decision about its use.

4.3.2 Marketed drugs with compliance actions

The SAP will consider authorizing access to drugs following compliance action provided that:

- the drug is considered to be medically necessary for the treatment, diagnosis or prevention of a serious or life-threatening condition;
- the manufacturer is willing to publicly disclose the reasons for regulatory action;
- there are no other dosage forms of the drug on the market that would be considered a reasonable alternative;
- there are no other drugs or therapies that would be considered to be reasonable alternatives;
- a clinical trial is inappropriate under the circumstances for gathering new or confirmatory evidence of the safety and efficacy of the drug.

4.3.3 Drug shortages and discontinued drugs

In circumstances where a drug is in short supply or is discontinued from the market, the SAP will consider authorizing access to an alternative source of an otherwise marketed drug in circumstances where:

- the drug is considered to be medically necessary for the treatment, diagnosis or prevention of a serious or life-threatening condition;
- the manufacturer is willing to disclose the reasons for the shortage or

discontinuance of the drug;
- there are no other dosage forms of the drug on the market that would be considered a reasonable alternative;
- there are no other drugs or therapies that would be considered to be reasonable alternatives; and
- in the case of a drug shortage, the manufacturer demonstrates that extraordinary efforts have been made to avoid and manage the shortage such as inventory control, rationing etc.

4.4 Processing of the SAR

Following consideration of the SAR, the SAP will either authorize or deny the request. Authorized requests are sent by facsimile to the manufacturer and copied to the practitioner.

SARs that are denied are returned promptly by fax to the practitioner with explanation. The SAP may also contact the practitioner by telephone to discuss the reasons for denial and the procedures for submitting a request with additional information.

5 HOURS OF OPERATION

The SAP operates 24 hours a day, 365 days a yearRegular business hours are weekdays from8:30 am to 4:30 pm Eastern Standard Time. Outside of regular business hours and during statutory holidays[7], an On Call service is available.

6 REPORTING AND RECORD KEEPING

6.1 What to report

Practitioners agree to report to the manufacturer and to the SAP on the use of a drug and any adverse drug reactions (ADRs) encountered. The use of a drug should also be reported by practitioners using the "Patient Follow-Up Report" form found on the Health Canada website. Reporting should be on a patient by patient basis.

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7 New Year's Day -January 1; Good Friday - Friday before Easter Sunday; Easter Monday; Victoria Day - Monday on or before May 24; Canada Day -July 1; Civic Holiday - first Monday in August; Labour Day - first Monday in September; Thanksgiving Day - second Monday in October; Remembrance Day - November 11; Christmas Day - December 25; Boxing Day - December 26.

The SAP has adopted the International Conference of Harmonization (ICH) guidelines[8] to be followed for ADR reporting in regards to what should be reported and the associated timeframes. Specifically, the practitioner shall inform the SAP of any serious unexpected adverse drug reaction within 15 days after becoming aware of the information if the reaction is neither fatal nor life threatening and within seven days after becoming aware of the information if it is fatal or life threatening. ADRs should be reported using the Council for International Organizations of Medical Sciences (CIOMS) forms and sent by facsimile to the SAP (please refer to section 3 for contact information).

Reports from use other than through the SAP, both national and international, should not be reported.

6.2 Record Keeping

Consistent with the conduct of clinical trials in Canada, it is recommended that the practitioner maintain all records for a period of 25 years, in a manner that permits rapid retrieval if necessary. At any time the SAP may request that practitioners account for all quantities of drugs received under the auspices of the SAP.

The manufacturer is required to maintain complete and accurate records of all SAP transactions in a manner that permits rapid response to specific requests to verify the distribution of drug supplies to practitioners.

The SAP maintains electronic and paper records of all Letters of Authorization and Denial issued and all paper records of authorized and denied requests. In addition, the SAP keeps electronic records of requests that are returned as incomplete.

6.3 Return of Unused Products

As a general rule, unused supplies of a drug should bereturned to the manufacturer. Indeed some manufacturers require and enforce this policy. However, practitioners may request that unused supplies of a drug be transferred to a new patient by submitting a SAR and indicating the quantity to be transferred.

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8 E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (http://www.ich.org/cache/compo/475-272-1.html#E2A)

7 ADVERTISING

In accordance with section 3 of the *Food and Drugs Act* and section C.08.002 of the *Food and Drug Regulations*, advertising of unauthorized drugs accessed through the SAP is strictly prohibited.

APPENDIX A - Definitions

Adverse drug reaction (ADR): as per the *Food and Drug Regulations*, means noxious and unintended response to a drug which occurs with use or testing for the diagnosis, treatment or prevention of a disease or the modification of an organic function.

ADR reports: a summary of the patient's unexpected adverse drug reactions, as defined below, to the drug. For the most part, ADRs are only *suspected* associations, however, a temporal or possible association is sufficient for a report to be made. Reporting an ADR does not imply a causal link, rather it is a precautionary measure.

Biologic(al) drug: A drug listed under Schedule D of the *Food and Drugs Act*.

Drug: as per the *Food and Drugs Act*, includes any substance or mixture of substances manufactured, sold or represented for use in (a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals, (b) restoring, correcting or modifying organic functions in human beings or animals, or (c) disinfection in premises in which food is manufactured, prepared or kept.

Serious/Life-Threatening: In defining whether a condition is 'serious', Health Canada believes that a matter of discretionary judgement is required. Factors such as survival, day-to-day functioning or the likelihood that the disease if left untreated, will progress from a less severe condition to a more serious one are all taken into account. The latter includes, but is not limited to: acquired immunodeficiency syndrome (AIDS); all other stages of human immunodeficiency virus (HIV) infection; Alzheimer's dementia; Amyotrophic Lateral Sclerosis (ALS); Angina Pectoris; Heart Failure; Cancer; and other diseases that are clearly serious in their full manifestations. 'Serious' conditions are generally associated with morbidity with a substantial impact on day-to-day functioning.

Notice of Compliance (NOC): a notification, issued pursuant to paragraph C.08.004(1)(a) or C.08.004(3)(a), indicating that a manufacturer has complied with sections C.08.002 or C.08.003 and C.08.005.1 of the *Food and Drug Regulations*. Notices of Compliance are issued to a manufacturer following the satisfactory review of a submission.

Notice of Deficiency (NOD): If deficiencies and/or significant omissions that preclude continuing the review are identified during the review of a submission, a NOD will be issued.

Notice of Deficiency - Withdrawal (NOD/W): When the response to a NOD is received, a new Screening 1 period (with an associated performance target) begins. If during the screening process, the response to a NOD is found to contain unsolicited information, is incomplete or deficient, the response to the NOD will be rejected and the submission will be considered withdrawn without prejudice to a refiling. A NOD-Withdrawal Letter will be issued by Health Canada.

Notice of Non-compliance (NON): After the comprehensive review of a submission is complete, a NON will be issued if the submission is deficient or incomplete in complying with the requirements outlined in the *Food and Drugs Act and Regulations*.

Notice of Non-compliance - Withdrawal (NON/W): When the response to a NON is received, a Screening 2 period begins (with an associated performance target). If during the screening process, the response to a NON is found to contain unsolicited information, is incomplete or deficient, the response to the NON will be rejected and the submission will be considered withdrawn without prejudice to a refiling. A NON-Withdrawal Letter will be issued by the responsible Health Canada Directorate.

Practitioner: as per the *Food and Drug Regulations*, a person who is entitled under the laws of a province to treat patients with a prescription drug and is practising their profession in that province.

Serious adverse drug reaction: as per the *Food and Drug Regulations*, noxious and unintended response to a drug that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life threatening or results in death.

Serious unexpected adverse reaction: as per the *Food and Drug Regulations*, a serious adverse drug reaction that is not identified in nature, severity or frequency in the risk information set out in the investigator's brochure or on the label of the drug.

Special Access Request (SAR) form: a standard form used by the SAP to facilitate the request procedure. Practitioners fill out the SAR with the necessary information and submit it to the SAP.

This is **Exhibit "C"** referred to in
the Affidavit of **ERIC ORMSBY**
Affirmed before me at the City of
Ottawa, in the Province of Ontario,
this 15th day of January 2015.

A Commissioner for Taking Affidavits

Sherri Laureen Szabados, a Commissioner, etc.,
Province of Ontario, for the Government of Canada,
Department of Health.
Expires December 2, 2015

Health Canada Santé Canada

45

DRAFT GUIDANCE FOR INDUSTRY

Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs)

Published by authority of the
Minister of Health

Draft date	2001/07/18

Health Products and Food Branch
Guidance Document

Canada

Our mission is to help the people of Canada maintain and improve their health.

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FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with Health Canada policies, governing statutes and regulations. They also serve to provide review and compliance guidance to staff, thereby ensuring that Health Canada's mandate is implemented in a fair, consistent and effective manner.

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 scientific justification. Alternate approaches should be discussed in advance with Health Canada 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 for the adequate assessment of 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.

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G GENERAL

G 1 Purpose

This document is intended to provide guidance with regard to the Quality (i.e., Chemistry and Manufacturing) portion of New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs) containing drug substances and their corresponding products of synthetic or semi-synthetic origin, excluding Biotechnological/Biological (Schedule D) and Radiopharmaceutical (Schedule C) drugs, that are filed with Health Canada pursuant to Division C.08 of the *Food and Drug Regulations*. The purpose of the guidance document is to outline the Quality technical requirements and to assist submission sponsors in preparing the NDS and ANDS to ensure an effective and efficient review process. It can also be used as guidance on the requirements for related drug submissions (e.g., Supplemental NDSs, Supplemental ANDSs, Notifiable Changes, etc.).

This document covers variety of NDSs and ANDSs and may not be applicable in its entirety for all cases. Alternate approaches to the principles and practices described in this document can be acceptable provided they are supported by adequate scientific justification. Sponsors are advised to discuss, in advance, alternate approaches in their drug submission to avoid rejection or withdrawal of the drug submission.

G 2 Scope

This guidance document applies to New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs) containing drug substances and their corresponding products of synthetic or semi-synthetic origin, excluding Biotechnological/Biological (Schedule D) and Radiopharmaceutical (Schedule C) drugs, that are filed with Health Canada pursuant to Division C.08 of the *Food and Drug Regulations*. It can also be used as guidance on the requirements for related drug submissions (e.g., Supplemental NDSs, Supplemental ANDSs, Notifiable Changes, etc.).

This guidance document occasionally makes reference to "existing drugs". An "existing drug" is one that is not a new active substance but requires the filing of a New Drug Submission (NDS) or an Abbreviated New Drug Submission (ANDS) for which a Notice of Compliance has been previously issued pursuant to Division C.08 of the *Food and Drug Regulations* (e.g., generic products). This could also include submissions for new dosage forms, new strengths, etc..

G 3 Preamble

With the finalization of the *Common Technical Document (CTD)*, the International Conference on Harmonisation (ICH) has reached agreement upon a common *format* of applications for the registration of pharmaceuticals for human use. Within the CTD, is the *Common Technical Document - Quality (CTD-Q)* (Module 3) outlining the format for the Quality portion of applications for New Chemical Entities. Also as part of the CTD-Q exercise, the ICH process has produced a *Quality Overall*

Summary (QOS) (Module 2) which is a summary that follows the scope and the outline of the *Quality Module* (Module 3).

During the transitional period from July 2001 to the official CTD implementation date, drug submissions may be filed in the current Canadian, the "Modified NDA", or the CTD format. When filing in a particular format, the applicable filing requirements for that format apply.

This *Quality (C&M) Guidance: NDSs and ANDSs* follows the format recommended in ICH's CTD-Q. Where appropriate, the text from ICH's CTD-Q has been repeated **in bold** (*including spelling convention*) under each section, followed by further guidance to assist sponsors in the preparation of NDSs and ANDSs. This guidance document is an updated version of Health Canada's 1990 *Chemistry and Manufacturing: New Drugs* guideline.

Quality Summary (Module 2 of the CTD or *Part 2 of the NDS/ANDS)*:

Subsection C.08.005.1 of the *Food and Drug Regulations* stipulates that new drug submissions (NDSs), abbreviated new drug submissions (ANDSs), supplemental new drug submissions (SNDSs), and abbreviated new drug submissions (SANDSs) must include a comprehensive summary of each human, animal and *in vitro* study referred to or contained in the submission or supplement. The intent of this requirement is to facilitate the evaluation of the extensive experimental data and hence contribute toward a more effective and timely processing of drug submissions.

The *Quality Summary* is a comprehensive summary that follows the scope and the outline of the Quality Module (Module 3 of the CTD or Part 2 of the NDS/ANDS, whichever applies). The Quality Summary should not include information, data, or justification that was not already included in Quality Module or in other parts of the drug submission.

Since 1995, sponsors of NDSs and ANDSs have been required to complete the *Comprehensive Summary (Chemistry and Manufacturing) (CS(CM))*. This document provided a summary of the Quality data submitted to Health Canada according to a prescribed format and hence contributed towards a more effective and timely processing of these drug submissions. The template has since been updated according to current Quality standards and terminology, as well as to reflect the developments on the international level. With the completion of the updated version of the template, *Quality Overall Summary - Chemical Entities (New Drug Submissions and Abbreviated New Drug Submissions) (QOS-CE (NDS))*, sponsors share responsibility the for the generation of the Quality evaluation report. The objectives of this document are two-fold:

(a) expediting the review process by enabling Evaluators to more efficiently spend their time on drug submission assessment; and

(b) improving drug submission quality by way of a more thorough compilation and appraisal of data requirements by sponsors in conjunction with the completion of the *QOS-CE (NDS)*.

The QOS-CE is an updated version of Health Canada's earlier Quality Summary templates (i.e., the *Comprehensive Summary (Chemistry and Manufacturing) (CS(CM))* and the *Quality Information Summary - Pharmaceuticals (QIS-P)*).

While both ICH's *Quality Overall Summary (QOS)* and Health Canada's *Quality Overall Summary - Chemical Entities (New Drug Submissions and Abbreviated New Drug Submissions) (QOS-CE (NDS))* provide an overview of the information presented in the Quality Module (also referred to as the Quality portion of the drug submission), the latter is meant to precisely define the type and extent of information considered necessary to produce a Canadian Quality evaluation report, once supplemented by the Evaluator's comments. Given their specific role within the Quality review process, sponsors of NDSs are encouraged to complete Health Canada's QOS-CE (NDS) to help ensure an effective and efficient review of drug submissions. Until such time that the CTD is a required format for ANDSs, and/or the eCTD is available for voluntary filing, sponsors of ANDSs are expected to use the QOS-CE (NDS).

ICH's *QOS* and Health Canada's *QOS-CE (NDS)* are collectively referred to as the *Quality Summary* throughout the remainder of this document.

Paper and electronic versions of the Quality Summary should be provided. The electronic version should be in a WordPerfect® format.

Quality Module (Module 3 of the CTD or *Part 2 of the NDS/ANDS*):

This guidance document is intended to provide direction to sponsors as to what information should be included in the Quality Module (also referred to as the Quality portion of the drug submission). The following sections describe the elements of the Quality technical requirements. ICH's CTD should be consulted for other portions of the Quality Module (e.g., Table of Contents, Literature References).

Certified Product Information Document - Chemical Entities (CPID-CE):

The CPID-CE constitutes part of the Notice of Compliance (NOC) package. The CPID-CE is provides an accurate record of technical data in the drug submission at the time the NOC is issued, and thereafter serves as an official reference document during the course of post-approval inspections and post-approval change evaluations as performed by Health Canada. The CPID-CE template represents an condensed version of the Quality Summary template which represents the final, agreed upon *key* data from the drug submission review (e.g., minimal data on the manufacturer(s), drug substance/drug product specifications, stability conclusions, etc.).

The CPID-CE template file is structured to permit the rapid assembly of the CPID-CE by copying requisite information from the corresponding portions of the Quality Summary filed with the original drug submission. It is understood that the numbering system of this document is not sequential. This was intentional to retain the same numbering as the parent *Quality Overall Summary - Chemical Entities (QOS-CE)* or *Quality Overall Summary (QOS)*.

For New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs), the CPID-CE should be provided *upon request* (i.e., typically when the review of the drug submission is near completion). For SNDSs, SANDSs, and Notifiable Changes (NC's), the CPID-CE should be submitted *at the time of filing* and provided in *Module 1*. It is acknowledged that when filing a Supplement or NC, the updated CPID-CE may include changes that did not require prior approval by Health Canada (e.g., as for Level 3 and 4 changes).

G 4 Notes on the Preparation of the *Quality Summary* and the *Quality Module*

Sponsors are encouraged to devote the sufficient time necessary to prepare a clear, precise Quality Summary which is based on the detailed information that is submitted in the Quality Module. The filing of an inaccurate or an incomplete Quality Summary will result in greater expenditure of an Evaluator's time in reviewing and summarizing data.

In developing Health Canada's Quality Summary template, a balance was needed between providing sufficient instruction regarding the format and content of information sought and designing a document that could accommodate variability in the types of studies and products described in these drug submissions. With respect to the latter consideration, it is expected that the tables included in the QOS-CE (NDS) template may need to be modified (e.g., with data cells being split or joined, as necessary). Additional modification of table structure or the substitution of a narrative paragraph, can also be warranted in certain circumstances in order to best summarize the data. All titles/parameters listed in the default tables should nonetheless be retained or addressed, regardless of their perceived relevance, unless the subject matter of the entire table does not apply to the drug submission in question.

For NDSs and ANDSs, if portions of the Quality Summary are clearly not relevant due to the nature of the drug substance or drug product, this should be indicated by the designation "Not Applicable" (e.g., under the heading of section P 4.5 if there are not any excipients of human or animal origin used in the manufacture of the drug product). Any portions that are "Not applicable" *should not be deleted* and should be accompanied by an explanatory note describing the reasons for the inapplicability.

When the information in a section has been submitted in a prior drug submission in its entirety, without changes, the relevant section should be deleted and so noted under the Introduction, along with the name of the drug product, sponsor's name, date of the Notice of Compliance, and file number and submission control number of the cross-referenced submission. As in a SNDS, SANDS, or Notifiable Change (NC), those sections of the Quality Summary and the Quality Module affected by the proposed change should be submitted. Those sections not affected by the change can be deleted. As an example, Section "S Drug Substance", should not be included in a Supplement for an additional strength when there is not any change proposed to the information of the drug substance as described in the approved, cross-referenced submission.

The above practice should *not* be followed with respect to cross-referenced Drug Master Files (DMF's). DMF's should be identified in the appropriate sections (e.g., S 2.1, P 3.1). The sections of the Quality Summary should not be deleted. It is the sponsor's responsibility to submit the relevant non-proprietary information provided by the DMF Holder (e.g., from the Open DMF), obtained in the public domain, and/or developed by the sponsor. For DMF requirements, consult Health Canada's guidance document *Product Master Files* (soon to be renamed *Drug Master Files*). When the sponsor summarizes data obtained from the DMF Holder or the scientific literature, the source of reproduced information should be specified.

The following information is intended to provide assistance to sponsors in preparing the Quality Summary and the Quality Module:

(a) Reference to applicable Quality guidance documents are identified under the various sections.

Those developed by ICH are identified by their code name only (e.g., Q1A). Also provided, as an appendix to this document, is a comprehensive list of applicable Quality guidance documents. During the preparation of the drug submission, these Quality guidance documents should also be consulted as their content has not been repeated here.

(b) Abbreviations should not be used in the Quality Summary unless initially defined and consistently used (e.g., N/A = Not applicable), or unless they represent well-established scientific abbreviations (e.g., HPLC, UV, etc.).

(c) For "old drug substances in new drug products", submit sections *S 2.1 Manufacturer(s), S 4.1 Specifications, S 4.4 Batch Analyses, S 6 Container Closure System,* and *S 7.1 Stability Summary and Conclusions*, and any other pertinent components (e.g., particle size distribution); delete all the other non-applicable sections of the Drug Substance ("S") portion.

(d) This guidance document makes reference to "Schedule B compendial monographs", these are those compendial monographs that are recognized as official according to Schedule B to the *Food and Drugs Act* (e.g., USP, Ph.Eur., BP, etc.).

(e) The Quality information associated with any or all of the following scenarios may be submitted under one complete drug submission in the CTD format:

For a drug product containing more than one drug substance (e.g., substance "X", substance "Y"), the entire Drug Substance ("S") section for one drug substance should be followed by the entire "S" section for the next drug substance, then followed by a single Drug Product ("P") section. The name of the drug substance should be included in the headings of all applicable sections and subsections, to clearly distinguish the information for each drug substance.

For a drug substance and/or drug product which is manufactured by more than one manufacturer (e.g. Manufacturer "A" and Manufacturer "B", both manufacture the drug product using different equipment and separate facilities) and where there are differences in the Quality information associated with each manufacturer, the name of the manufacturer should be included in the heading of any affected sections and subsections, to clearly distinguish the drug substance and/or drug product information for each manufacturer. The numbering of the sections and subsections in this case should still be sequential. (e.g., *P 3.3 Description of Manufacturing Process and Process Controls [Manufacturer "A"]; P 3.3 Description of Manufacturing Process and Process Controls [Manufacturer "B"]*). NOTE the exceptions: Under *S.2.1 Manufacturer(s)* and *P 3.1 Manufacturer(s)*, multiple manufacturers should be listed without the need for any unique identifiers.

For a drug product with more than one dosage form (e.g., tablets, oral solution), the entire Drug Product ("P") section for one dosage form should be followed by the entire "P" section for the next dosage form. The name of the dosage form should be included in the headings of all applicable sections and subsections, to clearly distinguish the quality information for each dosage form.

For a drug product with more than one strength (e.g.. 10, 50, and 100 mg tablets), identification of the strength should be included in the heading of any affected sections, subsections, and/or

presentation of the information, to clearly distinguish the information for each strength. The numbering of the sections and subsections in this case should still be sequential.

(f) When filing a response to a deficiency request from Health Canada (e.g., Request for Clarification (Clarifax), Notice of Non-compliance (NON), Notice of Deficiency (NOD)), sponsors should use the *applicable sections* of the Quality Summary to summarize new or updated data (e.g., specifications, analytical procedures, stability results, etc.). A refiled/updated Quality Summary should *not* be submitted. However, in the case of an NOD or an extensive NON where the magnitude of deficiency comments warrants the filing of replacement volumes, a refiled/updated Quality Summary can be necessary.

(g) In order to facilitate the processing and evaluation of responses to deficiency requests from Health Canada, an *electronic version* of the consolidated deficiency comments and responses pertaining to the Quality issues should be provided in a question and answer format in a WordPerfect® format.

Reference Guidances: M4Q (i.e., CTD-Q)
Preparation of a Drug Submission in CTD Format (for CTD-based submissions)
Preparation of Human New Drug Submissions (for NDS-based submissions)
Modified FDA Format Drug Submissions for Products in Human Use

I INTRODUCTION

The introduction should include proprietary name, non-proprietary name or common name of the drug substance, company name, dosage form(s), strength(s), route of administration, and proposed indication(s).

Sponsors may provide a contact person's name, phone number, fax number, and e-mail address for ease of communication.

S DRUG SUBSTANCE

Some of the information included under the "S Drug Substance" section may not be available to the sponsor for the New Drug Submission or Abbreviated New Drug Submission. If such is the case, the supplier of the drug substance can file a Drug Master File directly with Health Canada. The supplier would then be considered the DMF Holder. This DMF will be held in strict confidence and will be used in support of the drug submission only upon receipt of written authorization from the supplier/DMF Holder of the drug substance (i.e., via a letter of access).

The sponsor should be able to provide most of the information on the drug substance, except possibly the proprietary information found in sections S 2.2, S 2.3, S 2.4 and S 2.6 (see below). It is the responsibility of the sponsor to obtain all other information from the supplier of the drug substance and include this in the drug submission. The information from the Open DMF should be provided in the drug submission and summarized in the Quality Summary.

Regardless of the information provided by the supplier of the drug substance, the manufacturer of the dosage form is responsible for ensuring that acceptable specifications and properly validated analytical procedures for the drug substance are developed by the manufacturer's facilities and for providing the results of batch analyses performed at the manufacturer's facilities.

For further information on the requirements for Drug Master Files, see Health Canada's guidance document *Product Master Files* (soon to be renamed *Drug Master Files*).

S 1 General Information

S 1.1 Nomenclature

Information on the nomenclature of the drug substance should be provided. For example:

(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, United States Adopted Name (USAN), British Approved Name (BAN)); and

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

The listed chemical names should be consistent with those appearing in scientific literature and those appearing on the product labelling (e.g., Product Monograph). Where several names exist, indicate the preferred name.

Where a chemical moiety is formed *in-situ* (e.g., by chemical reaction), both the starting and chemical moiety should be described.

S 1.2 Structure

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.

This information should be consistent with that provided in section S 1.1. For drug substances existing as salts, the molecular mass of the free base should also be provided.

S 1.3 General Properties

A list should be provided of physicochemical and other relevant properties of the drug substance.

This information can be used in developing the specifications, in formulating dosage forms, and in the testing for release and stability purposes. Give the physical and chemical properties of the drug substance such as the physical description, solubilities in common solvents (e.g., water, alcohols, chloroform, acetone, etc.), quantitative aqueous pH solubility profile (e.g., pH 1 to 8, dose/solubility volume), polymorphism, particle size distribution, pH and pKa values, UV absorption maxima and molar absorptivity, melting point, refractive index (for a liquid), hygroscopicity, partition coefficient, etc.. This list is by no means exhaustive, but provides an indication as to the type of information that could be included.

Some of the more important properties to be considered for all drug substances are discussed below in greater detail.

Physical description:

The description should include appearance, colour, and physical state. Solid forms should be identified as being crystalline or amorphous.

Solubilities/quantitative aqueous pH solubility profile:

The solubility should be provided in a number of common solvents (e.g., water, alcohols, chloroform, acetone, etc.). The solubilities over the physiological pH range (pH 1 to 8) in several buffered media should also be provided. Phrases such as "sparingly soluble" or "freely soluble" should be quantitatively defined or a literature reference can be provided (e.g., "as per USP"). If this information is not readily available (e.g., literature references, Open Drug Master File), it should be generated in-house.

The dose/solubility volume should be provided. The dose/solubility volume[1] is calculated based on the minimum concentration of the drug (in mg/mL), in the largest dosage strength, determined in the physiological pH range (pH 1 to 8) and temperature (37 ± 0.5°C). High solubility drugs are those with a dose/solubility volume of less than or equal to 250 mL. For example, Compound A has as its lowest solubility at 37 ± 0.5°C, 1.0 mg/mL at pH 7, and is available in 100 mg, 200 mg, and 400 mg strengths. This drug would be considered a low solubility drug as its dose/solubility volume is greater than 250 mL (400 mg/1.0 mg/mL = 400 mL).

Polymorphs:

If the potential for polymorphism is a concern, results from an investigation of several batches of the drug substance, recrystallized from several solvents, should be provided to determine if the drug substance exists in more than one crystalline form. The study should include the characterization of the batch(es) used in the clinical and/or comparative bioavailability studies, using a suitable method (e.g., X-ray Diffraction (XRD), Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR)). The absence of the potential for polymorphism can further be confirmed by providing the results of a literature search.

If the results of studies conducted on the physical and chemical properties of the various crystalline forms indicate that there is a preferred polymorph, criteria should be incorporated into the drug substance specification to ensure polymorphic equivalence of the commercial material to the batch(es) used in the clinical and/or comparative bioavailability studies.

Generally, controls on polymorphism are not a concern for drug substances that are considered highly soluble. Justification for the exclusion of the controls for polymorphism should be provided.

Polymorphism can also include solvation or hydration products (also known as pseudopolymorphs). If the drug substance is used in a solvated form, the following information should be provided:

(a) specifications for the solvent-free drug substance, if that compound is a synthetic precursor;

(b) specifications for the solvated drug substance including appropriate limits on the weight ratio of drug substance to solvent (with data to support the proposed limits); and

(c) a description of the method used to prepare the solvate.

Particle size distribution:

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[1] *Immediate Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation,* Center for Drug Evaluation and Research (CDER), November 1995.

For poorly soluble drug substances, the particle size distribution of the material can have an effect on the *in vitro* and/or *in vivo* behaviour of the drug product. Particle size can also be important in dosage form performance (e.g. delivery of inhalation products), achieving uniformity of content in low-dose tablets (e.g., 2 mg or less), desired smoothness in ophthalmic preparations, and stability of suspensions.

If particle size distribution is important (e.g., as in the above cases), results from an investigation of several batches of the drug substance should be provided, including characterization of the batch(es) used in the clinical and/or comparative bioavailability studies. If applicable, the acceptance criteria should include controls on the particle size distribution to ensure consistency with the material in the batch(es) used in the clinical and/or comparative bioavailability studies (e.g., limits for d_{10}, d_{50}, and d_{90}). This criteria should be established statistically based on the standard deviation of the test results from the previously mentioned studies. The following is provided for illustrative purposes as possible acceptance criteria for particle size limits:

d_{10}	NMT 10% of total volume less than X µm
d_{50}	XX µm - XXX µm
d_{90}	NLT 90% of total volume less than XXXX µm

Other controls on particle size can be considered acceptable, if scientifically justified.

Reference Guidances: Q6A

S 2 Manufacture

If a Drug Master File (DMF) is filed with Health Canada and cross-referenced for certain proprietary information (e.g., sections S 2.2, S 2.3, S 2.4, and S 2.6), provide the DMF number assigned by Health Canada. It should be ensured that the information included in the DMF is up to date (e.g., updated every two years) and that the data has been received by Health Canada. Copies of the letters of access should be provided under the Regional Information section. If a Canadian agent is used by the DMF Holder, a letter *from the DMF Holder* should be submitted allowing the agent to act on their behalf, rather than the letter coming from the Canadian agent.

S 2.1 Manufacturer(s)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

This includes the facilities involved in the fabrication, packaging, labelling, testing, importing, storage, and distribution of the drug substance. If certain companies are responsible only for specific steps (e.g., milling of the drug substance), this should be indicated. The list of manufacturers should specify the actual production or manufacturing site(s) involved, rather than the administrative offices.

S 2.2 Description of Manufacturing Process and Process Controls

A flow diagram of the synthetic process(es) should be provided that includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and drug substance reflecting stereochemistry, and identifies operating conditions and solvents.

A sequential procedural narrative of the manufacturing process should be submitted. The narrative should include, for example, quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, process controls, equipment and operating conditions (e.g., temperature, pressure, pH, time).

Alternate processes should be explained and described with the same level of detail as the primary process.

Reprocessing steps should be identified and justified. Any data to support this justification should be either referenced or filed in S 2.5.

The information on the manufacturing process should start from commercially available or well-characterized starting materials. The manufacturing process for the batch(es) used in the clinical and/or comparative bioavailability studies should be representative of the process for commercial purposes (i.e., laboratory scale batches are *not* considered acceptable).

If the drug substance is prepared as sterile, a complete description should be provided for the method used in the sterilization. The controls used to maintain the sterility of the drug substance during storage and transportation should be provided.

In addition to the above information, the data provided for a drug substance produced by fermentation should include:

(a) source and type of micro-organism used;

(b) composition of media;

(c) precursors;

(d) additional details on how the reaction conditions are controlled (e.g., times, temperatures, rates of aeration, etc.); and

(e) name and composition of preservatives.

For drug substances of plant origin, include a description of the botanical species and the part of plant used, the geographical origin and, where relevant, the time of year harvested. The nature of chemical fertilizers, pesticides, fungicides, etc. should be recorded, if these have been employed during cultivation. It may be necessary to include limits for residues resulting from such treatments in the drug substance specification. Absence of toxic metals and radioactivity may also have to be confirmed.

S 2.3 Control of Materials

Materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials meet standards appropriate for their intended use should be provided, as appropriate.

Copies of the specifications for the materials used in the synthesis, fermentation, extraction, isolation, and purification steps should be provided in the drug submission.

Drug substances of animal origin should be free of Bovine Spongiform Encephalopathy (BSE) / Transmissible Spongiform Encephalopathy (TSE) and a letter of attestation confirming this should be included with the drug submission. Details in A2.

Reference Guidances: Q6A

S 2.4 Controls of Critical Steps and Intermediates

Critical Steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in S2.2 of the manufacturing process to ensure that the process is controlled should be provided.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Generally, these specifications would include tests and acceptance criteria for identity, purity, and potency, where applicable. Well-defined controls of potential impurities should be included for the starting material. Special consideration should be given to potential isomeric impurities in the starting material, as such contaminants that could be carried through the synthesis to the drug substance.

Reference Guidances: Q6A

S 2.5 Process Validation and/or Evaluation

Process validation and/or evaluation studies for aseptic processing and sterilisation should be included.

It is expected that the manufacturing processes for all drug substances are properly controlled. Justification should be provided for alternate manufacturing processes.

S 2.6 Manufacturing Process Development

A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing nonclinical, clinical, scale-up, pilot, and, if available, production scale batches.

Reference should be made to the drug substance data provided in section S 4.4.

The above information should also be provided for comparative (e.g., for existing drugs) and stability batches.

Reference Guidances: Q3A

S 3 Characterisation

S 3.1 Elucidation of Structure and other Characteristics

Confirmation of structure based on e.g., synthetic route and spectral analyses should be provided.

The Quality Summary should include a list of the studies performed 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 an interpretation of the data.

The studies carried out to elucidate and/or confirm the chemical structure of New Chemical Entities normally include elemental analysis, Infrared (IR), Ultraviolet (UV), Nuclear Magnetic Resonance (NMR), and Mass Spectra (MS) studies. Other tests could include X-ray diffraction (XRD). For existing drugs (e.g., generics), it is generally sufficient to provide copies of the IR and UV spectra of the drug substance from the proposed suppliers run concomitantly with suitable reference standard. A suitable primary reference standard could be obtained from the Schedule B compendia (e.g., USP, Ph.Eur, BP, etc.) or a batch of the drug substance that has been fully characterized (e.g., IR, UV, NMR, MS, etc.). See section S 5 for further details on References Standards or Materials.

When a drug substance is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the nonclinical and clinical studies, and information should be given as to the stereoisomer of the drug substance that is to be used in the final product intended for marketing.

A discussion should be included of the possible isomers that can result from the manufacturing process, the steps where they were introduced, and a summary of the results of the studies carried out to investigate the physical, chemical, and biological properties of these isomers. If there is a preferred isomer or isomeric mixture, the drug substance specification should include a test to ensure isomeric identity and purity.

If the drug substance is a single isomer or a fixed ratio of isomers, provide the rationale for this decision, including a discussion of the material that was used in the clinical and/or comparative bioavailability study. For existing drugs (e.g., generics), include a summary of any comparative studies performed.

For drug substances that contain an asymmetric centre, where there has not been any information provided regarding the manufacture of the starting material through which it has been introduced, results of a study should be submitted demonstrating that the material exists as a racemic mixture (e.g., specific optical rotation).

It is recognized that some drugs (e.g., certain antibiotics, enzymes, and peptides) present difficulties with respect to structural investigation. In such cases, more emphasis should be placed on the purification and the specification for the drug substance. If a drug substance consists of more than one component, the physicochemical characterization of the components and their ratio should be submitted.

If, based the structure of the drug substance, there is not a potential for isomerism, it could be sufficient to include a statement to this effect.

Reference Guidances: Q6A
Stereochemical Issues in Chiral Drug Development

S 3.2 Impurities

Information on impurities should be provided.

The study of impurities can be considered one of the most important aspects of the Quality portion of the drug submission. The sponsor should provide a discussion of the potential and actual impurities arising from the synthesis, manufacture, and/or degradation. The tables in Health Canada's Quality Summary template can be used to summarize the information on impurities (e.g., names, structures, origin, results, etc.). The origin refers to how the impurity was introduced (e.g., "Synthetic intermediate from Step 4 of the synthesis", "Potential by-product due to rearrangement from Step 6 of the synthesis, etc.). It should also be indicated if the impurity is a metabolite of the drug substance.

The basis for setting the acceptance criteria for the impurities should be provided. This is established by considering the identification and qualification thresholds for drug-related impurities (e.g., starting materials, by-products, intermediates, chiral impurities, or degradation products) and the concentration limits for process-related impurities (e.g., residual solvents) as per the applicable ICH guidance document (e.g., Q3A, Q3C). These thresholds are determined on the basis of potential exposure to the impurity, i.e., by the maximum daily dose (MDD) of the drug substance. For drugs available in multiple dosage forms and strengths, having different MDD values, it is imperative that the thresholds and corresponding controls for each of the presentations be considered to ensure that the risks posed by impurities have been addressed. This is normally achieved by using the highest potential daily MDD, rather than the maintenance dose. For parenteral products, the maximum hourly dose of the drug substance should also be included.

The acceptance criteria is also set taking into consideration the actual levels of impurities found in several batches of the drug substance from each source, including the levels found in the batches used for the nonclinical, clinical, and comparative studies. For quantitative tests, it should be ensured that *actual numerical results* are provided rather than vague statements such as "within limits" or "conforms". In the cases where a large number of batches have been tested, it is acceptable to summarize the total number of batches tested with a range of analytical results.

Qualifying limits for specified impurities is normally based on the levels found in the nonclinical and clinical batches at the time the studies were conducted, rather than levels observed on stability or levels found in subsequent batches manufactured according to the proposed commercial process. Results on the drug product can also be presented for comparative batches (e.g., for a comparative purity study of a generic product against the Canadian reference product).

It is recognized by the compendia that drug substances can be obtained from various sources, and thus can contain impurities not considered during the preparation of the monograph. Furthermore, a change in the production or source may give rise to impurities that are not adequately controlled by the published compendial monograph. As a result, each drug submission is reviewed independently to consider the potential impurities that may arise from the proposed route(s) of synthesis. For these reasons, the ICH limits for unspecified impurities (e.g., Not More Than (NMT) 0.1% for drug substances having a maximum daily dose • 2 g/day) are generally recommended, rather than the general limits for unspecified impurities that appear in the compendial monograph that could be potentially higher than the ICH limit.

Depending on the nature of the drug substance, and the extent of the chemical modification steps, the principles on the control of impurities (e.g., identification and qualification) can also be extended to drug substances of semi-synthetic origin. As an illustrative example, a drug substance whose precursor molecule was derived from a fermentation process, or a natural product of plant or animal origin, and has subsequently undergone several chemical modification reactions generally would fall within this scope, whereas a drug whose sole chemical step was the formation of a salt from a fermentation product generally would not fall within this scope. It is understood that there is some latitude for these types of drug substances (e.g., NMT 0.2% for unspecified impurities may be appropriate, rather than NMT 0.1%).

If there are identified impurities specified in a compendial monograph (e.g., as in a Ph.Eur. Transparency Monograph) that are not monitored by the proposed routine method (e.g., House method), a justification should be provided for their exclusion. If acceptable justification cannot be provided, it should be demonstrated that the alternate method is capable of detecting the impurities specified in the compendial monograph at an acceptable level (e.g., 0.1%).

Reference Guidances: Q3A, Q3C, Q6A
Identification, Qualification, and Control of Related Impurities in New Drugs
Identification, Qualification, and Control of Related Impurities in Existing Drugs
Stereochemical Issues in Chiral Drug Development

S 4 Control of the Drug Substance

S 4.1 Specification

The specification for the drug substance should be provided.

As defined in ICH's Q6A guidance document, a specification is a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug substance, when tested according to the listed analytical procedures, will meet the listed acceptance

criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

A copy of the drug substance specification from the company responsible for release testing should be provided, dated and signed by authorized personnel (i.e., the person in charge of the Quality Control department). The specification reference number, version, and date should be provided for version control purposes. The standard declared by the sponsor could be a Schedule B compendial standard (e.g., USP, Ph.Eur., BP, etc.), Manufacturer's or House Standard, Prescribed Standard (e.g., Canadian Standard Drugs in Division C.06 of the *Food and Drug Regulations*), or a Professed Standard.

Although a Schedule B compendial monograph may exist, a sponsor can choose to use a Manufacturer's Standard which indicates that the material may differ in some respect from the compendial standard. However, according to section C.01.011 of the *Food and Drug Regulations*, no person shall use a manufacturer's standard for a drug that provides (a) a lesser degree of purity than the highest degree of purity and (b) a greater variance in potency than the least variation in potency, provided for that drug in any publication mentioned in Schedule B to the *Act*. Therefore, if a manufacturer's standard is used, the controls on purity (e.g., limits on specified impurities) and potency should be as tight as the most stringent of those listed in the Schedule B compendial monographs.

If the drug submission is for a non-official drug (e.g., where neither a Prescribed nor a Schedule B compendial standard exists), a professed standard is used and the product labelling for such products does not carry any standard.

The specification can be summarized according to Health Canada's Quality Summary template including the Tests, Method Types, Sources, and Code Number/Version/Date. The acceptance criteria should also be provided in the summary of the specification. The Method Type should indicate the kind of analytical procedure used (e.g., visual, IR, UV, HPLC, laser diffraction, etc.); the Source refers to the origin of the analytical procedure (e.g., USP, Ph.Eur., BP, House, etc.); and the Code Number/Version/Date should be provided for version control purposes.

ICH's Q6A guidance document outlines recommendations for a number of universal and specific tests and criteria for drug substances.

Reference Guidances: Q3A, Q3C, Q6A

S 4.2 Analytical Procedures

The analytical procedures used for testing the drug substance should be provided.

Copies of the House analytical procedures used during the drug development (if used to support testing results in the drug submission) as well as those proposed for routine testing should be provided. The tables in Health Canada's Quality Summary template can be used to summarize the analytical procedures. Unless modified, it is not necessary to provide copies of Schedule B compendial analytical procedures.

Although HPLC is normally considered the method of choice for determining drug-related impurities, other chromatographic methods such as GC and TLC can also be used, if appropriate. For impurity

methods, reference standards should be prepared for each of the identified impurities, particularly those known to be toxic, and the concentration of the impurities quantitated against their own reference standards. It is considered acceptable to use the drug substance as an external standard to estimate the levels of impurities, provided the response factors of those impurities are sufficiently close to that of the drug substance (e.g., greater than 80%). In cases where the response factor is not close, it may still be acceptable to use the drug substance, provided a correction factor is applied or the impurities are, in fact, being overestimated. Unspecified impurities should be quantitated using a solution of the drug substance as the reference standard at a concentration corresponding to the limit established for individual unspecified impurities (e.g., 0.1%).

The system suitability tests (SST's) are an integral part of chromatographic analytical procedures. As a minimum, HPLC and GC methods should include SST's for resolution and repeatability. For HPLC methods to control drug-related impurities, this is typically done using a solution of the drug substance with a concentration corresponding to the limit for unspecified impurities. Resolution of the two closest eluting peaks is generally recommended. However, choice of alternate peaks can be used if justified (e.g., choice of a toxic impurity). In accordance with the USP General Chapter on *Chromatography* and Health Canada's guidance document *Acceptable Methods*, the repeatability test should include an acceptable number of replicate injections (i.e., five or six). For TLC methods, the SST's should verify the sensitivity and ability of the system to separate (e.g., by applying a spot corresponding to the drug substance spiked at a concentration corresponding to the limit of unspecified impurities).

Reference Guidances: Q2A
Acceptable Methods

S 4.3 Validation of Analytical Procedures

Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance, should be provided.

Copies of the validation reports for the analytical procedures used during the drug development (if used to support testing results in the drug submission) as well as those proposed for routine testing should be provided. The tables in Health Canada's Quality Summary template can be used to summarize the validation information.

As outlined in Health Canada's guidance document *Acceptable Methods*, partial revalidation is necessary for methods that appear in a Schedule B compendial monograph. These revalidation criteria are recognized by other Regulatory Agencies and the compendia themselves. The compendial methods, as published, are typically validated using a drug substance or a drug product originating from a specific manufacturer. Different sources of the same drug substance or drug product can contain impurities and degradation products that were not considered during the development of the monograph.

In general, revalidation is not necessary for Schedule B compendial *potency* methods. However, specificity of the compendial potency method should be demonstrated if there are any potential impurities that are not specified in the compendial monograph. If a Schedule B compendial method is used to control drug-related impurities that are not specified in the monograph, full validation is expected.

If a Schedule B compendial standard is claimed and a House method is used in lieu of the compendial method (e.g., for potency or for specified impurities), equivalency of the House and compendial methods should be demonstrated. This could be accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study.

With respect to the control of residual solvents, it is acknowledged that GC methods for determining residual solvents are generally sensitive, linear, and reproducible. In past experience, it has been found that a sponsor will use essentially the same GC method to determine residual solvents in a number of drug substances and drug products. Therefore, although it is expected that a company will initially perform full validation of the methods used to determine residual solvents, it is acceptable that only limited validation data be submitted (e.g., recovery, repeatability, limit of detection, limit of quantitation, and selectivity of the method). Recovery and repeatability should be determined using a sample of the drug substance or drug product spiked with the residual solvents at their acceptance criteria.

Reference Guidances: Q2A, Q2B
Acceptable Methods

S 4.4 Batch Analyses

Description of batches and results of batch analyses should be provided.

This would include information such as batch number, batch size, date and site of production, etc. on relevant drug substance batches (e.g., used in nonclinical, clinical, comparative, stability, pilot, scale-up, and, if available, production-scale batches) used to establish the specification(s) and evaluate consistency in manufacturing.

Analytical results tested by the company responsible for release testing should be provided from at least two batches from each proposed manufacturing site of the drug substance. The testing results should include the batch(es) used in the nonclinical, clinical and/or comparative bioavailability studies. Copies of the certificates of analyses for these batches should be provided in the drug submission and the company responsible for generating the testing results should be identified.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "All tests meet specifications". This should include ranges of analytical results and any trends that were observed. For quantitative tests (e.g., as in individual and total impurity tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such as "within limits" or "conforms". A discussion and justification should be provided for any incomplete analyses (e.g., results not tested according to the proposed specification).

Reference Guidances: Q3A, Q3C, Q6A

S 4.5 Justification of Specification

Justification for the drug substance specification should be provided.

This should include a discussion on the inclusion of certain tests, evolution of tests, analytical procedures, and acceptance criteria, differences from compendial standard, etc.. If the Schedule B compendial methods have been modified or replaced, a discussion should be included.

The justification for certain tests, analytical procedures, and acceptance criteria may have been discussed in other sections of the drug submission (e.g., impurities, particle size) and do not need to be repeated here, although a cross-reference to their location should be provided.

Reference Guidances: Q3A, Q3C, Q6A

S 5 Reference Standards or Materials

Information on the reference standards or reference materials used for testing of the drug substance should be provided.

The source(s) of the reference standards or materials used in the testing of the drug substance should be provided (e.g., for the identification, purity, potency tests).

Primary reference standards can be obtained from official sources such those recognized in the Schedule B compendia. Primary reference standards from official sources do not need further structural elucidation. A primary standard could also be validated as a batch of drug substance that has been fully characterized and structurally elucidated (e.g., IR, UV, NMR, MS, etc.).

A secondary (or House) reference standard can be used by providing a copy of its certificate of analysis and validating it against a suitable primary reference standard (e.g., by providing legible copies of the IR and UV of the secondary and primary reference standards run concomitantly). A secondary reference standard is often characterized and evaluated for its intended purpose with additional procedures other than those used in routine testing (e.g., if additional solvents are used for purification during the manufacturing process that are not used for routine purposes). A brief description of the manufacture process of the secondary reference standard should be provided, if it differs from commercial process for the drug substance.

Reference Guidances: Q6A
Acceptable Methods

S 6 Container Closure System

A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification (and critical dimensions with drawings, where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

For non-functional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging

components, additional information should be provided.

The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance, including sorption to container and leaching, and/or safety of materials of construction.

S 7 Stability

As outlined in ICH's Q1A guidance document, the purpose of stability testing is to provide evidence on how the quality of a drug substance varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance and recommended storage conditions.

Reference Guidances: Q1A, Q1B
Stability Testing of Existing Drug Substances and Products

S 7.1 Stability Summary and Conclusions

The types of studies conducted, protocols used, and the results of the studies should be summarised. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

Stress testing:

As outlined ICH's Q1A guidance document, stress testing of the drug substance can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance and the type of drug product involved.

The table in Health Canada's Quality Summary template can be used to summarize the results from the stress testing. This summary should include the treatment conditions (e.g., concentrations of solutions prepared, storage temperatures and durations) and the observations for the various test parameters (e.g., potency, degradation products).

Accelerated and long term testing:

The conditions for stability testing of new drug substances are outlined in ICH's Q1A guidance document. The following storage conditions and minimum data at the time of submission are recommended by ICH's Q1A guidance document for the Primary Batches. When "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. See ICH's Q1A guidance document for definition of "significant change".

Study	Storage Condition	Minimum Time Period Covered by Data at Submission
Long term	25°C ± 2°C / 60% RH ± 5% RH	12 months
Intermediate	30°C ± 2°C / 60% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C / 75% RH ± 5% RH	6 months

RH = relative humidity

Other conditions are outlined in the ICH's Q1A guidance document for drug substances intended for storage in a refrigerator and those intended for storage in a freezer. Drug substances intended for storage below -20°C should be treated on a case-by-case basis.

For existing drugs (e.g., generics), available information on the stability of the drug substance under accelerated and long term conditions should be provided, including information in the public domain or obtained from DMF Holders. The source of the information should be identified. In certain cases, information available in the public domain may be sufficient to establish an appropriate re-test period, e.g., when a substantial body of evidence exists that establishes that the drug substance is inherently stable. In all instances, sponsors are encouraged to provide all relevant information available on the stability of the drug substance.

The information on the stability studies should include details such as storage conditions, batch number, batch size, container closure system, and completed (and proposed) test intervals. The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "All tests meet specifications". This should include ranges of analytical results and any trends that were observed. For quantitative tests (e.g., as in individual and total degradation product tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such as "within limits" or "conforms".

Proposed storage conditions and re-test period:

The proposed storage conditions with suitable tolerances (e.g., a temperature range with upper and lower criteria) and re-test period for the drug substance should be provided.

When the drug substance has been shown to be stable (e.g., under the ICH conditions with long term studies at 25• C ± 2• C/60% RH ± 5% RH and accelerated studies at 40• C ± 2• C/75% RH ± 5% RH), the following storage recommendation would generally be considered acceptable:

"Store at controlled room temperature (15• C to 30• C)."

Based on the results of the stability evaluation, other storage precautions may be warranted (e.g., "Protect from light", "Protect from moisture").

Re-test periods are generally one or two years. A re-test period longer than two years should be fully supported by the results from stability studies conducted under the conditions recommended by ICH's Q1A guidance document. After this period, a batch of drug substance destined for use in the manufacture

of a drug product should be re-tested for compliance with the specification and then used *immediately* (e.g., within 30 days). If re-tested, the batch does *not* receive the period of time established for the re-test period.

For drug substances known to be labile (e.g., certain antibiotics), it is more appropriate to establish a shelf life than a re-test period.

Limited extrapolation of the real time data from the long term storage condition beyond the observed range to extend the re-test period can be undertaken at approval time, if justified.

S 7.2 Post-approval Stability Protocol and Stability Commitment

The post-approval stability protocol and stability commitment should be provided.

When available long term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, a commitment should be made to continue the stability studies post-approval in order to firmly establish the shelf life. The long term stability studies for the *Commitment Batches* should be conducted through the proposed shelf life (and the accelerated studies for six months) on at least three production batches of each strength (or two production batches of each strength for existing drugs).

The stability protocol for the *Commitment Batches* and should include, but not limited to:

(a) Number of batches and batch sizes;

(b) Tests and acceptance criteria;

(c) Container closure system(s);

(d) Testing frequency; and

(e) Storage conditions (and tolerances) of samples

Any differences in the stability protocols used for the primary batches and those proposed for the *Commitment Batches* or should be scientifically justified.

S 7.3 Stability Data

Results of the stability studies (e.g., forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

This would include the actual stability results (i.e., raw data) used to support the proposed re-test period or shelf life. For quantitative tests (e.g., as in individual and total degradation product tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such

as "within limits" or "conforms".

P DRUG PRODUCT

P 1 Description and Composition of the Drug Product

A description of the drug product and its composition should be provided. The information provided should include, for example:

(a) Description of the dosage form;

The description of the dosage form should include the physical description, available strengths, release mechanism, as well as any other distinguishable characteristics (e.g., "The proposed drug product is available as oval, round, immediate-release, aqueous film-coated tablet in three strengths (5 mg, 10 mg, and 20 mg). The two higher strengths include a vertical score line to facilitate the breaking of the tablets.").

(b) Composition, i.e., list of all components of the dosage form, and their amount on a per unit basis (including overages, if any) the function of the components, and a reference to their quality standards (e.g., compendial monographs or manufacturer's specifications);

The composition should express the quantity of each component on a per unit basis (e.g., mg per tablet, mg per mL, mg per vial, etc.) and percentage basis, including a statement of the total weight or measure of the dosage unit. This 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, etc.). If the drug product is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g., "1 mg of active ingredient base = 1.075 mg active ingredient hydrochloride"). All overages should be clearly indicated (e.g., "Contains 2% overage of the drug substance to compensate for manufacturing losses.").

The components should be declared by their proper or common names, Quality standards (e.g., USP, Ph.Eur., House, etc.) and, if applicable, their grades (e.g., "Microcrystalline Cellulose NF (PH 102)").

The qualitative composition should be provided for all proprietary components or blends (e.g., capsule shells, colouring blends, imprinting inks, etc.). This information is used for product labelling purposes. Reference to a Drug Master File can be provided for the actual *quantitative* composition.

The function of each component (e.g., diluent/filler, binder, disintegrant, lubricant, glidant, granulating solvent, coating agent, antimicrobial preservative, etc.) should be provided.

(c) Description of accompanying reconstitution diluent(s); and

For drug products supplied with reconstitution diluent(s) that are not commercially available in Canada or have not been reviewed and approved in connection with another drug submission with

Health Canada, information on the diluent(s) should be provided in a separate Drug Product ("P") portion, as appropriate.

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

The description for the container closure used for the dosage form (and accompanying reconstitution diluent, if applicable) should be brief with further details provided under P 7 Container Closure System (e.g., "The product is available in HDPE bottles with polypropylene caps and in PVC/Aluminum foil unit dose blisters.").

Reference Guidances: Q6A

P 2 Pharmaceutical Development

The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the application. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and drug product quality. Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical Development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the application.

Reference Guidances: Q6A

P 2.1 Components of the Drug Product

P 2.1.1 Drug Substance

The compatibility of the drug substance with excipients listed in P1 should be discussed. Additionally, 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 should be discussed. For combination products, the compatibility of drug substances with each other should be discussed.

P 2.1.2 Excipients

The choice of excipients listed in P1, their concentration, their characteristics that can influence the drug product performance should be discussed relative to their respective functions.

Alternates for excipients are generally not accepted. Ranges for excipients normally are not accepted, unless supported by appropriate process validation data. Where relevant, compatibility study results (e.g., primary

and secondary compatibility of an amine drug with lactose) should be included to justify the choice of excipients. Specific details should be provided where necessary (e.g., use of potato or corn starch).

Where antioxidants are included in the formulation, the effectiveness of the proposed concentration of the antioxidant should be justified and verified by appropriate studies.

A certification should be provided that none of the excipients which appear in the drug product are prohibited for use in drugs by the Canadian *Food and Drugs Act and Regulations*.

P 2.2 Drug Product

P 2.2.1 Formulation Development

A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e., composition) described in P1 should be discussed. Results from comparative *in vitro* studies (e.g., dissolution) or comparative *in vivo* studies (e.g., bioequivalence) should be discussed, when appropriate.

The tables in Health Canada's Quality Summary template can be used to summarize the above information.

When assessing the data elements needed for multiple strengths, Health Canada's policy *Bioequivalence of Proportional Formulations: Solid Oral Dosage Forms* should be consulted.

P 2.2.2 Overages

Any overages in the formulation(s) described in P1 should be justified.

Overages for the sole purpose of extending the shelf life of the drug product are generally not acceptable.

P 2.2.3 Physicochemical and Biological Properties

Parameters relevant to the performance of the drug product, such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency, and/or immunological activity, should be addressed.

P 2.3 Manufacturing Process Development

The selection and optimisation of the manufacturing process described in P3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilisation should be explained and justified.

Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in P3.3 that can influence the performance of the product should be

discussed.

The rationale for choosing the particular type of drug delivery system should be provided (e.g., matrix or membrane based controlled delivery, liposomal, microemulsion, depot injection). The scientific rationale for the choice of the manufacturing, filling, and packaging processes that can influence drug product quality and performance should be explained (e.g., wet granulation using high shear granulator). Any developmental work undertaken to protect the drug product from deterioration should also be included (e.g., protection from light or moisture).

The scientific rationale for the selection, optimization, and scale-up of the manufacturing process described in P 3.3 should be explained, in particular the critical aspects (e.g., rate of addition of granulating fluid, massing time). The equipment should be identified by type and working capacity.

P 2.4 Container Closure System

The suitability of the container closure system (described in P7) used for the storage, transportation (shipping) and use of the drug product should be discussed. This discussion should consider, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the drug product).

See section P 7 for a discussion on the information that could be included for the qualification of the container closure system.

P 2.5 Microbiological Attributes

Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

Where an antimicrobial preservative is included in the formulation, the effectiveness of the agent should be justified and verified by appropriate studies using a batch of the drug product. If the lower bound for the proposed acceptance criteria for the assay of the preservative is less than 90.0%, the effectiveness of the agent should be established with a batch of the drug product containing a concentration of the antimicrobial preservative corresponding to the lower proposed acceptance criteria.

As outlined in ICH's Q1A guidance document, a single primary stability batch of the drug product should be tested for antimicrobial preservative effectiveness (in addition to preservative content)*at the proposed shelf life* for verification purposes, regardless of whether there is a difference between the release and shelf life acceptance criteria for preservative content.

If this information is not available at the time of submission, a commitment should be provided that a single

primary stability batch will be tested for antimicrobial preservative effectiveness at the proposed shelf life.

P 2.6 Compatibility

The compatibility of the drug product with reconstitution diluent(s) or dosage devices (e.g., precipitation of drug substance in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labeling.

Where sterile, reconstituted products are to be further diluted, compatibility should be demonstrated with all diluents over the range of dilution proposed in the labelling. These studies should preferably be conducted on aged samples. Where the labelling does not specify the type of containers, compatibility (with respect to parameters such as appearance, pH, assay, levels of individual and total degradation products, sub-visible particulate matter and extractables from the packaging components) should be demonstrated in glass, PVC, and polyolefin containers. However, if one or more containers are identified in the labelling, compatibility of admixtures needs to be demonstrated only in the specified containers.

Studies should cover the duration of storage reported in the labelling (e.g., 24 hours under controlled room temperature and 72 hours under refrigeration). Where the labelling specifies co-administration with other drugs, compatibility should be demonstrated with respect to the principal drug as well as the co-administered drug (i.e., in addition to other aforementioned parameters for the mixture, the assay and degradation levels of each co-administered drug should be reported).

For existing drugs (e.g., generics), if levels of impurities or other parameters warrant, these studies should be carried out in parallel with the reference product to adequately qualify the impurity and other limits proposed in the drug product specification(s).

P 3 Manufacture

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. It should be ensured that the information included in the DMF is up to date (e.g., updated every two years) and that the data has been received by Health Canada. Copies of the letters of access should be provided under the Regional Information section. If a Canadian agent is used by the DMF Holder, a letter *from the DMF Holder* should be submitted allowing the agent to act on their behalf, rather than the letter coming from the Canadian agent.

P 3.1 Manufacturer(s)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

This includes the facilities involved in the fabrication, packaging, labelling, testing, importing, storage, and distribution of the drug product. If certain companies are responsible only for specific steps (e.g., manufacturing of an intermediate), this should be indicated. The list of manufacturers should specify the actual production or manufacturing site(s) involved, rather than the administrative offices.

P 3.2 Batch Formula

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.

The batch formula should express the quantity of each component on a per batch basis including a statement of the total weight or measure of the batch. This 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, etc.). If the drug product is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g., "1 mg of active ingredient base = 1.075 mg active ingredient hydrochloride"). All overages should be clearly indicated (e.g., "Contains 5 kg overage of the drug substance to compensate for manufacturing losses.").

The components should be declared by their proper or common names, Quality standards (e.g., USP, Ph.Eur., House, etc.) and, if applicable, their grades (e.g., "Microcrystalline Cellulose NF (PH 102)").

P 3.3 Description of Manufacturing Process and Process Controls

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

A narrative description of the manufacturing process, including packaging, that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g., tumble blender, in-line homogeniser) and working capacity, where relevant.

Steps in the process should have the appropriate process parameters identified, such as time, temperature, or pH. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in Section P 3.4. In certain cases, environmental conditions (e.g., low humidity for an effervescent product) should be stated.

Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either referenced or filed in this section (P 3.3).

The proposed commercial batch sizes should be stated. See section R 1 for discussion on production scale.

P 3.4 Controls of Critical Steps and Intermediates

Critical Steps: Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified in P3.3 of the manufacturing process, to ensure that the process is controlled.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Examples of applicable in-process controls include: (i) *granulations:* moisture, blend uniformity, bulk and tapped densities, particle size distribution; (ii)*solid oral products:* average weight, weight variation, hardness, thickness, friability, disintegration, weight gain during coating; (iii) *semi-solids:* viscosity, homogeneity, pH; (iv) *transdermal patches:* assay of drug-adhesive mixture, weight per area of coated patch without backing; (v) *metered dose inhalers:* fill weight/volume, leak testing, valve delivery; (vi) *dry powder inhalers*: assay of drug-excipient blend, moisture, weight variation of individually contained doses such as capsules or blisters; (vii) *liquids:* pH, specific gravity, clarity of solutions; (viii) *parenterals:* appearance, clarity, fill volume/weight, pH, filter integrity tests, particulate matter.

Reference Guidances: Q2A, Q2B, Q6A

P 3.5 Process Validation and/or Evaluation

Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process (e.g., validation of the sterilisation process or aseptic processing or filling). Viral safety evaluation should be provided in A2, if necessary.

The following information should be provided:

(a) a copy of the process validation protocol, specific to this drug product, which identifies the critical equipment and process parameters that can affect the quality of the drug product and defines testing parameters, sampling plans, analytical procedures, and acceptance criteria;

(b) confirmation that three consecutive, production-scale batches of this drug product will be subjected to prospective validation in accordance with Health Canada's *Validation Guidelines for Pharmaceutical Dosage Forms* and *Cleaning Validation Guidelines*;

(c) if the process validation studies have already been conducted (e.g., as for sterile products), a copy of process validation report should be submitted in lieu of (a) and (b) above, a summary of these process validation studies should also be provided.

The manufacture of sterile drugs needs a well-controlled manufacturing area (e.g., a strictly controlled environment, highly reliable procedures, and numerous in-process controls). A detailed description of these conditions, procedures, and controls should be provided, together with actual copies of the following standard operating procedures:

(a) washing, treatment, sterilizing, and depyrogenating of containers, closures, and equipment;

(b) filtration of solutions;

(c) lyophilization process;

(d) leaker test of filled and sealed ampoules;

(e) final inspection of the product; and

(f) sterilization cycle.

The sterilization process used to destroy or remove microorganisms is probably the single most important process in the manufacture of parenteral drugs. The process can make use of moist heat (e.g., steam), dry heat, filtration, gaseous sterilization (e.g., ethylene oxide), or radiation. It should be noted that terminal steam sterilization, when practical, is considered to be the method of choice to ensure sterility of the final drug product. Therefore, scientific justification for selecting any other method of sterilization should be provided.

The sterilization process should be described in detail, and evidence should be provided to confirm that it will produce a sterile product with a high degree of reliability and that the physical and chemical properties as well as the safety of the drug product will not be affected. Details such as F_o range, temperature range, and peak dwell time for a drug product and the container closure should be provided. Although standard autoclaving cycles of 121°C, 15 minutes or more, would not need a detailed rationale; such justifications should be provided for reduced temperature cycles or elevated temperature cycles with shortened exposure times. If ethylene oxide is used, studies and acceptance criteria should control the levels of residual ethylene oxide and related compounds.

Filters used should be validated with respect to pore size, compatibility with the product, absence of extractables and lack of adsorption of the drug substance or any of the components.

Reference Guidances: Good Manufacturing Practices
Validation Guidelines for Pharmaceutical Dosage Forms and Cleaning Validation Guidelines
Validation Documentation Requirements and Responsibilities for Drug Fabricators, Packagers / Labellers, Distributors and Importers
Sterilization Guidances: Aseptic Processes for Pharmaceuticals, Form-Fill-Seal for Pharmaceuticals, Gaseous Sterilization for Pharmaceuticals, Irradiation Sterilization for Pharmaceuticals, Moist Heat Sterilization for Pharmaceuticals

P 4 Control of Excipients

P 4.1 Specifications

The specifications for excipients should be provided.

This would include the specifications for all excipients, including those that do not appear in the final drug product (e.g., solvents, nitrogen, silicon for stoppers, etc.).

If the standard claimed for an excipient is a Schedule B compendial monograph, it is sufficient to state that the excipient is tested according to the requirements of that standard, rather than reproducing the specifications found in the Schedule B compendial monograph. If the standard claimed for an excipient is a non-Schedule B compendial monograph (e.g., House standard) or includes tests that are supplementary to those appearing in the Schedule B compendial monograph, a copy of the specification for the excipient should be provided.

Testing for microbial requirements should be at least as stringent as those specified in the corresponding USP monograph should one exist (e.g., as for Magnesium Stearate). Excipients derived from natural sources should have appropriate microbial tests and limits.

If additional purification is undertaken on commercially available excipients, details of the process of purification and modified specifications should be submitted.

Reference Guidances: Q6A

P 4.2 Analytical Procedures

The analytical procedures used for testing the excipients should be provided, where appropriate.

Copies of analytical procedures from Schedule B compendial monographs do not need to be submitted.

Reference Guidances: Q2A
Acceptable Methods

P 4.3 Validation of Analytical Procedures

Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided, where appropriate.

Copies of analytical validation information are normally not submitted for the testing of excipients.

Reference Guidances: Q2A, Q2B
Acceptable Methods

P 4.4 Justification of Specifications

Justification for the proposed excipient specifications should be provided, where appropriate.

This would include the tests that are supplementary to those appearing in the Schedule B compendial monograph.

Reference Guidances: Q3C

P 4.5 Excipients of Human or Animal Origin

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications, description of the testing performed, viral safety data). (Details in A2).

This information should include biological source, country of origin, manufacturer, and a brief description of the suitability of use based on the proposed controls.

For gelatin for use in pharmaceuticals, a letter of access from the proposed supplier should be provided to their Drug Master File, which is registered with Health Canada. Furthermore, confirmation should be included with a letter of attestation that the gelatin used is free of Bovine Spongiform Encephalopathy (BSE) / Transmissible Spongiform Encephalopathy (TSE).

Reference Guidances: Q5A, Q5D, Q6B

P 4.6 Novel Excipients

For excipient(s) used for the first time in a drug product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data (nonclinical and/or clinical) should be provided according to the drug substance and/or drug product format. (Details in A3).

P 5 Control of Drug Product

P 5.1 Specification(s)

The specification(s) for the drug product should be provided.

As defined in ICH's Q6A guidance document, a specification is a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

A copy of the drug product specification(s) from the sponsor (as well from the company responsible for release testing, if different from the sponsor) should be provided, dated and signed by authorized personnel (i.e., the person in charge of the Quality Control department). The specification reference number, version, and date should be provided for version control purposes. The standard declared by the sponsor could be a

Schedule B compendial standard (e.g., USP, BP, etc.), Manufacturer's or House Standard, Prescribed Standard (e.g., Canadian Standard Drugs in Division C.06 of the *Food and Drug Regulations*), or a Professed Standard.

Although a Schedule B compendial monograph may exist, a sponsor can choose to use a Manufacturer's Standard which indicates that the material may differ in some respect from the compendial standard. However, according to section C.01.011 of the *Food and Drug Regulations*, no person shall use a manufacturer's standard for a drug that provides (a) a lesser degree of purity than the highest degree of purity and (b) a greater variance in potency than the least variation in potency, provided for that drug in any publication mentioned in Schedule B to the *Act*. Therefore, if a manufacturer's standard is used, the controls on purity (e.g., limits on specified degradation products) and potency should be as tight as the most stringent of those listed in the Schedule B compendial monographs.

If the drug submission is for a non-official drug (e.g., where neither a Prescribed nor a Schedule B compendial standard exists), a professed standard is used and the product labelling for such products does not carry any standard.

The specification can be summarized according to Health Canada's Quality Summary template including the Tests, Method Types, Sources, and Code Number/Version/Date. The acceptance criteria should also be provided in the summary of the specification(s). The Method Type should indicate the kind of analytical procedure used (e.g., visual, IR, UV, HPLC, etc.); the Source refers to the origin of the analytical procedure (e.g., USP, BP, House, etc.); and the Code Number/Version/Date should be provided for version control purposes.

ICH's Q6A guidance document outlines recommendations for a number of universal and specific tests and criteria for drug products.

The following information provides suggestions on specific tests and criteria that are not addressed by ICH's Q6A guidance document:

Dosage Form	Specific Tests
Modified-release products	a meaningful drug-release method
Inhalation and Nasal Products	consistency of delivered dose (throughout the use of the product), particle or droplet size distribution profiles (comparable to the product used in *in vivo* studies, where applicable), and if applicable for the dosage form, moisture content, leak rate, microbial limits, preservative assay, sterility, and weight loss
Suppositories	uniformity of dosage units, melting point
Transdermals	peal or shear force, mean weight per unit area, dissolution

The test for uniformity of dosage units should be included in the specifications of all dosage forms where a variation in uniformity of dose from unit to unit can occur. The test for uniformity of dosage units could be physical (weight variation) or chemical (content uniformity), depending on the formulation, method of

manufacture, and in-process testing. The requirements for testing the uniformity of dosage units have been developed by the Schedule B compendia, and it is recommended that these be used in order that an appropriate test be established. It is expected that the strictest compendial standard (e.g., for acceptance criteria) will be adopted.

Reference Guidances: Q3B, Q3C, Q6A

P 5.2 Analytical Procedures

The analytical procedures used for testing the drug product should be provided.

Copies of the House analytical procedures used during the drug development (if used to support testing results in the drug submission) as well as those proposed for routine testing should be provided. The tables in Health Canada's Quality Summary template can be used to summarize the analytical procedures. Unless modified, it is not necessary to provide copies of Schedule B compendial analytical procedures.

The system suitability tests (SST's) are an integral part of chromatographic analytical procedures. As a minimum, HPLC and GC methods should include SST's for resolution and repeatability. For HPLC methods to control degradation products, this is typically done using a solution of the drug substance with a concentration corresponding to the limit for unspecified degradation products. Resolution of the two closest eluting peaks is generally recommended. However, choice of alternate peaks can be used if justified (e.g., choice of a toxic impurity). In accordance with the USP General Chapter on *Chromatography* and Health Canada's guidance document *Acceptable Methods*, the repeatability test should include an acceptable number of replicate injections (i.e., five or six).

Reference Guidances: Q2A
Acceptable Methods

P 5.3 Validation of Analytical Procedures

Analytical validation information, including experimental data, for the analytical procedures used for testing the drug product, should be provided.

Copies of the validation reports for the analytical procedures used during the drug development (if used to support testing results in the drug submission) as well as those proposed for routine testing should be provided. The tables in Health Canada's Quality Summary template can be used to summarize the validation information.

As outlined in Health Canada's guidance document *Acceptable Methods*, partial revalidation is necessary for methods that appear in a Schedule B compendial monograph. These revalidation criteria are recognized by other Regulatory Agencies and the compendia themselves. The compendial methods, as published, are typically validated using a drug substance or a drug product originating from a specific manufacturer. Different sources of the same drug substance or drug product can contain impurities and degradation products that were not considered during the development of the monograph.

If a Schedule B compendial standard is claimed and a House method is used in lieu of the compendial method (e.g., for potency or for specified degradation products), equivalency of the House and compendial methods should be demonstrated. This could be accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study.

Reference Guidances: Q2A, Q2B
Acceptable Methods

P 5.4 Batch Analyses

A description of batches and results of batch analyses should be provided.

This would include information such as strength, batch number, batch size, date and site of production, etc. on relevant drug product batches (e.g., used in nonclinical, clinical, comparative, stability, pilot, scale-up, and, if available, production-scale batches) used to establish the specification(s) and evaluate consistency in manufacturing.

Analytical results tested by the company responsible for release testing should be provided from at least two batches of each strength. Bracketing and matrixing of proportional strengths can be applied, if scientifically justified. The testing results should include the batch(es) used in the nonclinical, clinical and/or comparative bioavailability studies. Copies of the certificates of analyses for these batches should be provided in the drug submission and the company responsible for generating the testing results should be identified. The individual results or the mean, the RSD, and the range for the content uniformity and dissolution tests should be included.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "All tests meet specifications". This should include ranges of analytical results and any trends that were observed. For quantitative tests (e.g., as in individual and total degradation product tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such as "within limits" or "conforms". A discussion and justification should be provided for any incomplete analyses (e.g., results not tested according to the proposed specification).

If the proposed dosage form is a scored tablet, the results of a study should be provided testing the uniformity of dosage units of the manually-split tablet halves. The data provided in the drug submission should include a description of the test method, individual values, mean, and relative standard deviation (RSD). Uniformity testing (i.e., content uniformity or weight variation, depending on the dosage form) should be performed on each split portion from a minimum of 10 randomly selected whole tablets. As an illustrative example, the number of units (i.e., the splits) would be 20 halves for bisected tablets or 40 quarters for quadrisected tablets. At least one batch of each strength should be tested. Ideally, the study should cover a range of the hardness values. The splitting of the tablets should be performed in a manner that would be representative of that used by the consumer (i.e., manually split by hand). The uniformity test on split portions can be demonstrated on a one-time basis and does not need to be added to the drug product specification(s). The acceptance criteria (range and variation) should be as described in the USP General Chapter <905> *Uniformity of Dosage Units* for whole tablets. The tablet description on the drug product specifications, and under the Availability section of the Product Monograph, should reflect the presence of a score.

Reference Guidances: Q3B, Q3C, Q6A

P 5.5 Characterisation of Impurities

Information on the characterisation of impurities should be provided, if not previously provided in "S 3.2 Impurities".

This information would include degradation products (e.g., from interaction of the drug substance with excipients or the container closure system), solvents in the manufacturing process for the drug product, etc.. The tables in Health Canada's Quality Summary template in section S 3.2 can be used to summarize this information.

Reference Guidances: Q3B, Q3C, Q6A
Identification, Qualification, and Control of Related Impurities in New Drugs
Identification, Qualification, and Control of Related Impurities in Existing Drugs

P 5.6 Justification of Specification(s)

Justification for the proposed drug product specification(s) should be provided.

This should include a discussion on the inclusion of certain tests, evolution of tests, analytical procedures, and acceptance criteria, differences from compendial standard, etc.. If the Schedule B compendial methods have been modified or replaced, a discussion should be included.

The justification for certain tests, analytical procedures, and acceptance criteria may have been discussed in other sections of the drug submission (e.g., degradation products) and do not need to be repeated here, although a cross-reference to their location should be provided.

The following sections outline considerations for the justification of specifications of some testing procedures and dosage forms. Other considerations are outlined in ICH's Q6A guidance document.

In vitro Dissolution or Drug Release

The results of studies justifying the choice of *in vitro* dissolution or drug release conditions (apparatus, rotation speed, medium) should be provided. Data should also be submitted to demonstrate whether the method is sensitive to changes in manufacturing processes and/or changes in grades and/or amounts of critical excipients. The dissolution method should be sensitive to any changes in the product that would result in a change in one or more of the pharmacokinetic parameters. Use of single point test or a dissolution range should be justified based on the solubility and/or biopharmaceutical classification of the drug.

Modified-release dosage forms should have a meaningful *in vitro* release rate (dissolution) test that is used for routine quality control. Preferably this test should possess *in vitro-in vivo* correlation. Results demonstrating the effect of pH on the dissolution profile should be submitted if appropriate for the type of dosage form.

The testing conditions should be set to cover the entire time period of expected release (e.g., at least three

test intervals chosen for a 12-hour release and additional test intervals for longer duration of release). One of the test points should be at the early stage of drug release (e.g., within the first hour) to demonstrate absence of dose dumping. At each test period, upper and lower limits should be set for individual units. Generally, the acceptance range at each intermediate test point should not exceed 25% or ± 12.5% of the targeted value. Dissolution results should be submitted for several lots, including those lots used for pharmacokinetic and bioavailability studies.

Transdermals

Adhesion of the patch should be tested to evaluate the patch's adhesive property (also termed a peel test or shear test). It is a numerical value obtained from an *in vitro* test and is useful to detect any manufacturing anomaly and serves as an index to monitor stability.

The results of studies justifying the choice of dissolution conditions (apparatus, rotation speed, medium) should be provided. Data should also be submitted to demonstrate whether the drug release method is sensitive to changes in manufacturing processes and/or changes in grades and/or amounts of critical excipients. The dissolution method should be sensitive to any changes in the product that would result in a change in one or more of the pharmacokinetic parameters.

P 6 Reference Standards or Materials

Information on the reference standards or reference materials used for testing of the drug product should be provided, if not previously provided in "S 5 Reference Standards or Materials".

See section S 5 for information that should be provided on reference standards or materials.

Reference Guidances: Q6A
Acceptable Methods

P 7 Container Closure System

A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

For non-functional secondary packaging components (e.g., those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

Suitability information should be located in P 2.

Provide a description and specifications for the packaging components that:

(a) come in direct contact with the dosage form (container, closure, liner, desiccant);

(b) are used as a protective barrier to help ensure stability or sterility;

(c) are used for drug delivery;

(d) are necessary to ensure drug product quality during transportation;

Include all proposed market containers as well as sample packs for physicians. The tables in Health Canada's Quality Summary template can be used to summarize the above information.

The information for the container closure system depends on the dosage form and route of administration. The following table outlines the general recommendations for the various dosage forms (some of this highlighted information can be performed on a one-time basis to establish the suitability of the container closure system and should be discussed in section P 2):

	Solid Oral Products	**Oral Liquid and Topical Products**	**Sterile Products (including Ophthalmics)**
Specifications for routine testing:			
- Name, physical description, dimensions (e.g., thickness, etc.)	x	x	x
- Specific identification tests (e.g., IR) for components that come in direct contact with the dosage form	x	x	x
Qualification of components:			
- Composition and drawings for all components (including cap liners, coatings for metal tubes, elastomers, adhesives, silicon, etc.)	x	x	x
- Description of any additional treatments*	x	x	x (sterilization and depyrogenation of the components)
- USP <661> Containers	x	x	x (includes USP <87> / <88> tests)
- USP <671> Containers - Permeation	x	x	x
- USP <381> Elastomeric Closures for Injections	--	--	x (includes USP <87> / <88> tests)

* e.g., coating of tubes, siliconization of rubber stoppers, sulphur treatment of ampoules/vials

x information should be submitted

-- information does not need to be submitted

Comparative studies can be necessary for changes in components (e.g., comparative delivery study (droplet size) for a change in supplier of dropper tips).

The information on the composition should be available to Health Canada either in the drug submission or in a Drug Master File. Refer to Health Canada's guidance document *Product Master Files* (soon to be renamed *Drug Master Files)* for filing requirements for Type II DMF's (packaging materials).

P 8 Stability

As outlined in ICH's Q1A guidance document, the purpose of stability testing is to provide evidence on how the quality of a drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a shelf life for the drug product and recommended storage conditions.

Reference Guidances: Q1A, Q1B, Q1C
Stability Testing of Existing Drug Substances and Products

P 8.1 Stability Summary and Conclusions

The types of studies conducted, protocols used, and the results of the studies should be summarised. The summary should include, for example, conclusions with respect to storage conditions and shelf life, and, if applicable, in-use storage conditions and shelf life.

Stress testing:

As outlined in ICH's Q1A guidance document, photostability testing should be conducted on at least one primary batch of the drug product if appropriate. Stress testing of other types of dosage forms may be appropriate (e.g., cyclic studies of semi-solids, freeze-thaw studies).

Accelerated and long term testing:

The conditions for stability testing of drug products are outlined in ICH's Q1A guidance document. The following storage conditions and minimum data at the time of submission are recommended by ICH's Q1A guidance document for the Primary Batches. When "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition. See ICH's Q1A guidance document for definition of "significant change".

Study	Storage Condition	Minimum Time Period Covered by Data at Submission
Long term	25°C ± 2°C / 60% RH ± 5% RH	12 months
Intermediate	30°C ± 2°C / 60% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C / 75% RH ± 5% RH	6 months

RH = relative humidity

Other conditions are outlined in the ICH's Q1A guidance document for drug products intended for storage in a refrigerator and those intended for storage in a freezer. Drug products intended for storage below -20°C should be treated on a case-by-case basis.

For existing drugs (e.g., generics), stability information from accelerated and long term testing should be provided on at least two batches of each strength in the container closure system proposed for marketing. Bracketing and matrixing can be applied, if scientifically justified. See Health Canada's guidance document *Stability Testing of Existing Drug Substances and Products* for further details.

For sterile products, sterility should be reported at the beginning and end of shelf life. For parenteral products, sub-visible particulate matter should be reported frequently, but not necessarily at every test interval. Bacterial endotoxins need only be reported at the initial test interval. Weight loss from plastic containers should be reported over the shelf life. In-use periods beyond 28 days for parenteral and ophthalmic products should be justified with experimental data.

The information on the stability studies should include details such as storage conditions, strength, batch number, batch size, container closure system, and completed (and proposed) test intervals. The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "All tests meet specifications". This should include ranges of analytical results and any trends that were observed. For quantitative tests (e.g., as in individual and total degradation product tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such as "within limits" or "conforms".

Proposed storage conditions and shelf life:

The proposed storage conditions with suitable tolerances (e.g., a temperature range with upper and lower criteria) and shelf life for the drug product should be provided.

When the drug product has been shown to be stable (e.g., under the ICH conditions with long term studies at 25• C ± 2• C/60% RH ± 5% RH and accelerated studies at 40• C ± 2• C/75% RH ± 5% RH), the following storage recommendation would generally be considered acceptable:

"Store at controlled room temperature (15• C to 30• C)."

Based on the results of the stability evaluation, other storage precautions may be warranted (e.g., "Protect from light", "Protect from moisture").

Limited extrapolation of the real time data from the long term storage condition beyond the observed range to extend the shelf life can be undertaken at approval time, if justified.

P 8.2 Post-approval Stability Protocol and Stability Commitment

The post-approval stability protocol and stability commitment should be provided.

When available long term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, a commitment should be made to continue the stability studies post-approval in order to firmly establish the shelf life. The long term stability studies for the *Commitment Batches* should be conducted through the proposed shelf life (and the accelerated studies for six months) on at least three production batches of each strength (or two production batches of each strength for existing drugs).

A *Continuing Stability Programme* is implemented to ensure compliance with the approved shelf life specifications. A minimum of one batch of every strength of the drug product is enrolled into the continuing stability programme each year.

The stability protocols for the *Commitment Batches* and *Continuing (i.e., ongoing) Batches* should include, but not limited to:

(a) Number of batches per strength and batch sizes;

(b) Tests and acceptance criteria;

(c) Container closure system(s);

(d) Testing frequency; and

(e) Storage conditions (and tolerances) of samples

Any differences in the stability protocols used for the primary batches and those proposed for the *Commitment Batches* or *Continuing Batches* should be scientifically justified.

P 8.3 Stability Data

Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Information on characterisation of impurities is located in P 5.5.

The actual stability results (i.e., raw data) used to support the proposed shelf life should be provided in the drug submission. For quantitative tests (e.g., as in individual and total degradation product tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such as

"within limits" or "conforms".

A APPENDICES

A 1 Facilities and Equipment

Not applicable (i.e., not a Biotech product).

A 2 Adventitious Agents Safety Evaluation

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications, description of the testing performed, viral safety data).

A 3 Novel Excipients

For excipient(s) used for the first time in a drug product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data (nonclinical and/or clinical) should be provided according to the drug substance and/or drug product format.

R REGIONAL INFORMATION

R 1 Production Documentation

R 1.1 Executed Production Documents

A minimum of two batches of each strength should be manufactured. Bracketing and matrixing of proportional strengths can be applied, if scientifically justified. These batches should be 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.

Copies of the executed production documents should be provided for the batches used in the pivotal clinical and/or comparative bioavailability studies. Any notations made by operators on the executed production documents should be clearly legible.

R 1.2 Master Production Documents

Copies of the drug product master production documents should be provided for each proposed strength, commercial batch size, and manufacturing site.

The details in the master production documents should include, but not limited to, the following:

(a) dispensing, processing and packaging sections with relevant material and operational details;

(b) relevant calculations (e.g., if the amount of drug substance is adjusted based on the potency results or on the anhydrous basis, etc.);

(c) identification of all equipment by type and working capacity;

(d) process parameters (e.g., mixing time, mixing speed, milling screen size, processing temperature range, tablet machine speed, etc.);

(e) list of in-process tests (e.g., appearance, pH, potency, blend uniformity, viscosity, particle size distribution, LOD, weight variation, hardness, disintegration time, weight gain during coating, leaker test, minimum fill, clarity);

(f) sampling plan with regard to the:

- (i) steps where sampling should be done (e.g., drying, lubrication, compression)
- (ii) number of samples that should be tested (e.g., blend drawn using a sampling thief from x number of different parts of the blender)
- (iii) frequency of testing (e.g., weight variation every x minutes during compression or capsule filling);

(g) precautions necessary to ensure product quality (e.g., temperature and humidity control, maximum holding times);

(h) theoretical and actual yield;

(i) compliance with the Good Manufacturing Practices (GMP) requirements as per the provisions of Division C.02 of the *Food and Drug Regulations*.

Reference Guidances: Good Manufacturing Practices

R 2 Medical Devices

According to the *Food and Drugs Act*:

A *device* means any article, instrument, apparatus or contrivance, including any component, part or

accessory thereof, manufactured, sold or represented for use in:

(a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals,

(b) restoring, correcting or modifying a body function or the body structure of human beings or animals,

(c) the diagnosis of pregnancy in human beings or animals, or

(d) the care of human beings or animals during pregnancy and at and after birth of the offspring, including care of the offspring,

and includes a contraceptive device but does not include a drug.

A *drug* includes any substance or mixture of substances manufactured, sold or represented for use in

(a) the diagnosis, treatment, mitigation or prevention of a disease, disorder, abnormal physical state, or its symptoms, in human beings or animals,

(b) restoring, correcting or modifying organic functions in human beings or animals, or

(c) disinfection in premises in which food is manufactured, prepared or kept.

Combination products will be classified as either medical devices or drugs according to the principal mechanism of action by which the claimed effect to purpose is achieved. Those combination products that have been classified as devices include drug coated devices such as catheters, pacemaker leads, drug impregnated devices. Those that have been classified as drugs include prefilled syringes, transdermal patches, peritoneal dialysis solutions, implants whose primary purpose is to release a drug.

A 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, etc.) should be provided.

M MISCELLANEOUS

M 1 ICH Quality Guidance Documents (Chemical Entities)

ICH Quality Guidances Documents (date adopted by Health Canada)	Access
Q1A/R - Stability Testing of New Drug Substances and Products	<not yet adopted>*
Q1B - Stability Testing: Photostability Testing of New Drug Substances and Products (1999)	TPD Website
Q1C - Stability Testing: Requirements for New Dosage Forms (1998)	TPD Website

Q2A - Text on Validation of Analytical Procedures (1999)	TPD Website
Q2B - Validation of Analytical Procedures: Methodology (1999)	TPD Website
Q3A - Impurities in New Drug Substances (1995)	Guidelines Order Form
Q3B - Impurities in New Drug Products (1999)	TPD Website
Q3C - Impurities: Guideline for Residual Solvents (1999)	TPD Website
Q6A - Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Products: Chemical Substances and Products	<not yet adopted>*
Q7A - Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients	<not yet adopted>*
M4Q - Common Technical Document - Quality	<not yet adopted>*

* Available on ICH's Website: www.ifpma.org/ich1.html

M 2 Health Canada Quality Templates and Guidance Documents (Chemical Entities)

Health Canada Quality Templates	Access
Quality Overall Summary - Chemical Entities (New Drug Submissions or Abbreviated New Drug Submissions) (QOS-CE (NDS)) (DRAFT, 2001)	TPD Website
Analytical Procedures and Validation Information Summaries (DRAFT, 2001)	TPD Website
Certified Product Information Document - Chemical Entities (CPID-CE) (DRAFT, 2001)	TPD Website

Health Canada Quality Guidance Documents	Access
Acceptable Methods (1994)	Guidelines Order Form
Chemistry and Manufacturing: New Drugs (1990)	Guidelines Order Form
Extension of Expiration Dates (1992)	TPD Website
Identification, Qualification, and Control of Related Impurities in New Drugs (DRAFT, 1999)	TPD Website
Identification, Qualification, and Control of Related Impurities in Existing Drugs (DRAFT, 1999)	TPD Website
Marketed New Drug Products, Changes to (1994)	TPD Website
Marketed New Drug Products, Stability Requirements for Changes to (1994)	TPD Website
Product Master Files (soon to be renamed Drug Master Files) (1994)	Guidelines Order Form
Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs) (DRAFT, 2001)	TPD Website
Reduction in the Use of Dichloromethane in Tablet Coating Operations (DRAFT, 1997)	TPD Website
Stability Testing of Existing Drug Substances and Products (DRAFT, 1997)	TPD Website
Stereochemical Issues in Chiral Drug Development (2000)	TPD Website

Guidelines Order Form: Guidelines listed on the Guidelines Order Form are available in printed form only, through the Canadian Government Publishing Centre (CGPC). The Order Form is available on the TPD Website under "Forms" or from the CGPC (Tel: (819) 956-4800; Fax: (819) 994-1498; Internet: http://publications.pwgsc.gc.ca).

Health Canada's Therapeutic Products Directorate (TPD) website:
www.hc-sc.gc.ca/hpb-dgps/therapeut

Health Canada Santé Canada

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DRAFT GUIDANCE FOR INDUSTRY

Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs)

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Health Products and Food Branch
Guidance Document

Canada

Our mission is to help the people of Canada maintain and improve their health.

Health Canada

Our mandate is to promote good nutrition and informed use of drugs, food, medical devices and natural health products, and to maximize the safety and efficacy of drugs, food, natural health products, medical devices, biologics and related biotechnology products in the Canadian marketplace and health system.

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FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with Health Canada policies, governing statutes and regulations. They also serve to provide review and compliance guidance to staff, thereby ensuring that Health Canada's mandate is implemented in a fair, consistent and effective manner.

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 scientific justification. Alternate approaches should be discussed in advance with Health Canada 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 for the adequate assessment of 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.

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G GENERAL

G 1 Purpose

This document is intended to provide guidance with regard to the Quality (i.e., Chemistry and Manufacturing) portion of New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs) containing drug substances and their corresponding products of synthetic or semi-synthetic origin, excluding Biotechnological/Biological (Schedule D) and Radiopharmaceutical (Schedule C) drugs, that are filed with Health Canada pursuant to Division C.08 of the *Food and Drug Regulations*. The purpose of the guidance document is to outline the Quality technical requirements and to assist submission sponsors in preparing the NDS and ANDS to ensure an effective and efficient review process. It can also be used as guidance on the requirements for related drug submissions (e.g., Supplemental NDSs, Supplemental ANDSs, Notifiable Changes, etc.).

This document covers variety of NDSs and ANDSs and may not be applicable in its entirety for all cases. Alternate approaches to the principles and practices described in this document can be acceptable provided they are supported by adequate scientific justification. Sponsors are advised to discuss, in advance, alternate approaches in their drug submission to avoid rejection or withdrawal of the drug submission.

G 2 Scope

This guidance document applies to New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs) containing drug substances and their corresponding products of synthetic or semi-synthetic origin, excluding Biotechnological/Biological (Schedule D) and Radiopharmaceutical (Schedule C) drugs, that are filed with Health Canada pursuant to Division C.08 of the *Food and Drug Regulations*. It can also be used as guidance on the requirements for related drug submissions (e.g., Supplemental NDSs, Supplemental ANDSs, Notifiable Changes, etc.).

This guidance document occasionally makes reference to "existing drugs". An "existing drug" is one that is not a new active substance but requires the filing of a New Drug Submission (NDS) or an Abbreviated New Drug Submission (ANDS) for which a Notice of Compliance has been previously issued pursuant to Division C.08 of the *Food and Drug Regulations* (e.g., generic products). This could also include submissions for new dosage forms, new strengths, etc..

G 3 Preamble

With the finalization of the *Common Technical Document (CTD)*, the International Conference on Harmonisation (ICH) has reached agreement upon a common *format* of applications for the registration of pharmaceuticals for human use. Within the CTD, is the *Common Technical Document - Quality (CTD-Q)* (Module 3) outlining the format for the Quality portion of applications for New Chemical Entities. Also as part of the CTD-Q exercise, the ICH process has produced a *Quality Overall*

Summary (QOS) (Module 2) which is a summary that follows the scope and the outline of the *Quality Module* (Module 3).

During the transitional period from July 2001 to the official CTD implementation date, drug submissions may be filed in the current Canadian, the "Modified NDA", or the CTD format. When filing in a particular format, the applicable filing requirements for that format apply.

This *Quality (C&M) Guidance: NDSs and ANDSs* follows the format recommended in ICH's CTD-Q. Where appropriate, the text from ICH's CTD-Q has been repeated **in bold** (*including spelling convention*) under each section, followed by further guidance to assist sponsors in the preparation of NDSs and ANDSs. This guidance document is an updated version of Health Canada's 1990 *Chemistry and Manufacturing: New Drugs* guideline.

Quality Summary (Module 2 of the CTD or *Part 2 of the NDS/ANDS)*:

Subsection C.08.005.1 of the *Food and Drug Regulations* stipulates that new drug submissions (NDSs), abbreviated new drug submissions (ANDSs), supplemental new drug submissions (SNDSs), and abbreviated new drug submissions (SANDSs) must include a comprehensive summary of each human, animal and *in vitro* study referred to or contained in the submission or supplement. The intent of this requirement is to facilitate the evaluation of the extensive experimental data and hence contribute toward a more effective and timely processing of drug submissions.

The *Quality Summary* is a comprehensive summary that follows the scope and the outline of the Quality Module (Module 3 of the CTD or Part 2 of the NDS/ANDS, whichever applies). The Quality Summary should not include information, data, or justification that was not already included in Quality Module or in other parts of the drug submission.

Since 1995, sponsors of NDSs and ANDSs have been required to complete the *Comprehensive Summary (Chemistry and Manufacturing) (CS(CM))*. This document provided a summary of the Quality data submitted to Health Canada according to a prescribed format and hence contributed towards a more effective and timely processing of these drug submissions. The template has since been updated according to current Quality standards and terminology, as well as to reflect the developments on the international level. With the completion of the updated version of the template, *Quality Overall Summary - Chemical Entities (New Drug Submissions and Abbreviated New Drug Submissions) (QOS-CE (NDS))*, sponsors share responsibility the for the generation of the Quality evaluation report. The objectives of this document are two-fold:

(a) expediting the review process by enabling Evaluators to more efficiently spend their time on drug submission assessment; and

(b) improving drug submission quality by way of a more thorough compilation and appraisal of data requirements by sponsors in conjunction with the completion of the *QOS-CE (NDS)*.

The QOS-CE is an updated version of Health Canada's earlier Quality Summary templates (i.e., the *Comprehensive Summary (Chemistry and Manufacturing) (CS(CM))* and the *Quality Information Summary - Pharmaceuticals (QIS-P)*).

While both ICH's *Quality Overall Summary (QOS)* and Health Canada's *Quality Overall Summary - Chemical Entities (New Drug Submissions and Abbreviated New Drug Submissions) (QOS-CE (NDS))* provide an overview of the information presented in the Quality Module (also referred to as the Quality portion of the drug submission), the latter is meant to precisely define the type and extent of information considered necessary to produce a Canadian Quality evaluation report, once supplemented by the Evaluator's comments. Given their specific role within the Quality review process, sponsors of NDSs are encouraged to complete Health Canada's QOS-CE (NDS) to help ensure an effective and efficient review of drug submissions. Until such time that the CTD is a required format for ANDSs, and/or the eCTD is available for voluntary filing, sponsors of ANDSs are expected to use the QOS-CE (NDS).

ICH's *QOS* and Health Canada's *QOS-CE (NDS)* are collectively referred to as the *Quality Summary* throughout the remainder of this document.

Paper and electronic versions of the Quality Summary should be provided. The electronic version should be in a WordPerfect® format.

Quality Module (Module 3 of the CTD or *Part 2 of the NDS/ANDS*):

This guidance document is intended to provide direction to sponsors as to what information should be included in the Quality Module (also referred to as the Quality portion of the drug submission). The following sections describe the elements of the Quality technical requirements. ICH's CTD should be consulted for other portions of the Quality Module (e.g., Table of Contents, Literature References).

Certified Product Information Document - Chemical Entities (CPID-CE):

The CPID-CE constitutes part of the Notice of Compliance (NOC) package. The CPID-CE is provides an accurate record of technical data in the drug submission at the time the NOC is issued, and thereafter serves as an official reference document during the course of post-approval inspections and post-approval change evaluations as performed by Health Canada. The CPID-CE template represents an condensed version of the Quality Summary template which represents the final, agreed upon *key* data from the drug submission review (e.g., minimal data on the manufacturer(s), drug substance/drug product specifications, stability conclusions, etc.).

The CPID-CE template file is structured to permit the rapid assembly of the CPID-CE by copying requisite information from the corresponding portions of the Quality Summary filed with the original drug submission. It is understood that the numbering system of this document is not sequential. This was intentional to retain the same numbering as the parent *Quality Overall Summary - Chemical Entities (QOS-CE)* or *Quality Overall Summary (QOS)*.

For New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs), the CPID-CE should be provided *upon request* (i.e., typically when the review of the drug submission is near completion). For SNDSs, SANDSs, and Notifiable Changes (NC's), the CPID-CE should be submitted *at the time of filing* and provided in *Module 1*. It is acknowledged that when filing a Supplement or NC, the updated CPID-CE may include changes that did not require prior approval by Health Canada (e.g., as for Level 3 and 4 changes).

G 4 Notes on the Preparation of the *Quality Summary* and the *Quality Module*

Sponsors are encouraged to devote the sufficient time necessary to prepare a clear, precise Quality Summary which is based on the detailed information that is submitted in the Quality Module. The filing of an inaccurate or an incomplete Quality Summary will result in greater expenditure of an Evaluator's time in reviewing and summarizing data.

In developing Health Canada's Quality Summary template, a balance was needed between providing sufficient instruction regarding the format and content of information sought and designing a document that could accommodate variability in the types of studies and products described in these drug submissions. With respect to the latter consideration, it is expected that the tables included in the QOS-CE (NDS) template may need to be modified (e.g., with data cells being split or joined, as necessary). Additional modification of table structure or the substitution of a narrative paragraph, can also be warranted in certain circumstances in order to best summarize the data. All titles/parameters listed in the default tables should nonetheless be retained or addressed, regardless of their perceived relevance, unless the subject matter of the entire table does not apply to the drug submission in question.

For NDSs and ANDSs, if portions of the Quality Summary are clearly not relevant due to the nature of the drug substance or drug product, this should be indicated by the designation "Not Applicable" (e.g., under the heading of section P 4.5 if there are not any excipients of human or animal origin used in the manufacture of the drug product). Any portions that are "Not applicable" *should not be deleted* and should be accompanied by an explanatory note describing the reasons for the inapplicability.

When the information in a section has been submitted in a prior drug submission in its entirety, without changes, the relevant section should be deleted and so noted under the Introduction, along with the name of the drug product, sponsor's name, date of the Notice of Compliance, and file number and submission control number of the cross-referenced submission. As in a SNDS, SANDS, or Notifiable Change (NC), those sections of the Quality Summary and the Quality Module affected by the proposed change should be submitted. Those sections not affected by the change can be deleted. As an example, Section "S Drug Substance", should not be included in a Supplement for an additional strength when there is not any change proposed to the information of the drug substance as described in the approved, cross-referenced submission.

The above practice should *not* be followed with respect to cross-referenced Drug Master Files (DMF's). DMF's should be identified in the appropriate sections (e.g., S 2.1, P 3.1). The sections of the Quality Summary should not be deleted. It is the sponsor's responsibility to submit the relevant non-proprietary information provided by the DMF Holder (e.g., from the Open DMF), obtained in the public domain, and/or developed by the sponsor. For DMF requirements, consult Health Canada's guidance document *Product Master Files* (soon to be renamed *Drug Master Files*). When the sponsor summarizes data obtained from the DMF Holder or the scientific literature, the source of reproduced information should be specified.

The following information is intended to provide assistance to sponsors in preparing the Quality Summary and the Quality Module:

(a) Reference to applicable Quality guidance documents are identified under the various sections.

Those developed by ICH are identified by their code name only (e.g., Q1A). Also provided, as an appendix to this document, is a comprehensive list of applicable Quality guidance documents. During the preparation of the drug submission, these Quality guidance documents should also be consulted as their content has not been repeated here.

(b) Abbreviations should not be used in the Quality Summary unless initially defined and consistently used (e.g., N/A = Not applicable), or unless they represent well-established scientific abbreviations (e.g., HPLC, UV, etc.).

(c) For "old drug substances in new drug products", submit sections *S 2.1 Manufacturer(s), S 4.1 Specifications, S 4.4 Batch Analyses, S 6 Container Closure System,* and *S 7.1 Stability Summary and Conclusions*, and any other pertinent components (e.g., particle size distribution); delete all the other non-applicable sections of the Drug Substance ("S") portion.

(d) This guidance document makes reference to "Schedule B compendial monographs", these are those compendial monographs that are recognized as official according to Schedule B to the *Food and Drugs Act* (e.g., USP, Ph.Eur., BP, etc.).

(e) The Quality information associated with any or all of the following scenarios may be submitted under one complete drug submission in the CTD format:

For a drug product containing more than one drug substance (e.g., substance "X", substance "Y"), the entire Drug Substance ("S") section for one drug substance should be followed by the entire "S" section for the next drug substance, then followed by a single Drug Product ("P") section. The name of the drug substance should be included in the headings of all applicable sections and subsections, to clearly distinguish the information for each drug substance.

For a drug substance and/or drug product which is manufactured by more than one manufacturer (e.g. Manufacturer "A" and Manufacturer "B", both manufacture the drug product using different equipment and separate facilities) and where there are differences in the Quality information associated with each manufacturer, the name of the manufacturer should be included in the heading of any affected sections and subsections, to clearly distinguish the drug substance and/or drug product information for each manufacturer. The numbering of the sections and subsections in this case should still be sequential. (e.g., *P 3.3 Description of Manufacturing Process and Process Controls [Manufacturer "A"]*; *P 3.3 Description of Manufacturing Process and Process Controls [Manufacturer "B"]*). NOTE the exceptions: Under *S.2.1 Manufacturer(s)* and *P 3.1 Manufacturer(s)*, multiple manufacturers should be listed without the need for any unique identifiers.

For a drug product with more than one dosage form (e.g., tablets, oral solution), the entire Drug Product ("P") section for one dosage form should be followed by the entire "P" section for the next dosage form. The name of the dosage form should be included in the headings of all applicable sections and subsections, to clearly distinguish the quality information for each dosage form.

For a drug product with more than one strength (e.g.. 10, 50, and 100 mg tablets), identification of the strength should be included in the heading of any affected sections, subsections, and/or

presentation of the information, to clearly distinguish the information for each strength. The numbering of the sections and subsections in this case should still be sequential.

(f) When filing a response to a deficiency request from Health Canada (e.g., Request for Clarification (Clarifax), Notice of Non-compliance (NON), Notice of Deficiency (NOD)), sponsors should use the *applicable sections* of the Quality Summary to summarize new or updated data (e.g., specifications, analytical procedures, stability results, etc.). A refiled/updated Quality Summary should *not* be submitted. However, in the case of an NOD or an extensive NON where the magnitude of deficiency comments warrants the filing of replacement volumes, a refiled/updated Quality Summary can be necessary.

(g) In order to facilitate the processing and evaluation of responses to deficiency requests from Health Canada, an *electronic version* of the consolidated deficiency comments and responses pertaining to the Quality issues should be provided in a question and answer format in a WordPerfect® format.

Reference Guidances: M4Q (i.e., CTD-Q)
Preparation of a Drug Submission in CTD Format (for CTD-based submissions)
Preparation of Human New Drug Submissions (for NDS-based submissions)
Modified FDA Format Drug Submissions for Products in Human Use

I INTRODUCTION

The introduction should include proprietary name, non-proprietary name or common name of the drug substance, company name, dosage form(s), strength(s), route of administration, and proposed indication(s).

Sponsors may provide a contact person's name, phone number, fax number, and e-mail address for ease of communication.

S DRUG SUBSTANCE

Some of the information included under the "S Drug Substance" section may not be available to the sponsor for the New Drug Submission or Abbreviated New Drug Submission. If such is the case, the supplier of the drug substance can file a Drug Master File directly with Health Canada. The supplier would then be considered the DMF Holder. This DMF will be held in strict confidence and will be used in support of the drug submission only upon receipt of written authorization from the supplier/DMF Holder of the drug substance (i.e., via a letter of access).

The sponsor should be able to provide most of the information on the drug substance, except possibly the proprietary information found in sections S 2.2, S 2.3, S 2.4 and S 2.6 (see below). It is the responsibility of the sponsor to obtain all other information from the supplier of the drug substance and include this in the drug submission. The information from the Open DMF should be provided in the drug submission and summarized in the Quality Summary.

Regardless of the information provided by the supplier of the drug substance, the manufacturer of the dosage form is responsible for ensuring that acceptable specifications and properly validated analytical procedures for the drug substance are developed by the manufacturer's facilities and for providing the results of batch analyses performed at the manufacturer's facilities.

For further information on the requirements for Drug Master Files, see Health Canada's guidance document *Product Master Files* (soon to be renamed *Drug Master Files*).

S 1 General Information

S 1.1 Nomenclature

Information on the nomenclature of the drug substance should be provided. For example:

(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, United States Adopted Name (USAN), British Approved Name (BAN)); and

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

The listed chemical names should be consistent with those appearing in scientific literature and those appearing on the product labelling (e.g., Product Monograph). Where several names exist, indicate the preferred name.

Where a chemical moiety is formed *in-situ* (e.g., by chemical reaction), both the starting and chemical moiety should be described.

S 1.2 Structure

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.

This information should be consistent with that provided in section S 1.1. For drug substances existing as salts, the molecular mass of the free base should also be provided.

S 1.3 General Properties

A list should be provided of physicochemical and other relevant properties of the drug substance.

This information can be used in developing the specifications, in formulating dosage forms, and in the testing for release and stability purposes. Give the physical and chemical properties of the drug substance such as the physical description, solubilities in common solvents (e.g., water, alcohols, chloroform, acetone, etc.), quantitative aqueous pH solubility profile (e.g., pH 1 to 8, dose/solubility volume), polymorphism, particle size distribution, pH and pKa values, UV absorption maxima and molar absorptivity, melting point, refractive index (for a liquid), hygroscopicity, partition coefficient, etc.. This list is by no means exhaustive, but provides an indication as to the type of information that could be included.

Some of the more important properties to be considered for all drug substances are discussed below in greater detail.

Physical description:

The description should include appearance, colour, and physical state. Solid forms should be identified as being crystalline or amorphous.

Solubilities/quantitative aqueous pH solubility profile:

The solubility should be provided in a number of common solvents (e.g., water, alcohols, chloroform, acetone, etc.). The solubilities over the physiological pH range (pH 1 to 8) in several buffered media should also be provided. Phrases such as "sparingly soluble" or "freely soluble" should be quantitatively defined or a literature reference can be provided (e.g., "as per USP"). If this information is not readily available (e.g., literature references, Open Drug Master File), it should be generated in-house.

The dose/solubility volume should be provided. The dose/solubility volume[1] is calculated based on the minimum concentration of the drug (in mg/mL), in the largest dosage strength, determined in the physiological pH range (pH 1 to 8) and temperature (37 ± 0.5°C). High solubility drugs are those with a dose/solubility volume of less than or equal to 250 mL. For example, Compound A has as its lowest solubility at 37 ± 0.5°C, 1.0 mg/mL at pH 7, and is available in 100 mg, 200 mg, and 400 mg strengths. This drug would be considered a low solubility drug as its dose/solubility volume is greater than 250 mL (400 mg/1.0 mg/mL = 400 mL).

Polymorphs:

If the potential for polymorphism is a concern, results from an investigation of several batches of the drug substance, recrystallized from several solvents, should be provided to determine if the drug substance exists in more than one crystalline form. The study should include the characterization of the batch(es) used in the clinical and/or comparative bioavailability studies, using a suitable method (e.g., X-ray Diffraction (XRD), Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR)). The absence of the potential for polymorphism can further be confirmed by providing the results of a literature search.

If the results of studies conducted on the physical and chemical properties of the various crystalline forms indicate that there is a preferred polymorph, criteria should be incorporated into the drug substance specification to ensure polymorphic equivalence of the commercial material to the batch(es) used in the clinical and/or comparative bioavailability studies.

Generally, controls on polymorphism are not a concern for drug substances that are considered highly soluble. Justification for the exclusion of the controls for polymorphism should be provided.

Polymorphism can also include solvation or hydration products (also known as pseudopolymorphs). If the drug substance is used in a solvated form, the following information should be provided:

(a) specifications for the solvent-free drug substance, if that compound is a synthetic precursor;

(b) specifications for the solvated drug substance including appropriate limits on the weight ratio of drug substance to solvent (with data to support the proposed limits); and

(c) a description of the method used to prepare the solvate.

Particle size distribution:

[1] *Immediate Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation,* Center for Drug Evaluation and Research (CDER), November 1995.

For poorly soluble drug substances, the particle size distribution of the material can have an effect on the *in vitro* and/or *in vivo* behaviour of the drug product. Particle size can also be important in dosage form performance (e.g. delivery of inhalation products), achieving uniformity of content in low-dose tablets (e.g., 2 mg or less), desired smoothness in ophthalmic preparations, and stability of suspensions.

If particle size distribution is important (e.g., as in the above cases), results from an investigation of several batches of the drug substance should be provided, including characterization of the batch(es) used in the clinical and/or comparative bioavailability studies. If applicable, the acceptance criteria should include controls on the particle size distribution to ensure consistency with the material in the batch(es) used in the clinical and/or comparative bioavailability studies (e.g., limits for d_{10}, d_{50}, and d_{90}). This criteria should be established statistically based on the standard deviation of the test results from the previously mentioned studies. The following is provided for illustrative purposes as possible acceptance criteria for particle size limits:

d_{10}	NMT 10% of total volume less than X µm
d_{50}	XX µm - XXX µm
d_{90}	NLT 90% of total volume less than XXXX µm

Other controls on particle size can be considered acceptable, if scientifically justified.

Reference Guidances: Q6A

S 2 Manufacture

If a Drug Master File (DMF) is filed with Health Canada and cross-referenced for certain proprietary information (e.g., sections S 2.2, S 2.3, S 2.4, and S 2.6), provide the DMF number assigned by Health Canada. It should be ensured that the information included in the DMF is up to date (e.g., updated every two years) and that the data has been received by Health Canada. Copies of the letters of access should be provided under the Regional Information section. If a Canadian agent is used by the DMF Holder, a letter *from the DMF Holder* should be submitted allowing the agent to act on their behalf, rather than the letter coming from the Canadian agent.

S 2.1 Manufacturer(s)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

This includes the facilities involved in the fabrication, packaging, labelling, testing, importing, storage, and distribution of the drug substance. If certain companies are responsible only for specific steps (e.g., milling of the drug substance), this should be indicated. The list of manufacturers should specify the actual production or manufacturing site(s) involved, rather than the administrative offices.

S 2.2 Description of Manufacturing Process and Process Controls

A flow diagram of the synthetic process(es) should be provided that includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and drug substance reflecting stereochemistry, and identifies operating conditions and solvents.

A sequential procedural narrative of the manufacturing process should be submitted. The narrative should include, for example, quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, process controls, equipment and operating conditions (e.g., temperature, pressure, pH, time).

Alternate processes should be explained and described with the same level of detail as the primary process.

Reprocessing steps should be identified and justified. Any data to support this justification should be either referenced or filed in S 2.5.

The information on the manufacturing process should start from commercially available or well-characterized starting materials. The manufacturing process for the batch(es) used in the clinical and/or comparative bioavailability studies should be representative of the process for commercial purposes (i.e., laboratory scale batches are *not* considered acceptable).

If the drug substance is prepared as sterile, a complete description should be provided for the method used in the sterilization. The controls used to maintain the sterility of the drug substance during storage and transportation should be provided.

In addition to the above information, the data provided for a drug substance produced by fermentation should include:

(a) source and type of micro-organism used;

(b) composition of media;

(c) precursors;

(d) additional details on how the reaction conditions are controlled (e.g., times, temperatures, rates of aeration, etc.); and

(e) name and composition of preservatives.

For drug substances of plant origin, include a description of the botanical species and the part of plant used, the geographical origin and, where relevant, the time of year harvested. The nature of chemical fertilizers, pesticides, fungicides, etc. should be recorded, if these have been employed during cultivation. It may be necessary to include limits for residues resulting from such treatments in the drug substance specification. Absence of toxic metals and radioactivity may also have to be confirmed.

S 2.3 Control of Materials

Materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials meet standards appropriate for their intended use should be provided, as appropriate.

Copies of the specifications for the materials used in the synthesis, fermentation, extraction, isolation, and purification steps should be provided in the drug submission.

Drug substances of animal origin should be free of Bovine Spongiform Encephalopathy (BSE) / Transmissible Spongiform Encephalopathy (TSE) and a letter of attestation confirming this should be included with the drug submission. Details in A2.

Reference Guidances: Q6A

S 2.4 Controls of Critical Steps and Intermediates

Critical Steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in S2.2 of the manufacturing process to ensure that the process is controlled should be provided.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Generally, these specifications would include tests and acceptance criteria for identity, purity, and potency, where applicable. Well-defined controls of potential impurities should be included for the starting material. Special consideration should be given to potential isomeric impurities in the starting material, as such contaminants that could be carried through the synthesis to the drug substance.

Reference Guidances: Q6A

S 2.5 Process Validation and/or Evaluation

Process validation and/or evaluation studies for aseptic processing and sterilisation should be included.

It is expected that the manufacturing processes for all drug substances are properly controlled. Justification should be provided for alternate manufacturing processes.

S 2.6 Manufacturing Process Development

A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing nonclinical, clinical, scale-up, pilot, and, if available, production scale batches.

Reference should be made to the drug substance data provided in section S 4.4.

The above information should also be provided for comparative (e.g., for existing drugs) and stability batches.

Reference Guidances: Q3A

S 3 Characterisation

S 3.1 Elucidation of Structure and other Characteristics

Confirmation of structure based on e.g., synthetic route and spectral analyses should be provided.

The Quality Summary should include a list of the studies performed 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 an interpretation of the data.

The studies carried out to elucidate and/or confirm the chemical structure of New Chemical Entities normally include elemental analysis, Infrared (IR), Ultraviolet (UV), Nuclear Magnetic Resonance (NMR), and Mass Spectra (MS) studies. Other tests could include X-ray diffraction (XRD). For existing drugs (e.g., generics), it is generally sufficient to provide copies of the IR and UV spectra of the drug substance from the proposed suppliers run concomitantly with suitable reference standard. A suitable primary reference standard could be obtained from the Schedule B compendia (e.g., USP, Ph.Eur, BP, etc.) or a batch of the drug substance that has been fully characterized (e.g., IR, UV, NMR, MS, etc.). See section S 5 for further details on References Standards or Materials.

When a drug substance is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the nonclinical and clinical studies, and information should be given as to the stereoisomer of the drug substance that is to be used in the final product intended for marketing.

A discussion should be included of the possible isomers that can result from the manufacturing process, the steps where they were introduced, and a summary of the results of the studies carried out to investigate the physical, chemical, and biological properties of these isomers. If there is a preferred isomer or isomeric mixture, the drug substance specification should include a test to ensure isomeric identity and purity.

If the drug substance is a single isomer or a fixed ratio of isomers, provide the rationale for this decision, including a discussion of the material that was used in the clinical and/or comparative bioavailability study. For existing drugs (e.g., generics), include a summary of any comparative studies performed.

For drug substances that contain an asymmetric centre, where there has not been any information provided regarding the manufacture of the starting material through which it has been introduced, results of a study should be submitted demonstrating that the material exists as a racemic mixture (e.g., specific optical rotation).

It is recognized that some drugs (e.g., certain antibiotics, enzymes, and peptides) present difficulties with respect to structural investigation. In such cases, more emphasis should be placed on the purification and the specification for the drug substance. If a drug substance consists of more than one component, the physicochemical characterization of the components and their ratio should be submitted.

If, based the structure of the drug substance, there is not a potential for isomerism, it could be sufficient to include a statement to this effect.

Reference Guidances: Q6A
Stereochemical Issues in Chiral Drug Development

S 3.2 Impurities

Information on impurities should be provided.

The study of impurities can be considered one of the most important aspects of the Quality portion of the drug submission. The sponsor should provide a discussion of the potential and actual impurities arising from the synthesis, manufacture, and/or degradation. The tables in Health Canada's Quality Summary template can be used to summarize the information on impurities (e.g., names, structures, origin, results, etc.). The origin refers to how the impurity was introduced (e.g., "Synthetic intermediate from Step 4 of the synthesis", "Potential by-product due to rearrangement from Step 6 of the synthesis, etc.). It should also be indicated if the impurity is a metabolite of the drug substance.

The basis for setting the acceptance criteria for the impurities should be provided. This is established by considering the identification and qualification thresholds for drug-related impurities (e.g., starting materials, by-products, intermediates, chiral impurities, or degradation products) and the concentration limits for process-related impurities (e.g., residual solvents) as per the applicable ICH guidance document (e.g., Q3A, Q3C). These thresholds are determined on the basis of potential exposure to the impurity, i.e., by the maximum daily dose (MDD) of the drug substance. For drugs available in multiple dosage forms and strengths, having different MDD values, it is imperative that the thresholds and corresponding controls for each of the presentations be considered to ensure that the risks posed by impurities have been addressed. This is normally achieved by using the highest potential daily MDD, rather than the maintenance dose. For parenteral products, the maximum hourly dose of the drug substance should also be included.

The acceptance criteria is also set taking into consideration the actual levels of impurities found in several batches of the drug substance from each source, including the levels found in the batches used for the nonclinical, clinical, and comparative studies. For quantitative tests, it should be ensured that *actual numerical results* are provided rather than vague statements such as "within limits" or "conforms". In the cases where a large number of batches have been tested, it is acceptable to summarize the total number of batches tested with a range of analytical results.

Qualifying limits for specified impurities is normally based on the levels found in the nonclinical and clinical batches at the time the studies were conducted, rather than levels observed on stability or levels found in subsequent batches manufactured according to the proposed commercial process. Results on the drug product can also be presented for comparative batches (e.g., for a comparative purity study of a generic product against the Canadian reference product).

It is recognized by the compendia that drug substances can be obtained from various sources, and thus can contain impurities not considered during the preparation of the monograph. Furthermore, a change in the production or source may give rise to impurities that are not adequately controlled by the published compendial monograph. As a result, each drug submission is reviewed independently to consider the potential impurities that may arise from the proposed route(s) of synthesis. For these reasons, the ICH limits for unspecified impurities (e.g., Not More Than (NMT) 0.1% for drug substances having a maximum daily dose • 2 g/day) are generally recommended, rather than the general limits for unspecified impurities that appear in the compendial monograph that could be potentially higher than the ICH limit.

Depending on the nature of the drug substance, and the extent of the chemical modification steps, the principles on the control of impurities (e.g., identification and qualification) can also be extended to drug substances of semi-synthetic origin. As an illustrative example, a drug substance whose precursor molecule was derived from a fermentation process, or a natural product of plant or animal origin, and has subsequently undergone several chemical modification reactions generally would fall within this scope, whereas a drug whose sole chemical step was the formation of a salt from a fermentation product generally would not fall within this scope. It is understood that there is some latitude for these types of drug substances (e.g., NMT 0.2% for unspecified impurities may be appropriate, rather than NMT 0.1%).

If there are identified impurities specified in a compendial monograph (e.g., as in a Ph.Eur. Transparency Monograph) that are not monitored by the proposed routine method (e.g., House method), a justification should be provided for their exclusion. If acceptable justification cannot be provided, it should be demonstrated that the alternate method is capable of detecting the impurities specified in the compendial monograph at an acceptable level (e.g., 0.1%).

Reference Guidances: Q3A, Q3C, Q6A
Identification, Qualification, and Control of Related Impurities in New Drugs
Identification, Qualification, and Control of Related Impurities in Existing Drugs
Stereochemical Issues in Chiral Drug Development

S 4 Control of the Drug Substance

S 4.1 Specification

The specification for the drug substance should be provided.

As defined in ICH's Q6A guidance document, a specification is a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug substance, when tested according to the listed analytical procedures, will meet the listed acceptance

criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

A copy of the drug substance specification from the company responsible for release testing should be provided, dated and signed by authorized personnel (i.e., the person in charge of the Quality Control department). The specification reference number, version, and date should be provided for version control purposes. The standard declared by the sponsor could be a Schedule B compendial standard (e.g., USP, Ph.Eur., BP, etc.), Manufacturer's or House Standard, Prescribed Standard (e.g., Canadian Standard Drugs in Division C.06 of the *Food and Drug Regulations*), or a Professed Standard.

Although a Schedule B compendial monograph may exist, a sponsor can choose to use a Manufacturer's Standard which indicates that the material may differ in some respect from the compendial standard. However, according to section C.01.011 of the *Food and Drug Regulations*, no person shall use a manufacturer's standard for a drug that provides (a) a lesser degree of purity than the highest degree of purity and (b) a greater variance in potency than the least variation in potency, provided for that drug in any publication mentioned in Schedule B to the *Act*. Therefore, if a manufacturer's standard is used, the controls on purity (e.g., limits on specified impurities) and potency should be as tight as the most stringent of those listed in the Schedule B compendial monographs.

If the drug submission is for a non-official drug (e.g., where neither a Prescribed nor a Schedule B compendial standard exists), a professed standard is used and the product labelling for such products does not carry any standard.

The specification can be summarized according to Health Canada's Quality Summary template including the Tests, Method Types, Sources, and Code Number/Version/Date. The acceptance criteria should also be provided in the summary of the specification. The Method Type should indicate the kind of analytical procedure used (e.g., visual, IR, UV, HPLC, laser diffraction, etc.); the Source refers to the origin of the analytical procedure (e.g., USP, Ph.Eur., BP, House, etc.); and the Code Number/Version/Date should be provided for version control purposes.

ICH's Q6A guidance document outlines recommendations for a number of universal and specific tests and criteria for drug substances.

Reference Guidances: Q3A, Q3C, Q6A

S 4.2 Analytical Procedures

The analytical procedures used for testing the drug substance should be provided.

Copies of the House analytical procedures used during the drug development (if used to support testing results in the drug submission) as well as those proposed for routine testing should be provided. The tables in Health Canada's Quality Summary template can be used to summarize the analytical procedures. Unless modified, it is not necessary to provide copies of Schedule B compendial analytical procedures.

Although HPLC is normally considered the method of choice for determining drug-related impurities, other chromatographic methods such as GC and TLC can also be used, if appropriate. For impurity

methods, reference standards should be prepared for each of the identified impurities, particularly those known to be toxic, and the concentration of the impurities quantitated against their own reference standards. It is considered acceptable to use the drug substance as an external standard to estimate the levels of impurities, provided the response factors of those impurities are sufficiently close to that of the drug substance (e.g., greater than 80%). In cases where the response factor is not close, it may still be acceptable to use the drug substance, provided a correction factor is applied or the impurities are, in fact, being overestimated. Unspecified impurities should be quantitated using a solution of the drug substance as the reference standard at a concentration corresponding to the limit established for individual unspecified impurities (e.g., 0.1%).

The system suitability tests (SST's) are an integral part of chromatographic analytical procedures. As a minimum, HPLC and GC methods should include SST's for resolution and repeatability. For HPLC methods to control drug-related impurities, this is typically done using a solution of the drug substance with a concentration corresponding to the limit for unspecified impurities. Resolution of the two closest eluting peaks is generally recommended. However, choice of alternate peaks can be used if justified (e.g., choice of a toxic impurity). In accordance with the USP General Chapter on *Chromatography* and Health Canada's guidance document *Acceptable Methods*, the repeatability test should include an acceptable number of replicate injections (i.e., five or six). For TLC methods, the SST's should verify the sensitivity and ability of the system to separate (e.g., by applying a spot corresponding to the drug substance spiked at a concentration corresponding to the limit of unspecified impurities).

Reference Guidances: Q2A
Acceptable Methods

S 4.3 Validation of Analytical Procedures

Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance, should be provided.

Copies of the validation reports for the analytical procedures used during the drug development (if used to support testing results in the drug submission) as well as those proposed for routine testing should be provided. The tables in Health Canada's Quality Summary template can be used to summarize the validation information.

As outlined in Health Canada's guidance document *Acceptable Methods*, partial revalidation is necessary for methods that appear in a Schedule B compendial monograph. These revalidation criteria are recognized by other Regulatory Agencies and the compendia themselves. The compendial methods, as published, are typically validated using a drug substance or a drug product originating from a specific manufacturer. Different sources of the same drug substance or drug product can contain impurities and degradation products that were not considered during the development of the monograph.

In general, revalidation is not necessary for Schedule B compendial *potency* methods. However, specificity of the compendial potency method should be demonstrated if there are any potential impurities that are not specified in the compendial monograph. If a Schedule B compendial method is used to control drug-related impurities that are not specified in the monograph, full validation is expected.

If a Schedule B compendial standard is claimed and a House method is used in lieu of the compendial method (e.g., for potency or for specified impurities), equivalency of the House and compendial methods should be demonstrated. This could be accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study.

With respect to the control of residual solvents, it is acknowledged that GC methods for determining residual solvents are generally sensitive, linear, and reproducible. In past experience, it has been found that a sponsor will use essentially the same GC method to determine residual solvents in a number of drug substances and drug products. Therefore, although it is expected that a company will initially perform full validation of the methods used to determine residual solvents, it is acceptable that only limited validation data be submitted (e.g., recovery, repeatability, limit of detection, limit of quantitation, and selectivity of the method). Recovery and repeatability should be determined using a sample of the drug substance or drug product spiked with the residual solvents at their acceptance criteria.

Reference Guidances: Q2A, Q2B
Acceptable Methods

S 4.4 Batch Analyses

Description of batches and results of batch analyses should be provided.

This would include information such as batch number, batch size, date and site of production, etc. on relevant drug substance batches (e.g., used in nonclinical, clinical, comparative, stability, pilot, scale-up, and, if available, production-scale batches) used to establish the specification(s) and evaluate consistency in manufacturing.

Analytical results tested by the company responsible for release testing should be provided from at least two batches from each proposed manufacturing site of the drug substance. The testing results should include the batch(es) used in the nonclinical, clinical and/or comparative bioavailability studies. Copies of the certificates of analyses for these batches should be provided in the drug submission and the company responsible for generating the testing results should be identified.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "All tests meet specifications". This should include ranges of analytical results and any trends that were observed. For quantitative tests (e.g., as in individual and total impurity tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such as "within limits" or "conforms". A discussion and justification should be provided for any incomplete analyses (e.g., results not tested according to the proposed specification).

Reference Guidances: Q3A, Q3C, Q6A

S 4.5 Justification of Specification

Justification for the drug substance specification should be provided.

This should include a discussion on the inclusion of certain tests, evolution of tests, analytical procedures, and acceptance criteria, differences from compendial standard, etc.. If the Schedule B compendial methods have been modified or replaced, a discussion should be included.

The justification for certain tests, analytical procedures, and acceptance criteria may have been discussed in other sections of the drug submission (e.g., impurities, particle size) and do not need to be repeated here, although a cross-reference to their location should be provided.

Reference Guidances: Q3A, Q3C, Q6A

S 5 Reference Standards or Materials

Information on the reference standards or reference materials used for testing of the drug substance should be provided.

The source(s) of the reference standards or materials used in the testing of the drug substance should be provided (e.g., for the identification, purity, potency tests).

Primary reference standards can be obtained from official sources such those recognized in the Schedule B compendia. Primary reference standards from official sources do not need further structural elucidation. A primary standard could also be validated as a batch of drug substance that has been fully characterized and structurally elucidated (e.g., IR, UV, NMR, MS, etc.).

A secondary (or House) reference standard can be used by providing a copy of its certificate of analysis and validating it against a suitable primary reference standard (e.g., by providing legible copies of the IR and UV of the secondary and primary reference standards run concomitantly). A secondary reference standard is often characterized and evaluated for its intended purpose with additional procedures other than those used in routine testing (e.g., if additional solvents are used for purification during the manufacturing process that are not used for routine purposes). A brief description of the manufacture process of the secondary reference standard should be provided, if it differs from commercial process for the drug substance.

Reference Guidances: Q6A
Acceptable Methods

S 6 Container Closure System

A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification (and critical dimensions with drawings, where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

For non-functional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging

components, additional information should be provided.

The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance, including sorption to container and leaching, and/or safety of materials of construction.

S 7 Stability

As outlined in ICH's Q1A guidance document, the purpose of stability testing is to provide evidence on how the quality of a drug substance varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance and recommended storage conditions.

Reference Guidances: Q1A, Q1B
Stability Testing of Existing Drug Substances and Products

S 7.1 Stability Summary and Conclusions

The types of studies conducted, protocols used, and the results of the studies should be summarised. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

Stress testing:

As outlined ICH's Q1A guidance document, stress testing of the drug substance can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance and the type of drug product involved.

The table in Health Canada's Quality Summary template can be used to summarize the results from the stress testing. This summary should include the treatment conditions (e.g., concentrations of solutions prepared, storage temperatures and durations) and the observations for the various test parameters (e.g., potency, degradation products).

Accelerated and long term testing:

The conditions for stability testing of new drug substances are outlined in ICH's Q1A guidance document. The following storage conditions and minimum data at the time of submission are recommended by ICH's Q1A guidance document for the Primary Batches. When "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. See ICH's Q1A guidance document for definition of "significant change".

Study	Storage Condition	Minimum Time Period Covered by Data at Submission
Long term	25°C ± 2°C / 60% RH ± 5% RH	12 months
Intermediate	30°C ± 2°C / 60% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C / 75% RH ± 5% RH	6 months

RH = relative humidity

Other conditions are outlined in the ICH's Q1A guidance document for drug substances intended for storage in a refrigerator and those intended for storage in a freezer. Drug substances intended for storage below -20°C should be treated on a case-by-case basis.

For existing drugs (e.g., generics), available information on the stability of the drug substance under accelerated and long term conditions should be provided, including information in the public domain or obtained from DMF Holders. The source of the information should be identified. In certain cases, information available in the public domain may be sufficient to establish an appropriate re-test period, e.g., when a substantial body of evidence exists that establishes that the drug substance is inherently stable. In all instances, sponsors are encouraged to provide all relevant information available on the stability of the drug substance.

The information on the stability studies should include details such as storage conditions, batch number, batch size, container closure system, and completed (and proposed) test intervals. The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "All tests meet specifications". This should include ranges of analytical results and any trends that were observed. For quantitative tests (e.g., as in individual and total degradation product tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such as "within limits" or "conforms".

Proposed storage conditions and re-test period:

The proposed storage conditions with suitable tolerances (e.g., a temperature range with upper and lower criteria) and re-test period for the drug substance should be provided.

When the drug substance has been shown to be stable (e.g., under the ICH conditions with long term studies at 25• C ± 2• C/60% RH ± 5% RH and accelerated studies at 40• C ± 2• C/75% RH ± 5% RH), the following storage recommendation would generally be considered acceptable:

"Store at controlled room temperature (15• C to 30• C)."

Based on the results of the stability evaluation, other storage precautions may be warranted (e.g., "Protect from light", "Protect from moisture").

Re-test periods are generally one or two years. A re-test period longer than two years should be fully supported by the results from stability studies conducted under the conditions recommended by ICH's Q1A guidance document. After this period, a batch of drug substance destined for use in the manufacture

of a drug product should be re-tested for compliance with the specification and then used *immediately* (e.g., within 30 days). If re-tested, the batch does *not* receive the period of time established for the re-test period.

For drug substances known to be labile (e.g., certain antibiotics), it is more appropriate to establish a shelf life than a re-test period.

Limited extrapolation of the real time data from the long term storage condition beyond the observed range to extend the re-test period can be undertaken at approval time, if justified.

S 7.2 Post-approval Stability Protocol and Stability Commitment

The post-approval stability protocol and stability commitment should be provided.

When available long term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, a commitment should be made to continue the stability studies post-approval in order to firmly establish the shelf life. The long term stability studies for the *Commitment Batches* should be conducted through the proposed shelf life (and the accelerated studies for six months) on at least three production batches of each strength (or two production batches of each strength for existing drugs).

The stability protocol for the *Commitment Batches* and should include, but not limited to:

(a) Number of batches and batch sizes;

(b) Tests and acceptance criteria;

(c) Container closure system(s);

(d) Testing frequency; and

(e) Storage conditions (and tolerances) of samples

Any differences in the stability protocols used for the primary batches and those proposed for the *Commitment Batches* or should be scientifically justified.

S 7.3 Stability Data

Results of the stability studies (e.g., forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

This would include the actual stability results (i.e., raw data) used to support the proposed re-test period or shelf life. For quantitative tests (e.g., as in individual and total degradation product tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such

as "within limits" or "conforms".

P DRUG PRODUCT

P.1 Description and Composition of the Drug Product

A description of the drug product and its composition should be provided. The information provided should include, for example:

(a) Description of the dosage form;

The description of the dosage form should include the physical description, available strengths, release mechanism, as well as any other distinguishable characteristics (e.g., "The proposed drug product is available as oval, round, immediate-release, aqueous film-coated tablet in three strengths (5 mg, 10 mg, and 20 mg). The two higher strengths include a vertical score line to facilitate the breaking of the tablets.").

(b) Composition, i.e., list of all components of the dosage form, and their amount on a per unit basis (including overages, if any) the function of the components, and a reference to their quality standards (e.g., compendial monographs or manufacturer's specifications);

The composition should express the quantity of each component on a per unit basis (e.g., mg per tablet, mg per mL, mg per vial, etc.) and percentage basis, including a statement of the total weight or measure of the dosage unit. This 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, etc.). If the drug product is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g., "1 mg of active ingredient base = 1.075 mg active ingredient hydrochloride"). All overages should be clearly indicated (e.g., "Contains 2% overage of the drug substance to compensate for manufacturing losses.").

The components should be declared by their proper or common names, Quality standards (e.g., USP, Ph.Eur., House, etc.) and, if applicable, their grades (e.g., "Microcrystalline Cellulose NF (PH 102)").

The qualitative composition should be provided for all proprietary components or blends (e.g., capsule shells, colouring blends, imprinting inks, etc.). This information is used for product labelling purposes. Reference to a Drug Master File can be provided for the actual *quantitative* composition.

The function of each component (e.g., diluent/filler, binder, disintegrant, lubricant, glidant, granulating solvent, coating agent, antimicrobial preservative, etc.) should be provided.

(c) Description of accompanying reconstitution diluent(s); and

For drug products supplied with reconstitution diluent(s) that are not commercially available in Canada or have not been reviewed and approved in connection with another drug submission with

Health Canada, information on the diluent(s) should be provided in a separate Drug Product ("P") portion, as appropriate.

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

The description for the container closure used for the dosage form (and accompanying reconstitution diluent, if applicable) should be brief with further details provided under P 7 Container Closure System (e.g., "The product is available in HDPE bottles with polypropylene caps and in PVC/Aluminum foil unit dose blisters.").

Reference Guidances: Q6A

P 2 Pharmaceutical Development

The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the application. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and drug product quality. Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical Development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the application.

Reference Guidances: Q6A

P 2.1 Components of the Drug Product

P 2.1.1 Drug Substance

The compatibility of the drug substance with excipients listed in P1 should be discussed. Additionally, 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 should be discussed. For combination products, the compatibility of drug substances with each other should be discussed.

P 2.1.2 Excipients

The choice of excipients listed in P1, their concentration, their characteristics that can influence the drug product performance should be discussed relative to their respective functions.

Alternates for excipients are generally not accepted. Ranges for excipients normally are not accepted, unless supported by appropriate process validation data. Where relevant, compatibility study results (e.g., primary

and secondary compatibility of an amine drug with lactose) should be included to justify the choice of excipients. Specific details should be provided where necessary (e.g., use of potato or corn starch).

Where antioxidants are included in the formulation, the effectiveness of the proposed concentration of the antioxidant should be justified and verified by appropriate studies.

A certification should be provided that none of the excipients which appear in the drug product are prohibited for use in drugs by the Canadian *Food and Drugs Act and Regulations*.

P 2.2 Drug Product

P 2.2.1 Formulation Development

A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e., composition) described in P1 should be discussed. Results from comparative *in vitro* studies (e.g., dissolution) or comparative *in vivo* studies (e.g., bioequivalence) should be discussed, when appropriate.

The tables in Health Canada's Quality Summary template can be used to summarize the above information.

When assessing the data elements needed for multiple strengths, Health Canada's policy *Bioequivalence of Proportional Formulations: Solid Oral Dosage Forms* should be consulted.

P 2.2.2 Overages

Any overages in the formulation(s) described in P1 should be justified.

Overages for the sole purpose of extending the shelf life of the drug product are generally not acceptable.

P 2.2.3 Physicochemical and Biological Properties

Parameters relevant to the performance of the drug product, such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency, and/or immunological activity, should be addressed.

P 2.3 Manufacturing Process Development

The selection and optimisation of the manufacturing process described in P3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilisation should be explained and justified.

Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in P3.3 that can influence the performance of the product should be

discussed.

The rationale for choosing the particular type of drug delivery system should be provided (e.g., matrix or membrane based controlled delivery, liposomal, microemulsion, depot injection). The scientific rationale for the choice of the manufacturing, filling, and packaging processes that can influence drug product quality and performance should be explained (e.g., wet granulation using high shear granulator). Any developmental work undertaken to protect the drug product from deterioration should also be included (e.g., protection from light or moisture).

The scientific rationale for the selection, optimization, and scale-up of the manufacturing process described in P 3.3 should be explained, in particular the critical aspects (e.g., rate of addition of granulating fluid, massing time). The equipment should be identified by type and working capacity.

P 2.4 Container Closure System

The suitability of the container closure system (described in P7) used for the storage, transportation (shipping) and use of the drug product should be discussed. This discussion should consider, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the drug product).

See section P 7 for a discussion on the information that could be included for the qualification of the container closure system.

P 2.5 Microbiological Attributes

Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

Where an antimicrobial preservative is included in the formulation, the effectiveness of the agent should be justified and verified by appropriate studies using a batch of the drug product. If the lower bound for the proposed acceptance criteria for the assay of the preservative is less than 90.0%, the effectiveness of the agent should be established with a batch of the drug product containing a concentration of the antimicrobial preservative corresponding to the lower proposed acceptance criteria.

As outlined in ICH's Q1A guidance document, a single primary stability batch of the drug product should be tested for antimicrobial preservative effectiveness (in addition to preservative content) *at the proposed shelf life* for verification purposes, regardless of whether there is a difference between the release and shelf life acceptance criteria for preservative content.

If this information is not available at the time of submission, a commitment should be provided that a single

primary stability batch will be tested for antimicrobial preservative effectiveness at the proposed shelf life.

P 2.6 Compatibility

The compatibility of the drug product with reconstitution diluent(s) or dosage devices (e.g., precipitation of drug substance in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labeling.

Where sterile, reconstituted products are to be further diluted, compatibility should be demonstrated with all diluents over the range of dilution proposed in the labelling. These studies should preferably be conducted on aged samples. Where the labelling does not specify the type of containers, compatibility (with respect to parameters such as appearance, pH, assay, levels of individual and total degradation products, sub-visible particulate matter and extractables from the packaging components) should be demonstrated in glass, PVC, and polyolefin containers. However, if one or more containers are identified in the labelling, compatibility of admixtures needs to be demonstrated only in the specified containers.

Studies should cover the duration of storage reported in the labelling (e.g., 24 hours under controlled room temperature and 72 hours under refrigeration). Where the labelling specifies co-administration with other drugs, compatibility should be demonstrated with respect to the principal drug as well as the co-administered drug (i.e., in addition to other aforementioned parameters for the mixture, the assay and degradation levels of each co-administered drug should be reported).

For existing drugs (e.g., generics), if levels of impurities or other parameters warrant, these studies should be carried out in parallel with the reference product to adequately qualify the impurity and other limits proposed in the drug product specification(s).

P 3 Manufacture

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. It should be ensured that the information included in the DMF is up to date (e.g., updated every two years) and that the data has been received by Health Canada. Copies of the letters of access should be provided under the Regional Information section. If a Canadian agent is used by the DMF Holder, a letter *from the DMF Holder* should be submitted allowing the agent to act on their behalf, rather than the letter coming from the Canadian agent.

P 3.1 Manufacturer(s)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

This includes the facilities involved in the fabrication, packaging, labelling, testing, importing, storage, and distribution of the drug product. If certain companies are responsible only for specific steps (e.g., manufacturing of an intermediate), this should be indicated. The list of manufacturers should specify the actual production or manufacturing site(s) involved, rather than the administrative offices.

P 3.2 Batch Formula

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.

The batch formula should express the quantity of each component on a per batch basis including a statement of the total weight or measure of the batch. This 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, etc.). If the drug product is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g., "1 mg of active ingredient base = 1.075 mg active ingredient hydrochloride"). All overages should be clearly indicated (e.g., "Contains 5 kg overage of the drug substance to compensate for manufacturing losses.").

The components should be declared by their proper or common names, Quality standards (e.g., USP, Ph.Eur., House, etc.) and, if applicable, their grades (e.g., "Microcrystalline Cellulose NF (PH 102)").

P 3.3 Description of Manufacturing Process and Process Controls

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

A narrative description of the manufacturing process, including packaging, that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g., tumble blender, in-line homogeniser) and working capacity, where relevant.

Steps in the process should have the appropriate process parameters identified, such as time, temperature, or pH. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in Section P 3.4. In certain cases, environmental conditions (e.g., low humidity for an effervescent product) should be stated.

Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either referenced or filed in this section (P 3.3).

The proposed commercial batch sizes should be stated. See section R 1 for discussion on production scale.

P 3.4 Controls of Critical Steps and Intermediates

Critical Steps: Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified in P3.3 of the manufacturing process, to ensure that the process is controlled.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Examples of applicable in-process controls include: (i) *granulations:* moisture, blend uniformity, bulk and tapped densities, particle size distribution; (ii)*solid oral products:* average weight, weight variation, hardness, thickness, friability, disintegration, weight gain during coating; (iii) *semi-solids:* viscosity, homogeneity, pH; (iv) *transdermal patches:* assay of drug-adhesive mixture, weight per area of coated patch without backing; (v) *metered dose inhalers:* fill weight/volume, leak testing, valve delivery; (vi) *dry powder inhalers*: assay of drug-excipient blend, moisture, weight variation of individually contained doses such as capsules or blisters; (vii) *liquids:* pH, specific gravity, clarity of solutions; (viii) *parenterals:* appearance, clarity, fill volume/weight, pH, filter integrity tests, particulate matter.

Reference Guidances: Q2A, Q2B, Q6A

P 3.5 Process Validation and/or Evaluation

Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process (e.g., validation of the sterilisation process or aseptic processing or filling). Viral safety evaluation should be provided in A2, if necessary.

The following information should be provided:

(a) a copy of the process validation protocol, specific to this drug product, which identifies the critical equipment and process parameters that can affect the quality of the drug product and defines testing parameters, sampling plans, analytical procedures, and acceptance criteria;

(b) confirmation that three consecutive, production-scale batches of this drug product will be subjected to prospective validation in accordance with Health Canada's *Validation Guidelines for Pharmaceutical Dosage Forms* and *Cleaning Validation Guidelines*;

(c) if the process validation studies have already been conducted (e.g., as for sterile products), a copy of process validation report should be submitted in lieu of (a) and (b) above, a summary of these process validation studies should also be provided.

The manufacture of sterile drugs needs a well-controlled manufacturing area (e.g., a strictly controlled environment, highly reliable procedures, and numerous in-process controls). A detailed description of these conditions, procedures, and controls should be provided, together with actual copies of the following standard operating procedures:

(a) washing, treatment, sterilizing, and depyrogenating of containers, closures, and equipment;

(b) filtration of solutions;

(c) lyophilization process;

(d) leaker test of filled and sealed ampoules;

(e) final inspection of the product; and

(f) sterilization cycle.

The sterilization process used to destroy or remove microorganisms is probably the single most important process in the manufacture of parenteral drugs. The process can make use of moist heat (e.g., steam), dry heat, filtration, gaseous sterilization (e.g., ethylene oxide), or radiation. It should be noted that terminal steam sterilization, when practical, is considered to be the method of choice to ensure sterility of the final drug product. Therefore, scientific justification for selecting any other method of sterilization should be provided.

The sterilization process should be described in detail, and evidence should be provided to confirm that it will produce a sterile product with a high degree of reliability and that the physical and chemical properties as well as the safety of the drug product will not be affected. Details such as F_o range, temperature range, and peak dwell time for a drug product and the container closure should be provided. Although standard autoclaving cycles of 121°C, 15 minutes or more, would not need a detailed rationale; such justifications should be provided for reduced temperature cycles or elevated temperature cycles with shortened exposure times. If ethylene oxide is used, studies and acceptance criteria should control the levels of residual ethylene oxide and related compounds.

Filters used should be validated with respect to pore size, compatibility with the product, absence of extractables and lack of adsorption of the drug substance or any of the components.

Reference Guidances: Good Manufacturing Practices
Validation Guidelines for Pharmaceutical Dosage Forms and Cleaning Validation Guidelines
Validation Documentation Requirements and Responsibilities for Drug Fabricators, Packagers / Labellers, Distributors and Importers
Sterilization Guidances: Aseptic Processes for Pharmaceuticals, Form-Fill-Seal for Pharmaceuticals, Gaseous Sterilization for Pharmaceuticals, Irradiation Sterilization for Pharmaceuticals, Moist Heat Sterilization for Pharmaceuticals

P 4 Control of Excipients

P 4.1 Specifications

The specifications for excipients should be provided.

This would include the specifications for all excipients, including those that do not appear in the final drug product (e.g., solvents, nitrogen, silicon for stoppers, etc.).

If the standard claimed for an excipient is a Schedule B compendial monograph, it is sufficient to state that the excipient is tested according to the requirements of that standard, rather than reproducing the specifications found in the Schedule B compendial monograph. If the standard claimed for an excipient is a non-Schedule B compendial monograph (e.g., House standard) or includes tests that are supplementary to those appearing in the Schedule B compendial monograph, a copy of the specification for the excipient should be provided.

Testing for microbial requirements should be at least as stringent as those specified in the corresponding USP monograph should one exist (e.g., as for Magnesium Stearate). Excipients derived from natural sources should have appropriate microbial tests and limits.

If additional purification is undertaken on commercially available excipients, details of the process of purification and modified specifications should be submitted.

Reference Guidances: Q6A

P 4.2 Analytical Procedures

The analytical procedures used for testing the excipients should be provided, where appropriate.

Copies of analytical procedures from Schedule B compendial monographs do not need to be submitted.

Reference Guidances: Q2A
Acceptable Methods

P 4.3 Validation of Analytical Procedures

Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided, where appropriate.

Copies of analytical validation information are normally not submitted for the testing of excipients.

Reference Guidances: Q2A, Q2B
Acceptable Methods

P 4.4 Justification of Specifications

Justification for the proposed excipient specifications should be provided, where appropriate.

This would include the tests that are supplementary to those appearing in the Schedule B compendial monograph.

Reference Guidances: Q3C

P 4.5 Excipients of Human or Animal Origin

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications, description of the testing performed, viral safety data). (Details in A2).

This information should include biological source, country of origin, manufacturer, and a brief description of the suitability of use based on the proposed controls.

For gelatin for use in pharmaceuticals, a letter of access from the proposed supplier should be provided to their Drug Master File, which is registered with Health Canada. Furthermore, confirmation should be included with a letter of attestation that the gelatin used is free of Bovine Spongiform Encephalopathy (BSE) / Transmissible Spongiform Encephalopathy (TSE).

Reference Guidances: Q5A, Q5D, Q6B

P 4.6 Novel Excipients

For excipient(s) used for the first time in a drug product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data (nonclinical and/or clinical) should be provided according to the drug substance and/or drug product format. (Details in A3).

P 5 Control of Drug Product

P 5.1 Specification(s)

The specification(s) for the drug product should be provided.

As defined in ICH's Q6A guidance document, a specification is a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

A copy of the drug product specification(s) from the sponsor (as well from the company responsible for release testing, if different from the sponsor) should be provided, dated and signed by authorized personnel (i.e., the person in charge of the Quality Control department). The specification reference number, version, and date should be provided for version control purposes. The standard declared by the sponsor could be a

Schedule B compendial standard (e.g., USP, BP, etc.), Manufacturer's or House Standard, Prescribed Standard (e.g., Canadian Standard Drugs in Division C.06 of the *Food and Drug Regulations*), or a Professed Standard.

Although a Schedule B compendial monograph may exist, a sponsor can choose to use a Manufacturer's Standard which indicates that the material may differ in some respect from the compendial standard. However, according to section C.01.011 of the *Food and Drug Regulations*, no person shall use a manufacturer's standard for a drug that provides (a) a lesser degree of purity than the highest degree of purity and (b) a greater variance in potency than the least variation in potency, provided for that drug in any publication mentioned in Schedule B to the *Act*. Therefore, if a manufacturer's standard is used, the controls on purity (e.g., limits on specified degradation products) and potency should be as tight as the most stringent of those listed in the Schedule B compendial monographs.

If the drug submission is for a non-official drug (e.g., where neither a Prescribed nor a Schedule B compendial standard exists), a professed standard is used and the product labelling for such products does not carry any standard.

The specification can be summarized according to Health Canada's Quality Summary template including the Tests, Method Types, Sources, and Code Number/Version/Date. The acceptance criteria should also be provided in the summary of the specification(s). The Method Type should indicate the kind of analytical procedure used (e.g., visual, IR, UV, HPLC, etc.); the Source refers to the origin of the analytical procedure (e.g., USP, BP, House, etc.); and the Code Number/Version/Date should be provided for version control purposes.

ICH's Q6A guidance document outlines recommendations for a number of universal and specific tests and criteria for drug products.

The following information provides suggestions on specific tests and criteria that are not addressed by ICH's Q6A guidance document:

Dosage Form	Specific Tests
Modified-release products	a meaningful drug-release method
Inhalation and Nasal Products	consistency of delivered dose (throughout the use of the product), particle or droplet size distribution profiles (comparable to the product used in *in vivo* studies, where applicable), and if applicable for the dosage form, moisture content, leak rate, microbial limits, preservative assay, sterility, and weight loss
Suppositories	uniformity of dosage units, melting point
Transdermals	peal or shear force, mean weight per unit area, dissolution

The test for uniformity of dosage units should be included in the specifications of all dosage forms where a variation in uniformity of dose from unit to unit can occur. The test for uniformity of dosage units could be physical (weight variation) or chemical (content uniformity), depending on the formulation, method of

manufacture, and in-process testing. The requirements for testing the uniformity of dosage units have been developed by the Schedule B compendia, and it is recommended that these be used in order that an appropriate test be established. It is expected that the strictest compendial standard (e.g., for acceptance criteria) will be adopted.

Reference Guidances: Q3B, Q3C, Q6A

P 5.2 Analytical Procedures

The analytical procedures used for testing the drug product should be provided.

Copies of the House analytical procedures used during the drug development (if used to support testing results in the drug submission) as well as those proposed for routine testing should be provided. The tables in Health Canada's Quality Summary template can be used to summarize the analytical procedures. Unless modified, it is not necessary to provide copies of Schedule B compendial analytical procedures.

The system suitability tests (SST's) are an integral part of chromatographic analytical procedures. As a minimum, HPLC and GC methods should include SST's for resolution and repeatability. For HPLC methods to control degradation products, this is typically done using a solution of the drug substance with a concentration corresponding to the limit for unspecified degradation products. Resolution of the two closest eluting peaks is generally recommended. However, choice of alternate peaks can be used if justified (e.g., choice of a toxic impurity). In accordance with the USP General Chapter on *Chromatography* and Health Canada's guidance document *Acceptable Methods*, the repeatability test should include an acceptable number of replicate injections (i.e., five or six).

Reference Guidances: Q2A
Acceptable Methods

P 5.3 Validation of Analytical Procedures

Analytical validation information, including experimental data, for the analytical procedures used for testing the drug product, should be provided.

Copies of the validation reports for the analytical procedures used during the drug development (if used to support testing results in the drug submission) as well as those proposed for routine testing should be provided. The tables in Health Canada's Quality Summary template can be used to summarize the validation information.

As outlined in Health Canada's guidance document *Acceptable Methods*, partial revalidation is necessary for methods that appear in a Schedule B compendial monograph. These revalidation criteria are recognized by other Regulatory Agencies and the compendia themselves. The compendial methods, as published, are typically validated using a drug substance or a drug product originating from a specific manufacturer. Different sources of the same drug substance or drug product can contain impurities and degradation products that were not considered during the development of the monograph.

If a Schedule B compendial standard is claimed and a House method is used in lieu of the compendial method (e.g., for potency or for specified degradation products), equivalency of the House and compendial methods should be demonstrated. This could be accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study.

Reference Guidances: Q2A, Q2B
Acceptable Methods

P 5.4 Batch Analyses

A description of batches and results of batch analyses should be provided.

This would include information such as strength, batch number, batch size, date and site of production, etc. on relevant drug product batches (e.g., used in nonclinical, clinical, comparative, stability, pilot, scale-up, and, if available, production-scale batches) used to establish the specification(s) and evaluate consistency in manufacturing.

Analytical results tested by the company responsible for release testing should be provided from at least two batches of each strength. Bracketing and matrixing of proportional strengths can be applied, if scientifically justified. The testing results should include the batch(es) used in the nonclinical, clinical and/or comparative bioavailability studies. Copies of the certificates of analyses for these batches should be provided in the drug submission and the company responsible for generating the testing results should be identified. The individual results or the mean, the RSD, and the range for the content uniformity and dissolution tests should be included.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "All tests meet specifications". This should include ranges of analytical results and any trends that were observed. For quantitative tests (e.g., as in individual and total degradation product tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such as "within limits" or "conforms". A discussion and justification should be provided for any incomplete analyses (e.g., results not tested according to the proposed specification).

If the proposed dosage form is a scored tablet, the results of a study should be provided testing the uniformity of dosage units of the manually-split tablet halves. The data provided in the drug submission should include a description of the test method, individual values, mean, and relative standard deviation (RSD). Uniformity testing (i.e., content uniformity or weight variation, depending on the dosage form) should be performed on each split portion from a minimum of 10 randomly selected whole tablets. As an illustrative example, the number of units (i.e., the splits) would be 20 halves for bisected tablets or 40 quarters for quadrisected tablets. At least one batch of each strength should be tested. Ideally, the study should cover a range of the hardness values. The splitting of the tablets should be performed in a manner that would be representative of that used by the consumer (i.e., manually split by hand). The uniformity test on split portions can be demonstrated on a one-time basis and does not need to be added to the drug product specification(s). The acceptance criteria (range and variation) should be as described in the USP General Chapter <905> *Uniformity of Dosage Units* for whole tablets. The tablet description on the drug product specifications, and under the Availability section of the Product Monograph, should reflect the presence of a score.

Reference Guidances: Q3B, Q3C, Q6A

P 5.5 Characterisation of Impurities

Information on the characterisation of impurities should be provided, if not previously provided in "S 3.2 Impurities".

This information would include degradation products (e.g., from interaction of the drug substance with excipients or the container closure system), solvents in the manufacturing process for the drug product, etc.. The tables in Health Canada's Quality Summary template in section S 3.2 can be used to summarize this information.

Reference Guidances: Q3B, Q3C, Q6A
Identification, Qualification, and Control of Related Impurities in New Drugs
Identification, Qualification, and Control of Related Impurities in Existing Drugs

P 5.6 Justification of Specification(s)

Justification for the proposed drug product specification(s) should be provided.

This should include a discussion on the inclusion of certain tests, evolution of tests, analytical procedures, and acceptance criteria, differences from compendial standard, etc.. If the Schedule B compendial methods have been modified or replaced, a discussion should be included.

The justification for certain tests, analytical procedures, and acceptance criteria may have been discussed in other sections of the drug submission (e.g., degradation products) and do not need to be repeated here, although a cross-reference to their location should be provided.

The following sections outline considerations for the justification of specifications of some testing procedures and dosage forms. Other considerations are outlined in ICH's Q6A guidance document.

In vitro Dissolution or Drug Release

The results of studies justifying the choice of *in vitro* dissolution or drug release conditions (apparatus, rotation speed, medium) should be provided. Data should also be submitted to demonstrate whether the method is sensitive to changes in manufacturing processes and/or changes in grades and/or amounts of critical excipients. The dissolution method should be sensitive to any changes in the product that would result in a change in one or more of the pharmacokinetic parameters. Use of single point test or a dissolution range should be justified based on the solubility and/or biopharmaceutical classification of the drug.

Modified-release dosage forms should have a meaningful *in vitro* release rate (dissolution) test that is used for routine quality control. Preferably this test should possess *in vitro-in vivo* correlation. Results demonstrating the effect of pH on the dissolution profile should be submitted if appropriate for the type of dosage form.

The testing conditions should be set to cover the entire time period of expected release (e.g., at least three

test intervals chosen for a 12-hour release and additional test intervals for longer duration of release). One of the test points should be at the early stage of drug release (e.g., within the first hour) to demonstrate absence of dose dumping. At each test period, upper and lower limits should be set for individual units. Generally, the acceptance range at each intermediate test point should not exceed 25% or ± 12.5% of the targeted value. Dissolution results should be submitted for several lots, including those lots used for pharmacokinetic and bioavailability studies.

Transdermals

Adhesion of the patch should be tested to evaluate the patch's adhesive property (also termed a peel test or shear test). It is a numerical value obtained from an *in vitro* test and is useful to detect any manufacturing anomaly and serves as an index to monitor stability.

The results of studies justifying the choice of dissolution conditions (apparatus, rotation speed, medium) should be provided. Data should also be submitted to demonstrate whether the drug release method is sensitive to changes in manufacturing processes and/or changes in grades and/or amounts of critical excipients. The dissolution method should be sensitive to any changes in the product that would result in a change in one or more of the pharmacokinetic parameters.

P 6 Reference Standards or Materials

Information on the reference standards or reference materials used for testing of the drug product should be provided, if not previously provided in "S 5 Reference Standards or Materials".

See section S 5 for information that should be provided on reference standards or materials.

Reference Guidances: Q6A
Acceptable Methods

P 7 Container Closure System

A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

For non-functional secondary packaging components (e.g., those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

Suitability information should be located in P 2.

Provide a description and specifications for the packaging components that:

(a) come in direct contact with the dosage form (container, closure, liner, desiccant);

(b) are used as a protective barrier to help ensure stability or sterility;

(c) are used for drug delivery;

(d) are necessary to ensure drug product quality during transportation;

Include all proposed market containers as well as sample packs for physicians. The tables in Health Canada's Quality Summary template can be used to summarize the above information.

The information for the container closure system depends on the dosage form and route of administration. The following table outlines the general recommendations for the various dosage forms (some of this highlighted information can be performed on a one-time basis to establish the suitability of the container closure system and should be discussed in section P 2):

	Solid Oral Products	**Oral Liquid and Topical Products**	**Sterile Products (including Ophthalmics)**
Specifications for routine testing:			
- Name, physical description, dimensions (e.g., thickness, etc.)	x	x	x
- Specific identification tests (e.g., IR) for components that come in direct contact with the dosage form	x	x	x
Qualification of components:			
- Composition and drawings for all components (including cap liners, coatings for metal tubes, elastomers, adhesives, silicon, etc.)	x	x	x
- Description of any additional treatments*	x	x	x (sterilization and depyrogenation of the components)
- USP <661> Containers	x	x	x (includes USP <87> / <88> tests)
- USP <671> Containers - Permeation	x	x	x
- USP <381> Elastomeric Closures for Injections	--	--	x (includes USP <87> / <88> tests)

* e.g., coating of tubes, siliconization of rubber stoppers, sulphur treatment of ampoules/vials

x information should be submitted

-- information does not need to be submitted

Comparative studies can be necessary for changes in components (e.g., comparative delivery study (droplet size) for a change in supplier of dropper tips).

The information on the composition should be available to Health Canada either in the drug submission or in a Drug Master File. Refer to Health Canada's guidance document *Product Master Files* (soon to be renamed *Drug Master Files)* for filing requirements for Type II DMF's (packaging materials).

P 8 Stability

As outlined in ICH's Q1A guidance document, the purpose of stability testing is to provide evidence on how the quality of a drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a shelf life for the drug product and recommended storage conditions.

Reference Guidances: Q1A, Q1B, Q1C
Stability Testing of Existing Drug Substances and Products

P 8.1 Stability Summary and Conclusions

The types of studies conducted, protocols used, and the results of the studies should be summarised. The summary should include, for example, conclusions with respect to storage conditions and shelf life, and, if applicable, in-use storage conditions and shelf life.

Stress testing:

As outlined in ICH's Q1A guidance document, photostability testing should be conducted on at least one primary batch of the drug product if appropriate. Stress testing of other types of dosage forms may be appropriate (e.g., cyclic studies of semi-solids, freeze-thaw studies).

Accelerated and long term testing:

The conditions for stability testing of drug products are outlined in ICH's Q1A guidance document. The following storage conditions and minimum data at the time of submission are recommended by ICH's Q1A guidance document for the Primary Batches. When "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition. See ICH's Q1A guidance document for definition of "significant change".

Study	Storage Condition	Minimum Time Period Covered by Data at Submission
Long term	25°C ± 2°C / 60% RH ± 5% RH	12 months
Intermediate	30°C ± 2°C / 60% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C / 75% RH ± 5% RH	6 months

RH = relative humidity

Other conditions are outlined in the ICH's Q1A guidance document for drug products intended for storage in a refrigerator and those intended for storage in a freezer. Drug products intended for storage below -20°C should be treated on a case-by-case basis.

For existing drugs (e.g., generics), stability information from accelerated and long term testing should be provided on at least two batches of each strength in the container closure system proposed for marketing. Bracketing and matrixing can be applied, if scientifically justified. See Health Canada's guidance document *Stability Testing of Existing Drug Substances and Products* for further details.

For sterile products, sterility should be reported at the beginning and end of shelf life. For parenteral products, sub-visible particulate matter should be reported frequently, but not necessarily at every test interval. Bacterial endotoxins need only be reported at the initial test interval. Weight loss from plastic containers should be reported over the shelf life. In-use periods beyond 28 days for parenteral and ophthalmic products should be justified with experimental data.

The information on the stability studies should include details such as storage conditions, strength, batch number, batch size, container closure system, and completed (and proposed) test intervals. The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "All tests meet specifications". This should include ranges of analytical results and any trends that were observed. For quantitative tests (e.g., as in individual and total degradation product tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such as "within limits" or "conforms".

Proposed storage conditions and shelf life:

The proposed storage conditions with suitable tolerances (e.g., a temperature range with upper and lower criteria) and shelf life for the drug product should be provided.

When the drug product has been shown to be stable (e.g., under the ICH conditions with long term studies at 25• C ± 2• C/60% RH ± 5% RH and accelerated studies at 40• C ± 2• C/75% RH ± 5% RH), the following storage recommendation would generally be considered acceptable:

"Store at controlled room temperature (15• C to 30• C)."

Based on the results of the stability evaluation, other storage precautions may be warranted (e.g., "Protect from light", "Protect from moisture").

Limited extrapolation of the real time data from the long term storage condition beyond the observed range to extend the shelf life can be undertaken at approval time, if justified.

P 8.2 Post-approval Stability Protocol and Stability Commitment

The post-approval stability protocol and stability commitment should be provided.

When available long term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, a commitment should be made to continue the stability studies post-approval in order to firmly establish the shelf life. The long term stability studies for the *Commitment Batches* should be conducted through the proposed shelf life (and the accelerated studies for six months) on at least three production batches of each strength (or two production batches of each strength for existing drugs).

A *Continuing Stability Programme* is implemented to ensure compliance with the approved shelf life specifications. A minimum of one batch of every strength of the drug product is enrolled into the continuing stability programme each year.

The stability protocols for the *Commitment Batches* and *Continuing (i.e., ongoing) Batches* should include, but not limited to:

(a) Number of batches per strength and batch sizes;

(b) Tests and acceptance criteria;

(c) Container closure system(s);

(d) Testing frequency; and

(e) Storage conditions (and tolerances) of samples

Any differences in the stability protocols used for the primary batches and those proposed for the *Commitment Batches* or *Continuing Batches* should be scientifically justified.

P 8.3 Stability Data

Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Information on characterisation of impurities is located in P 5.5.

The actual stability results (i.e., raw data) used to support the proposed shelf life should be provided in the drug submission. For quantitative tests (e.g., as in individual and total degradation product tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such as

"within limits" or "conforms".

A APPENDICES

A 1 Facilities and Equipment

Not applicable (i.e., not a Biotech product).

A 2 Adventitious Agents Safety Evaluation

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications, description of the testing performed, viral safety data).

A 3 Novel Excipients

For excipient(s) used for the first time in a drug product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data (nonclinical and/or clinical) should be provided according to the drug substance and/or drug product format.

R REGIONAL INFORMATION

R 1 Production Documentation

R 1.1 Executed Production Documents

A minimum of two batches of each strength should be manufactured. Bracketing and matrixing of proportional strengths can be applied, if scientifically justified. These batches should be 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.

Copies of the executed production documents should be provided for the batches used in the pivotal clinical and/or comparative bioavailability studies. Any notations made by operators on the executed production documents should be clearly legible.

R 1.2 Master Production Documents

Copies of the drug product master production documents should be provided for each proposed strength, commercial batch size, and manufacturing site.

The details in the master production documents should include, but not limited to, the following:

(a) dispensing, processing and packaging sections with relevant material and operational details;

(b) relevant calculations (e.g., if the amount of drug substance is adjusted based on the potency results or on the anhydrous basis, etc.);

(c) identification of all equipment by type and working capacity;

(d) process parameters (e.g., mixing time, mixing speed, milling screen size, processing temperature range, tablet machine speed, etc.);

(e) list of in-process tests (e.g., appearance, pH, potency, blend uniformity, viscosity, particle size distribution, LOD, weight variation, hardness, disintegration time, weight gain during coating, leaker test, minimum fill, clarity);

(f) sampling plan with regard to the:

- (i) steps where sampling should be done (e.g., drying, lubrication, compression)
- (ii) number of samples that should be tested (e.g., blend drawn using a sampling thief from x number of different parts of the blender)
- (iii) frequency of testing (e.g., weight variation every x minutes during compression or capsule filling);

(g) precautions necessary to ensure product quality (e.g., temperature and humidity control, maximum holding times);

(h) theoretical and actual yield;

(i) compliance with the Good Manufacturing Practices (GMP) requirements as per the provisions of Division C.02 of the *Food and Drug Regulations*.

Reference Guidances: Good Manufacturing Practices

R 2 Medical Devices

According to the *Food and Drugs Act*:

A *device* means any article, instrument, apparatus or contrivance, including any component, part or

accessory thereof, manufactured, sold or represented for use in:

(a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals,

(b) restoring, correcting or modifying a body function or the body structure of human beings or animals,

(c) the diagnosis of pregnancy in human beings or animals, or

(d) the care of human beings or animals during pregnancy and at and after birth of the offspring, including care of the offspring,

and includes a contraceptive device but does not include a drug.

A *drug* includes any substance or mixture of substances manufactured, sold or represented for use in

(a) the diagnosis, treatment, mitigation or prevention of a disease, disorder, abnormal physical state, or its symptoms, in human beings or animals,

(b) restoring, correcting or modifying organic functions in human beings or animals, or

(c) disinfection in premises in which food is manufactured, prepared or kept.

Combination products will be classified as either medical devices or drugs according to the principal mechanism of action by which the claimed effect to purpose is achieved. Those combination products that have been classified as devices include drug coated devices such as catheters, pacemaker leads, drug impregnated devices. Those that have been classified as drugs include prefilled syringes, transdermal patches, peritoneal dialysis solutions, implants whose primary purpose is to release a drug.

A 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, etc.) should be provided.

M MISCELLANEOUS

M 1 ICH Quality Guidance Documents (Chemical Entities)

ICH Quality Guidances Documents (date adopted by Health Canada)	Access
Q1A/R - Stability Testing of New Drug Substances and Products	<not yet adopted>*
Q1B - Stability Testing: Photostability Testing of New Drug Substances and Products (1999)	TPD Website
Q1C - Stability Testing: Requirements for New Dosage Forms (1998)	TPD Website

Q2A - Text on Validation of Analytical Procedures (1999)	TPD Website
Q2B - Validation of Analytical Procedures: Methodology (1999)	TPD Website
Q3A - Impurities in New Drug Substances (1995)	Guidelines Order Form
Q3B - Impurities in New Drug Products (1999)	TPD Website
Q3C - Impurities: Guideline for Residual Solvents (1999)	TPD Website
Q6A - Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Products: Chemical Substances and Products	<not yet adopted>*
Q7A - Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients	<not yet adopted>*
M4Q - Common Technical Document - Quality	<not yet adopted>*

* Available on ICH's Website: www.ifpma.org/ich1.html

M 2 Health Canada Quality Templates and Guidance Documents (Chemical Entities)

Health Canada Quality Templates	Access
Quality Overall Summary - Chemical Entities (New Drug Submissions or Abbreviated New Drug Submissions) (QOS-CE (NDS)) (DRAFT, 2001)	TPD Website
Analytical Procedures and Validation Information Summaries (DRAFT, 2001)	TPD Website
Certified Product Information Document - Chemical Entities (CPID-CE) (DRAFT, 2001)	TPD Website

Health Canada Quality Guidance Documents	Access
Acceptable Methods (1994)	Guidelines Order Form
Chemistry and Manufacturing: New Drugs (1990)	Guidelines Order Form
Extension of Expiration Dates (1992)	TPD Website
Identification, Qualification, and Control of Related Impurities in New Drugs (DRAFT, 1999)	TPD Website
Identification, Qualification, and Control of Related Impurities in Existing Drugs (DRAFT, 1999)	TPD Website
Marketed New Drug Products, Changes to (1994)	TPD Website
Marketed New Drug Products, Stability Requirements for Changes to (1994)	TPD Website
Product Master Files (soon to be renamed Drug Master Files) (1994)	Guidelines Order Form
Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs) (DRAFT, 2001)	TPD Website
Reduction in the Use of Dichloromethane in Tablet Coating Operations (DRAFT, 1997)	TPD Website
Stability Testing of Existing Drug Substances and Products (DRAFT, 1997)	TPD Website
Stereochemical Issues in Chiral Drug Development (2000)	TPD Website

Guidelines Order Form: Guidelines listed on the Guidelines Order Form are available in printed form only, through the Canadian Government Publishing Centre (CGPC). The Order Form is available on the TPD Website under "Forms" or from the CGPC (Tel: (819) 956-4800; Fax: (819) 994-1498; Internet: http://publications.pwgsc.gc.ca).

Health Canada's Therapeutic Products Directorate (TPD) website:
www.hc-sc.gc.ca/hpb-dgps/therapeut