This is **Exhibit "D"** 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

FOOD AND DRUGS ACT

Food and Drug Regulations - Amendment

This notice is to advise the public of Health Canada's intention to proceed with the development of a regulatory framework for Active Pharmaceutical Ingredients (APIs).

Health Canada has a commitment to establish an open and transparent process for the development of regulatory frameworks and through this Notice of Intent, we would like to invite all interested parties to comment on the Health Canada, Health Products and Food Branch's (HPFB) proposal.

APIs destined for human use:

Over the past decade, the extension of Good Manufacturing Practices (GMP) to Active Pharmaceutical Ingredients (APIs) has been internationally recognized as a necessary element in ensuring the overall quality and consistency of marketed drug products. For this reason, the International Conference on Harmonization (ICH) formed a working group in 1997 to develop a GMP Guidance for APIs. A draft of this Guidance was published for comment by Health Canada in July 1999, followed by discussions with the pharmaceutical industry and associations as part of a workshop on selected ICH topics held in November of that year. The final consensus document entitled *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients* (Q7A) was adopted by the ICH Steering Committee on November 10th, 2000, and is currently being implemented by the three ICH regions (USA, Japan and European Union).

Thus, Health Canada is adopting the ICH Q7A Guidance for APIs. A proposed regulatory framework will be developed in order to ensure the implementation of the ICH Q7A Guidance for APIs destined for human use.

You may view the *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients* on the following website:

http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/

APIs destined for veterinary use:

While the scope of the ICH Q7A Guidance is limited, by virtue of the mandate of ICH, to APIs that will be used in the manufacture of pharmaceuticals for human use, the principles and practices described are internationally recognized as having relevance to APIs for veterinary use.

Thus, it is the intent that the proposed regulatory framework will be designed to allow future implementation of GMP requirements for APIs destined for veterinary use.

Proposed approach:

Until such time as the regulatory framework is in place, Health Canada encourages industry to familiarize themselves and apply the principles outlined in the ICH Q7A Guidance. However, whenever there is cause for safety concerns, Health Canada will follow the HPFB Inspectorate's Compliance and Enforcement Policy (POL-0001).

In addition, a step staged approach will be used in order to facilitate a transition towards confidence building and a fully implemented framework.

Consultations:

Once proposed regulations are developed, they will be published within *Canada Gazette* Part I for a period of at least 75 days. We anticipate that the proposed regulations would be published for comment in the Spring of 2004.

This Notice of Intent is posted on the Health Products and Food Branch Inspectorate website at the following address:

http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate

.../3

Comments on this notice may be sent to the Policy and Regulations Division, National Coordination Centre, Health Products and Food Branch Inspectorate, 11 Holland Avenue, Tower A, 2nd Floor, Address Locator: 3002C, Ottawa, Ontario, K1A 0K9 by January 24, 2003 or by Email to Insp_pol@hc-sc.gc.ca or by fax at 613-952-9805.

Persons submitting comments should stipulate any parts of the comments that should not be disclosed pursuant to the *Access to Information Act* (in particular, pursuant to sections 19 and 20 of that Act), the reason why those parts should not be disclosed and the period during which they should remain undisclosed. Representations should also stipulate those parts of the comments for which there is consent to disclosure pursuant to the *Access to Information Act*.

GUIDANCE FOR INDUSTRY

Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

ICH Topic Q7A

Published by authority of the
Minister of Health

Date Adopted	2002/10/03
Effective Date	The Effective Date will be the date the regulations associated with this guidance come into force.

Health Products and Food Branch
Guidance Document

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 the management of the risks and benefits to 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*

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Également disponible en français sous le titre: Ligne directrice sur les bonnes pratiques de fabrication applicables aux ingrédients pharmaceutiques actifs

Catalogue No. E
ISBN

FOREWORD

This guidance has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. The ICH Steering Committee has endorsed the final draft and recommended its adoption by the regulatory bodies of the European Union, Japan and USA.

In adopting this ICH guidance, Health Canada endorses the principles and practices described therein. This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidances.

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. They also serve to provide review and compliance guidance to staff, thereby ensuring that mandates are 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 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.

TABLE OF CONTENTS

1. INTRODUCTION

1.1 Objective

This guidance document is intended to provide guidance regarding good manufacturing practice (GMP) for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the requirements for quality and purity that they purport or are represented to possess.

In this guidance document "manufacturing" is defined to include all operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage and distribution of APIs and the related controls. In this guidance document the term "should" indicates recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance. For the purposes of this guidance document, the terms "current good manufacturing practices" and "good manufacturing practices" are equivalent.

The guidance document as a whole does not cover safety aspects for the personnel engaged in the manufacture, nor aspects of protection of the environment. These controls are inherent responsibilities of the manufacturer and are governed by national laws.

This guidance document is not intended to define registration/filing requirements or modify pharmacopoeial requirements. This guidance document does not affect the ability of the responsible regulatory agency to establish specific registration/filing requirements regarding APIs within the context of marketing/manufacturing authorizations or drug applications. All commitments in registration/filing documents must be met.

1.2 Regulatory Applicability

Within the world community, materials may vary as to the legal classification as an API. When a material is classified as an API in the region or country in which it is manufactured or used in a drug product, it should be manufactured according to this guidance document.

1.3 Scope

This guidance document applies to the manufacture of APIs for use in human drug (medicinal) products. It applies to the manufacture of sterile APIs only up to the point immediately prior to the APIs being rendered sterile. The sterilization and aseptic processing of sterile APIs are not covered by this guidance, but should be performed in accordance with GMP guidances for drug (medicinal)

products as defined by local authorities.

This guidance document covers APIs that are manufactured by chemical synthesis, extraction, cell culture/fermentation, by recovery from natural sources, or by any combination of these processes. Specific guidance for APIs manufactured by cell culture/fermentation is described in Section 18.

This guidance document excludes all vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation), and gene therapy APIs. However, it does include APIs that are produced using blood or plasma as raw materials. Note that cell substrates (mammalian, plant, insect or microbial cells, tissue or animal sources including transgenic animals) and early process steps may be subject to GMP but are not covered by this guidance document. In addition, the guidance document does not apply to medical gases, bulk-packaged drug (medicinal) products, and manufacturing/control aspects specific to radiopharmaceuticals. Section 19 contains guidance that only applies to the manufacture of APIs used in the production of drug (medicinal) products specifically for clinical trials (investigational medicinal products).

An "API Starting Material" is a raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials normally have defined chemical properties and structure.

The company should designate and document the rationale for the point at which production of the API begins. For synthetic processes, this is known as the point at which "API Starting Materials" are entered into the process. For other processes (e.g. fermentation, extraction, purification, etc), this rationale should be established on a case-by-case basis. Table 1 gives guidance on the point at which the API Starting Material is normally introduced into the process.

From this point on, appropriate GMP as defined in this guidance document should be applied to these intermediate and/or API manufacturing steps. This would include the validation of critical process steps determined to impact the quality of the API. However, it should be noted that the fact that a company chooses to validate a process step does not necessarily define that step as critical.

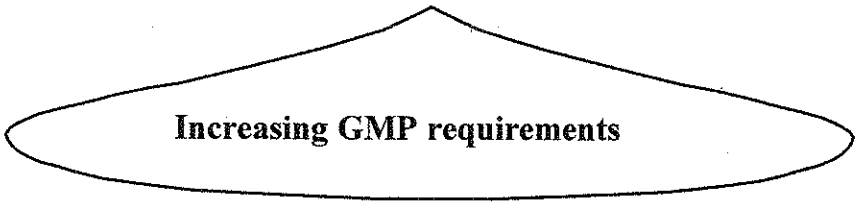
The guidance in this document would normally be applied to the steps shown in gray in Table 1. It does not imply that all steps shown should be completed. The stringency of GMP in API manufacturing should increase as the process proceeds from early API steps to final steps, purification, and packaging. Physical processing of APIs, such as granulation, coating or physical manipulation of particle size (e.g. milling, micronizing), should be conducted at least to the standards

of this guidance document.

This GMP guidance document does not apply to steps prior to the introduction of the defined "API Starting Material".

Table 1: Application of this Guidance to API Manufacturing

Type of Manufacturing	Application of this Guidance to steps (shown in grey) used in this type of manufacturing				
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
API extracted from plant sources	Collection of plants	Cutting and initial extraction(s)	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/ comminuting			Physical processing, and packaging
Biotechnology: fermentation/ cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, and packaging
"Classical" Fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging



2. QUALITY MANAGEMENT

2.1 Principles

2.10 Quality should be the responsibility of all persons involved in manufacturing.

2.11 Each manufacturer should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.

2.12 The system for managing quality should encompass the organisational structure, procedures, processes and resources, as well as activities necessary to ensure confidence that the API will meet its intended specifications for quality and purity. All quality related activities should be defined and documented.

2.13 There should be a quality unit(s) that is independent of production and that fulfills both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

2.14 The persons authorised to release intermediates and APIs should be specified.

2.15 All quality related activities should be recorded at the time they are performed.

2.16 Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented.

2.17 No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s) unless there are appropriate systems in place to allow for such use (e.g. release under quarantine as described in Section 10.20 or the use of raw materials or intermediates pending completion of evaluation).

2.18 Procedures should exist for notifying responsible management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects and related actions (e.g. quality related complaints, recalls, regulatory actions, etc.).

2.2 Responsibilities of the Quality Unit(s)

2.20 The quality unit(s) should be involved in all quality-related matters.

2.21 The quality unit(s) should review and approve all appropriate quality-related documents.

2.22 The main responsibilities of the independent quality unit(s) should not be delegated. These responsibilities should be described in writing and should include but not necessarily be limited to:

1. Releasing or rejecting all APIs. Releasing or rejecting intermediates for use outside the control of the manufacturing company;
2. Establishing a system to release or reject raw materials, intermediates, packaging and labelling materials;
3. Reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution;
4. Making sure that critical deviations are investigated and resolved;
5. Approving all specifications and master production instructions;
6. Approving all procedures impacting the quality of intermediates or APIs;
7. Making sure that internal audits (self-inspections) are performed;
8. Approving intermediate and API contract manufacturers;
9. Approving changes that potentially impact intermediate or API quality;
10. Reviewing and approving validation protocols and reports;
11. Making sure that quality related complaints are investigated and resolved;
12. Making sure that effective systems are used for maintaining and calibrating critical equipment;
13. Making sure that materials are appropriately tested and the results are reported;
14. Making sure that there is stability data to support retest or expiry dates and storage conditions on APIs and/or intermediates where appropriate; and
15. Performing product quality reviews (as defined in Section 2.5).

2.3 Responsibility for Production Activities

The responsibility for production activities should be described in writing, and should include but not necessarily be limited to:

1. Preparing, reviewing, approving and distributing the instructions for the production of intermediates or APIs according to written procedures;
2. Producing APIs and, when appropriate, intermediates according to pre-approved instructions;
3. Reviewing all production batch records and ensuring that these are completed and

signed;

4. Making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded;
5. Making sure that production facilities are clean and when appropriate disinfected;
6. Making sure that the necessary calibrations are performed and records kept;
7. Making sure that the premises and equipment are maintained and records kept;
8. Making sure that validation protocols and reports are reviewed and approved;
9. Evaluating proposed changes in product, process or equipment; and
10. Making sure that new and, when appropriate, modified facilities and equipment are qualified.

2.4 Internal Audits (Self Inspection)

2.40 In order to verify compliance with the principles of GMP for APIs, regular internal audits should be performed in accordance with an approved schedule.

2.41 Audit findings and corrective actions should be documented and brought to the attention of responsible management of the firm. Agreed corrective actions should be completed in a timely and effective manner.

2.5 Product Quality Review

2.50 Regular quality reviews of APIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually and should include at least:

- A review of critical in-process control and critical API test results;
- A review of all batches that failed to meet established specification(s);
- A review of all critical deviations or non-conformances and related investigations;
- A review of any changes carried out to the processes or analytical methods;
- A review of results of the stability monitoring program;
- A review of all quality-related returns, complaints and recalls; and
- A review of adequacy of corrective actions.

2.51 The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken. Reasons for such corrective action should be documented. Agreed corrective actions should be completed in a timely and effective manner.

3. PERSONNEL

3.1 Personnel Qualifications

3.10 There should be an adequate number of personnel qualified by appropriate education, training and/or experience to perform and supervise the manufacture of intermediates and APIs.

3.11 The responsibilities of all personnel engaged in the manufacture of intermediates and APIs should be specified in writing.

3.12 Training should be regularly conducted by qualified individuals and should cover, at a minimum, the particular operations that the employee performs and GMP as it relates to the employee's functions. Records of training should be maintained. Training should be periodically assessed.

3.2 Personnel Hygiene

3.20 Personnel should practice good sanitation and health habits.

3.21 Personnel should wear clean clothing suitable for the manufacturing activity with which they are involved and this clothing should be changed when appropriate. Additional protective apparel, such as head, face, hand, and arm coverings, should be worn when necessary, to protect intermediates and APIs from contamination.

3.22 Personnel should avoid direct contact with intermediates or APIs.

3.23 Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas.

3.24 Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of APIs. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions should be excluded from activities where the health condition could adversely affect the quality of the APIs until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the APIs.

3.3 Consultants

3.30 Consultants advising on the manufacture and control of intermediates or APIs should have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained.

3.31 Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants.

4. BUILDINGS AND FACILITIES

4.1 Design and Construction

4.10 Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture. Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants as appropriate.

4.11 Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.

4.12 Where the equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.

4.13 The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination.

4.14 There should be defined areas or other control systems for the following activities:

- Receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection;
- Quarantine before release or rejection of intermediates and APIs;
- Sampling of intermediates and APIs;
- Holding rejected materials before further disposition (e.g., return, reprocessing or destruction);
- Storage of released materials;
- Production operations;

- Packaging and labelling operations; and
- Laboratory operations.

4.15 Adequate, clean washing and toilet facilities should be provided for personnel. These washing facilities should be equipped with hot and cold water as appropriate, soap or detergent, air driers or single service towels. The washing and toilet facilities should be separate from, but easily accessible to, manufacturing areas. Adequate facilities for showering and/or changing clothes should be provided, when appropriate.

4.16 Laboratory areas/operations should normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements, and the laboratory and its operations do not adversely affect the production process or intermediate or API.

4.2 Utilities

4.20 All utilities that could impact on product quality (e.g. steam, gases, compressed air, and heating, ventilation and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded. Drawings for these utility systems should be available.

4.21 Adequate ventilation, air filtration and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimise risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where APIs are exposed to the environment.

4.22 If air is recirculated to production areas, appropriate measures should be taken to control risks of contamination and cross-contamination.

4.23 Permanently installed pipework should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipework should be located to avoid risks of contamination of the intermediate or API.

4.24 Drains should be of adequate size and should be provided with an air break or a suitable device to prevent back-siphonage, when appropriate.

4.3 Water

4.30 Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use.

4.31 Unless otherwise justified, process water should, at a minimum, meet World Health Organization (WHO) guidelines for drinking (potable) water quality.

4.32 If drinking (potable) water is insufficient to assure API quality, and tighter chemical and/or microbiological water quality specifications are called for, appropriate specifications for physical/chemical attributes, total microbial counts, objectionable organisms and/or endotoxins should be established.

4.33 Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process should be validated and monitored with appropriate action limits.

4.34 Where the manufacturer of a non-sterile API either intends or claims that it is suitable for use in further processing to produce a sterile drug (medicinal) product, water used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms, and endotoxins.

4.4 Containment

4.40 Dedicated production areas, which can include facilities, air handling equipment and/or process equipment, should be employed in the production of highly sensitizing materials, such as penicillins or cephalosporins.

4.41 Dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g., certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.

4.42 Appropriate measures should be established and implemented to prevent cross-contamination from personnel, materials, etc. moving from one dedicated area to another.

4.43 Any production activities (including weighing, milling, or packaging) of highly toxic non-pharmaceutical materials such as herbicides and pesticides should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic non-pharmaceutical materials should be separate from APIs.

4.5 Lighting

4.50 Adequate lighting should be provided in all areas to facilitate cleaning, maintenance, and proper operations.

4.6 Sewage and Refuse

4.60 Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Containers and/or pipes for waste material should be clearly identified.

4.7 Sanitation and Maintenance

4.70 Buildings used in the manufacture of intermediates and APIs should be properly maintained and repaired and kept in a clean condition.

4.71 Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities.

4.72 When necessary, written procedures should also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging/labelling materials, intermediates, and APIs.

5. PROCESS EQUIPMENT

5.1 Design and Construction

5.10 Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitization (where appropriate), and maintenance.

5.11 Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.

5.12 Production equipment should only be used within its qualified operating range.

5.13 Major equipment (e.g., reactors, storage containers) and permanently installed processing lines used during the production of an intermediate or API should be appropriately identified.

5.14 Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants, should not contact intermediates or APIs so as to alter their quality beyond the official or other established specifications. Any deviations from this should be evaluated to ensure that there are no detrimental effects upon the fitness for purpose of the material. Wherever possible, food grade lubricants and oils should be used.

5.15 Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.

5.16 A set of current drawings should be maintained for equipment and critical installations (e.g., instrumentation and utility systems).

5.2 Equipment Maintenance and Cleaning

5.20 Schedules and procedures (including assignment of responsibility) should be established for the preventative maintenance of equipment.

5.21 Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include:

- Assignment of responsibility for cleaning of equipment;
- Cleaning schedules, including, where appropriate, sanitizing schedules;
- A complete description of the methods and materials, including dilution of cleaning agents used to clean equipment;
- When appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning;
- Instructions for the removal or obliteration of previous batch identification;
- Instructions for the protection of clean equipment from contamination prior to use;
- Inspection of equipment for cleanliness immediately before use, if practical; and
- Establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate.

5.22 Equipment and utensils should be cleaned, stored, and, where appropriate, sanitized or sterilized to prevent contamination or carry-over of a material that would alter the quality

of the intermediate or API beyond the official or other established specifications.

5.23 Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or API, equipment should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g. degradants or objectionable levels of micro-organisms).

5.24 Non-dedicated equipment should be cleaned between production of different materials to prevent cross-contamination.

5.25 Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.

5.26 Equipment should be identified as to its contents and its cleanliness status by appropriate means.

5.3 Calibration

5.30 Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule.

5.31 Equipment calibrations should be performed using standards traceable to certified standards, if existing.

5.32 Records of these calibrations should be maintained.

5.33 The current calibration status of critical equipment should be known and verifiable.

5.34 Instruments that do not meet calibration criteria should not be used.

5.35 Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an impact on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration.

5.4 Computerized Systems

5.40 GMP related computerized systems should be validated. The depth and scope of

validation depends on the diversity, complexity and criticality of the computerized application.

5.41 Appropriate installation qualification and operational qualification should demonstrate the suitability of computer hardware and software to perform assigned tasks.

5.42 Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at time of installation, a retrospective validation could be conducted if appropriate documentation is available.

5.43 Computerized systems should have sufficient controls to prevent unauthorized access or changes to data. There should be controls to prevent omissions in data (e.g. system turned off and data not captured). There should be a record of any data change made, the previous entry, who made the change, and when the change was made.

5.44 Written procedures should be available for the operation and maintenance of computerized systems.

5.45 Where critical data are being entered manually, there should be an additional check on the accuracy of the entry. This can be done by a second operator or by the system itself.

5.46 Incidents related to computerized systems that could affect the quality of intermediates or APIs or the reliability of records or test results should be recorded and investigated.

5.47 Changes to the computerized system should be made according to a change procedure and should be formally authorized, documented and tested. Records should be kept of all changes, including modifications and enhancements made to the hardware, software and any other critical component of the system. These records should demonstrate that the system is maintained in a validated state.

5.48 If system breakdowns or failures would result in the permanent loss of records, a back-up system should be provided. A means of ensuring data protection should be established for all computerized systems.

5.49 Data can be recorded by a second means in addition to the computer system.

6. DOCUMENTATION AND RECORDS

6.1 Documentation System and Specifications

6.10 All documents related to the manufacture of intermediates or APIs should be prepared, reviewed, approved and distributed according to written procedures. Such documents can be in paper or electronic form.

6.11 The issuance, revision, superseding and withdrawal of all documents should be controlled with maintenance of revision histories.

6.12 A procedure should be established for retaining all appropriate documents (e.g., development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records, and distribution records). The retention periods for these documents should be specified.

6.13 All production, control, and distribution records should be retained for at least 1 year after the expiry date of the batch. For APIs with retest dates, records should be retained for at least 3 years after the batch is completely distributed.

6.14 When entries are made in records, these should be made indelibly in spaces provided for such entries, directly after performing the activities, and should identify the person making the entry. Corrections to entries should be dated and signed and leave the original entry still readable.

6.15 During the retention period, originals or copies of records should be readily available at the establishment where the activities described in such records occurred. Records that can be promptly retrieved from another location by electronic or other means are acceptable.

6.16 Specifications, instructions, procedures, and records can be retained either as originals or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques such as microfilming or electronic records are used, suitable retrieval equipment and a means to produce a hard copy should be readily available.

6.17 Specifications should be established and documented for raw materials, intermediates where necessary, APIs, and labelling and packaging materials. In addition, specifications may be appropriate for certain other materials, such as process aids, gaskets, or other materials used during the production of intermediates or APIs that could critically impact on quality. Acceptance criteria should be established and documented for in-process controls.

6.18 If electronic signatures are used on documents, they should be authenticated and secure.

6.2 Equipment Cleaning and Use Record

6.20 Records of major equipment use, cleaning, sanitization and/or sterilization and maintenance should show the date, time (if appropriate), product, and batch number of each batch processed in the equipment, and the person who performed the cleaning and maintenance.

6.21 If equipment is dedicated to manufacturing one intermediate or API, then individual equipment records are not necessary if batches of the intermediate or API follow in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use can be part of the batch record or maintained separately.

6.3 Records of Raw Materials, Intermediates, API Labelling and Packaging Materials

6.30 Records should be maintained including:

- The name of the manufacturer, identity and quantity of each shipment of each batch of raw materials, intermediates or labelling and packaging materials for API's; the name of the supplier; the supplier's control number(s), if known, or other identification number; the number allocated on receipt; and the date of receipt;
- The results of any test or examination performed and the conclusions derived from this;
- Records tracing the use of materials;
- Documentation of the examination and review of API labelling and packaging materials for conformity with established specifications; and
- The final decision regarding rejected raw materials, intermediates or API labelling and packaging materials.

6.31 Master (approved) labels should be maintained for comparison to issued labels.

6.4 Master Production Instructions (Master Production and Control Records)

6.40 To ensure uniformity from batch to batch, master production instructions for each intermediate and API should be prepared, dated, and signed by one person and independently checked, dated, and signed by a person in the quality unit(s).

6.41 Master production instructions should include:

- The name of the intermediate or API being manufactured and an identifying document reference code, if applicable;

A complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics;

- An accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production should be included. Variations to quantities should be included where they are justified;
- The production location and major production equipment to be used;
- Detailed production instructions, including the:
    - sequences to be followed,
    - ranges of process parameters to be used,
    - sampling instructions and in-process controls with their acceptance criteria, where appropriate,
    - time limits for completion of individual processing steps and/or the total process, where appropriate; and
    - expected yield ranges at appropriate phases of processing or time;
- Where appropriate, special notations and precautions to be followed, or cross-references to these; and
- The instructions for storage of the intermediate or API to assure its suitability for use, including the labelling and packaging materials and special storage conditions with time limits, where appropriate.

6.5 Batch Production Records (Batch Production and Control Records)

6.50 Batch production records should be prepared for each intermediate and API and should include complete information relating to the production and control of each batch. The batch production record should be checked before issuance to assure that it is the correct version and a legible accurate reproduction of the appropriate master production instruction. If the batch production record is produced from a separate part of the master document, that document should include a reference to the current master production instruction being used.

6.51 These records should be numbered with a unique batch or identification number, dated and signed when issued. In continuous production, the product code together with the date and time can serve as the unique identifier until the final number is allocated.

6.52 Documentation of completion of each significant step in the batch production records (batch production and control records) should include:

- Dates and, when appropriate, times;

Identity of major equipment (e.g., reactors, driers, mills, etc.) used;

- Specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing;
- Actual results recorded for critical process parameters;
- Any sampling performed;
- Signatures of the persons performing and directly supervising or checking each critical step in the operation;
- In-process and laboratory test results;
- Actual yield at appropriate phases or times;
- Description of packaging and label for intermediate or API;
- Representative label of API or intermediate if made commercially available;
- Any deviation noted, its evaluation, investigation conducted (if appropriate) or reference to that investigation if stored separately; and
- Results of release testing.

6.53 Written procedures should be established and followed for investigating critical deviations or the failure of a batch of intermediate or API to meet specifications. The investigation should extend to other batches that may have been associated with the specific failure or deviation.

6.6 Laboratory Control Records

6.60 Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows:

- A description of samples received for testing, including the material name or source, batch number or other distinctive code, date sample was taken, and, where appropriate, the quantity and date the sample was received for testing;
- A statement of or reference to each test method used;
- A statement of the weight or measure of sample used for each test as described by the method; data on or cross-reference to the preparation and testing of reference standards, reagents and standard solutions;
- A complete record of all raw data generated during each test, in addition to graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested;
- A record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors, and equivalency factors;
- A statement of the test results and how they compare with established acceptance criteria;

The signature of the person who performed each test and the date(s) the tests were performed; and

- The date and signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

6.61 Complete records should also be maintained for:

- Any modifications to an established analytical method;
- Periodic calibration of laboratory instruments, apparatus, gauges, and recording devices;
- All stability testing performed on APIs; and
- Out-of-specification (OOS) investigations.

6.7 Batch Production Record Review

6.70 Written procedures should be established and followed for the review and approval of batch production and laboratory control records, including packaging and labelling, to determine compliance of the intermediate or API with established specifications before a batch is released or distributed.

6.71 Batch production and laboratory control records of critical process steps should be reviewed and approved by the quality unit(s) before an API batch is released or distributed. Production and laboratory control records of non-critical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality unit(s).

6.72 All deviation, investigation, and OOS reports should be reviewed as part of the batch record review before the batch is released.

6.73 The quality unit(s) can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.

7. MATERIALS MANAGEMENT

7.1 General Controls

7.10 There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials.

7.11 Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials.

7.12 Materials should be purchased against an agreed specification, from a supplier or suppliers approved by the quality unit(s).

7.13 If the supplier of a critical material is not the manufacturer of that material, the name and address of that manufacturer should be known by the intermediate and/or API manufacturer.

7.14 Changing the source of supply of critical raw materials should be treated according to Section 13, Change Control.

7.2 Receipt and Quarantine

7.20 Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labelling (including correlation between the name used by the supplier and the in-house name, if these are different), container damage, broken seals and evidence of tampering or contamination. Materials should be held under quarantine until they have been sampled, examined or tested as appropriate, and released for use.

7.21 Before incoming materials are mixed with existing stocks (e.g., solvents or stocks in silos), they should be identified as correct, tested, if appropriate, and released. Procedures should be available to prevent discharging incoming materials wrongly into the existing stock.

7.22 If bulk deliveries are made in non-dedicated tankers, there should be assurance of no cross-contamination from the tanker. Means of providing this assurance could include one or more of the following:

- certificate of cleaning
- testing for trace impurities
- audit of the supplier.

7.23 Large storage containers, and their attendant manifolds, filling and discharge lines should be appropriately identified.

7.24 Each container or grouping of containers (batches) of materials should be assigned and identified with a distinctive code, batch, or receipt number. This number should be used in recording the disposition of each batch. A system should be in place to identify the status of each batch.

7.3 Sampling and Testing of Incoming Production Materials

7.30 At least one test to verify the identity of each batch of material should be conducted, with the exception of the materials described below in 7.32. A supplier's Certificate of Analysis can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers.

7.31 Supplier approval should include an evaluation that provides adequate evidence (e.g., past quality history) that the manufacturer can consistently provide material meeting specifications. Full analyses should be conducted on at least three batches before reducing in-house testing. However, as a minimum, a full analysis should be performed at appropriate intervals and compared with the Certificates of Analysis. Reliability of Certificates of Analysis should be checked at regular intervals.

7.32 Processing aids, hazardous or highly toxic raw materials, other special materials, or materials transferred to another unit within the company's control do not need to be tested if the manufacturer's Certificate of Analysis is obtained, showing that these raw materials conform to established specifications. Visual examination of containers, labels, and recording of batch numbers should help in establishing the identity of these materials. The lack of on-site testing for these materials should be justified and documented.

7.33 Samples should be representative of the batch of material from which they are taken. Sampling methods should specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The number of containers to sample and the sample size should be based upon a sampling plan that takes into consideration the criticality of the material, material variability, past quality history of the supplier, and the quantity needed for analysis.

7.34 Sampling should be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.

7.35 Containers from which samples are withdrawn should be opened carefully and subsequently reclosed. They should be marked to indicate that a sample has been taken.

7.4 Storage

7.40 Materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination.

7.41 Materials stored in fiber drums, bags, or boxes should be stored off the floor and, when appropriate, suitably spaced to permit cleaning and inspection.

7.42 Materials should be stored under conditions and for a period that have no adverse affect on their quality, and should normally be controlled so that the oldest stock is used first.

7.43 Certain materials in suitable containers can be stored outdoors, provided identifying labels remain legible and containers are appropriately cleaned before opening and use.

7.44 Rejected materials should be identified and controlled under a quarantine system designed to prevent their unauthorised use in manufacturing.

7.5 Re-evaluation

7.50 Materials should be re-evaluated as appropriate to determine their suitability for use (e.g., after prolonged storage or exposure to heat or humidity).

8. PRODUCTION AND IN-PROCESS CONTROLS

8.1 Production Operations

8.10 Raw materials for intermediate and API manufacturing should be weighed or measured under appropriate conditions that do not affect their suitability for use. Weighing and measuring devices should be of suitable accuracy for the intended use.

8.11 If a material is subdivided for later use in production operations, the container receiving the material should be suitable and should be so identified that the following information is available:

- Material name and/or item code;
- Receiving or control number;
- Weight or measure of material in the new container; and
- Re-evaluation or retest date if appropriate.

8.12 Critical weighing, measuring, or subdividing operations should be witnessed or subjected to an equivalent control. Prior to use, production personnel should verify that the materials are those specified in the batch record for the intended intermediate or API.

8.13 Other critical activities should be witnessed or subjected to an equivalent control.

8.14 Actual yields should be compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges should be established based on previous laboratory, pilot scale, or manufacturing data. Deviations in yield associated with critical process steps should be investigated to determine their impact or potential impact on the resulting quality of affected batches.

8.15 Any deviation should be documented and explained. Any critical deviation should be investigated.

8.16 The processing status of major units of equipment should be indicated either on the individual units of equipment or by appropriate documentation, computer control systems, or alternative means.

8.17 Materials to be reprocessed or reworked should be appropriately controlled to prevent unauthorized use.

8.2 Time Limits

8.20 If time limits are specified in the master production instruction (see 6.41), these time limits should be met to ensure the quality of intermediates and APIs. Deviations should be documented and evaluated. Time limits may be inappropriate when processing to a target value (e.g., pH adjustment, hydrogenation, drying to predetermined specification) because completion of reactions or processing steps are determined by in-process sampling and testing.

8.21 Intermediates held for further processing should be stored under appropriate conditions to ensure their suitability for use.

8.3 In-process Sampling and Controls

8.30 Written procedures should be established to monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs. In-process controls and their acceptance criteria should be defined based on the information gained during the development stage or historical data.

8.31 The acceptance criteria and type and extent of testing can depend on the nature of the intermediate or API being manufactured, the reaction or process step being conducted, and the degree to which the process introduces variability in the product's quality. Less stringent in-process controls may be appropriate in early processing steps, whereas tighter controls may be appropriate for later processing steps (e.g., isolation and purification steps).

8.32 Critical in-process controls (and critical process monitoring), including the control points and methods, should be stated in writing and approved by the quality unit(s).

8.33 In-process controls can be performed by qualified production department personnel and the process adjusted without prior quality unit(s) approval if the adjustments are made

within pre-established limits approved by the quality unit(s). All tests and results should be fully documented as part of the batch record.

8.34 Written procedures should describe the sampling methods for in-process materials, intermediates, and APIs. Sampling plans and procedures should be based on scientifically sound sampling practices.

8.35 In-process sampling should be conducted using procedures designed to prevent contamination of the sampled material and other intermediates or APIs. Procedures should be established to ensure the integrity of samples after collection.

8.36 Out-of-specification (OOS) investigations are not normally needed for in-process tests that are performed for the purpose of monitoring and/or adjusting the process.

8.4 Blending Batches of Intermediates or APIs

8.40 For the purpose of this guidance document, blending is defined as the process of combining materials within the same specification to produce a homogeneous intermediate or API. In-process mixing of fractions from single batches (e.g., collecting several centrifuge loads from a single crystallization batch) or combining fractions from several batches for further processing is considered to be part of the production process and is not considered to be blending.

8.41 Out-Of-Specification batches should not be blended with other batches for the purpose of meeting specifications. Each batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending.

8.42 Acceptable blending operations include but are not limited to:

- Blending of small batches to increase batch size
- Blending of tailings (i.e., relatively small quantities of isolated material) from batches of the same intermediate or API to form a single batch.

8.43 Blending processes should be adequately controlled and documented and the blended batch should be tested for conformance to established specifications where appropriate.

8.44 The batch record of the blending process should allow traceability back to the individual batches that make up the blend.

8.45 Where physical attributes of the API are critical (e.g., APIs intended for use in solid oral

dosage forms or suspensions), blending operations should be validated to show homogeneity of the combined batch. Validation should include testing of critical attributes (e.g., particle size distribution, bulk density, and tap density) that may be affected by the blending process.

8.46 If the blending could adversely affect stability, stability testing of the final blended batches should be performed.

8.47 The expiry or retest date of the blended batch should be based on the manufacturing date of the oldest tailings or batch in the blend.

8.5 Contamination Control

8.50 Residual materials can be carried over into successive batches of the same intermediate or API if there is adequate control. Examples include residue adhering to the wall of a micronizer, residual layer of damp crystals remaining in a centrifuge bowl after discharge, and incomplete discharge of fluids or crystals from a processing vessel upon transfer of the material to the next step in the process. Such carryover should not result in the carryover of degradants or microbial contamination that may adversely alter the established API impurity profile.

8.51 Production operations should be conducted in a manner that will prevent contamination of intermediates or APIs by other materials.

8.52 Precautions to avoid contamination should be taken when APIs are handled after purification.

9. PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

9.1 General

9.10 There should be written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release, and handling of packaging and labelling materials.

9.11 Packaging and labelling materials should conform to established specifications. Those that do not comply with such specifications should be rejected to prevent their use in operations for which they are unsuitable.

9.12 Records should be maintained for each shipment of labels and packaging materials showing

receipt, examination, or testing, and whether accepted or rejected.

9.2 Packaging Materials

9.20 Containers should provide adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation and recommended storage.

9.21 Containers should be clean and, where indicated by the nature of the intermediate or API, sanitized to ensure that they are suitable for their intended use. These containers should not be reactive, additive, or absorptive so as to alter the quality of the intermediate or API beyond the specified limits.

9.22 If containers are re-used, they should be cleaned in accordance with documented procedures and all previous labels should be removed or defaced.

9.3 Label Issuance and Control

9.30 Access to the label storage areas should be limited to authorised personnel.

9.31 Procedures should be used to reconcile the quantities of labels issued, used, and returned and to evaluate discrepancies found between the number of containers labelled and the number of labels issued. Such discrepancies should be investigated, and the investigation should be approved by the quality unit(s).

9.32 All excess labels bearing batch numbers or other batch-related printing should be destroyed. Returned labels should be maintained and stored in a manner that prevents mix-ups and provides proper identification.

9.33 Obsolete and out-dated labels should be destroyed.

9.34 Printing devices used to print labels for packaging operations should be controlled to ensure that all imprinting conforms to the print specified in the batch production record.

9.35 Printed labels issued for a batch should be carefully examined for proper identity and conformity to specifications in the master production record. The results of this examination should be documented.

9.36 A printed label representative of those used should be included in the batch production record.

9.4 Packaging and Labelling Operations

9.40 There should be documented procedures designed to ensure that correct packaging materials and labels are used.

9.41 Labelling operations should be designed to prevent mix-ups. There should be physical or spatial separation from operations involving other intermediates or APIs.

9.42 Labels used on containers of intermediates or APIs should indicate the name or identifying code, the batch number of the product, and storage conditions, when such information is critical to assure the quality of intermediate or API.

9.43 If the intermediate or API is intended to be transferred outside the control of the manufacturer's material management system, the name and address of the manufacturer, quantity of contents, and special transport conditions and any special legal requirements should also be included on the label. For intermediates or APIs with an expiry date, the expiry date should be indicated on the label and Certificate of Analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or Certificate of Analysis.

9.44 Packaging and labelling facilities should be inspected immediately before use to ensure that all materials not needed for the next packaging operation have been removed. This examination should be documented in the batch production records, the facility log, or other documentation system.

9.45 Packaged and labelled intermediates or APIs should be examined to ensure that containers and packages in the batch have the correct label. This examination should be part of the packaging operation. Results of these examinations should be recorded in the batch production or control records.

9.46 Intermediate or API containers that are transported outside of the manufacturer's control should be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the contents may have been altered.

10. STORAGE AND DISTRIBUTION

10.1 Warehousing Procedures

10.10 Facilities should be available for the storage of all materials under appropriate conditions (e.g. controlled temperature and humidity when necessary). Records should be maintained of these conditions if they are critical for the maintenance of material characteristics.

10.11 Unless there is an alternative system to prevent the unintentional or unauthorised use of

quarantined, rejected, returned, or recalled materials, separate storage areas should be assigned for their temporary storage until the decision as to their future use has been taken.

10.2 Distribution Procedures

10.20 APIs and intermediates should only be released for distribution to third parties after they have been released by the quality unit(s). APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the quality unit(s) and if appropriate controls and documentation are in place.

10.21 APIs and intermediates should be transported in a manner that does not adversely affect their quality.

10.22 Special transport or storage conditions for an API or intermediate should be stated on the label.

10.23 The manufacturer should ensure that the contract acceptor (contractor) for transportation of the API or intermediate knows and follows the appropriate transport and storage conditions.

10.24 A system should be in place by which the distribution of each batch of intermediate and/or API can be readily determined to permit its recall.

11. LABORATORY CONTROLS

11.1 General Controls

11.10 The independent quality unit(s) should have at its disposal adequate laboratory facilities.

11.11 There should be documented procedures describing sampling, testing, approval or rejection of materials, and recording and storage of laboratory data. Laboratory records should be maintained in accordance with Section 6.6.

11.12 All specifications, sampling plans, and test procedures should be scientifically sound and appropriate to ensure that raw materials, intermediates, APIs, and labels and packaging materials conform to established standards of quality and/or purity. Specifications and test procedures should be consistent with those included in the registration/filing. There can be specifications in addition to those in the registration/filing. Specifications, sampling plans, and test procedures, including changes to them, should be drafted by the appropriate organizational unit and reviewed and approved by the quality unit(s).

11.13 Appropriate specifications should be established for APIs in accordance with accepted standards and consistent with the manufacturing process. The specifications should include a control of the impurities (e.g. organic impurities, inorganic impurities, and residual solvents). If the API has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms should be established and met. If the API has a specification for endotoxins, appropriate action limits should be established and met.

11.14 Laboratory controls should be followed and documented at the time of performance. Any departures from the above described procedures should be documented and explained.

11.15 Any out-of-specification result obtained should be investigated and documented according to a procedure. This procedure should require analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions, and conclusions. Any resampling and/or retesting after OOS results should be performed according to a documented procedure.

11.16 Reagents and standard solutions should be prepared and labelled following written procedures. "Use by" dates should be applied as appropriate for analytical reagents or standard solutions.

11.17 Primary reference standards should be obtained as appropriate for the manufacture of APIs. The source of each primary reference standard should be documented. Records should be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations. Primary reference standards obtained from an officially recognised source are normally used without testing if stored under conditions consistent with the supplier's recommendations.

11.18 Where a primary reference standard is not available from an officially recognized source, an "in-house primary standard" should be established. Appropriate testing should be performed to establish fully the identity and purity of the primary reference standard. Appropriate documentation of this testing should be maintained.

11.19 Secondary reference standards should be appropriately prepared, identified, tested, approved, and stored. The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard should be periodically requalified in accordance with a written protocol.

11.2 Testing of Intermediates and APIs

11.20 For each batch of intermediate and API, appropriate laboratory tests should be conducted to determine conformance to specifications.

11.21 An impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process should normally be established for each API. The impurity profile should include the identity or some qualitative analytical designation (e.g. retention time), the range of each impurity observed, and classification of each identified impurity (e.g. inorganic, organic, solvent). The impurity profile is normally dependent upon the production process and origin of the API. Impurity profiles are normally not necessary for APIs from herbal or animal tissue origin. Biotechnology considerations are covered in ICH Guidance Q6B.

11.22 The impurity profile should be compared at appropriate intervals against the impurity profile in the regulatory submission or compared against historical data in order to detect changes to the API resulting from modifications in raw materials, equipment operating parameters, or the production process.

11.23 Appropriate microbiological tests should be conducted on each batch of intermediate and API where microbial quality is specified.

11.3 Validation of Analytical Procedures - see Section 12.

11.4 Certificates of Analysis

11.40 Authentic Certificates of Analysis should be issued for each batch of intermediate or API on request.

11.41 Information on the name of the intermediate or API including where appropriate its grade, the batch number, and the date of release should be provided on the Certificate of Analysis. For intermediates or APIs with an expiry date, the expiry date should be provided on the label and Certificate of Analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or Certificate of Analysis.

11.42 The Certificate should list each test performed in accordance with compendial or customer requirements, including the acceptance limits, and the numerical results obtained (if test results are numerical).

11.43 Certificates should be dated and signed by authorised personnel of the quality unit(s) and should show the name, address and telephone number of the original manufacturer. Where the analysis has been carried out by a repacker or reprocessor, the Certificate of Analysis should show the name, address and telephone number of the repacker/reprocessor and

a reference to the name of the original manufacturer.

11.44 If new Certificates are issued by or on behalf of repackers/reprocessors, agents or brokers, these Certificates should show the name, address and telephone number of the laboratory that performed the analysis. They should also contain a reference to the name and address of the original manufacturer and to the original batch Certificate, a copy of which should be attached.

11.5 Stability Monitoring of APIs

11.50 A documented, on-going testing program should be designed to monitor the stability characteristics of APIs, and the results should be used to confirm appropriate storage conditions and retest or expiry dates.

11.51 The test procedures used in stability testing should be validated and be stability indicating.

11.52 Stability samples should be stored in containers that simulate the market container. For example, if the API is marketed in bags within fiber drums, stability samples can be packaged in bags of the same material and in smaller-scale drums of similar or identical material composition to the market drums.

11.53 Normally the first three commercial production batches should be placed on the stability monitoring program to confirm the retest or expiry date. However, where data from previous studies show that the API is expected to remain stable for at least two years, fewer than three batches can be used.

11.54 Thereafter, at least one batch per year of API manufactured (unless none is produced that year) should be added to the stability monitoring program and tested at least annually to confirm the stability.

11.55 For APIs with short shelf-lives, testing should be done more frequently. For example, for those biotechnological/biologic and other APIs with shelf-lives of one year or less, stability samples should be obtained and should be tested monthly for the first three months, and at three month intervals after that. When data exist that confirm that the stability of the API is not compromised, elimination of specific test intervals (e.g. 9 month testing) can be considered.

11.56 Where appropriate, the stability storage conditions should be consistent with the ICH guidances on stability.

11.6 Expiry and Retest Dating

11.60 When an intermediate is intended to be transferred outside the control of the manufacturer's material management system and an expiry or retest date is assigned, supporting stability information should be available (e.g. published data, test results).

11.61 An API expiry or retest date should be based on an evaluation of data derived from stability studies. Common practice is to use a retest date, not an expiration date.

11.62 Preliminary API expiry or retest dates can be based on pilot scale batches if (1) the pilot batches employ a method of manufacture and procedure that simulates the final process to be used on a commercial manufacturing scale; and (2) the quality of the API represents the material to be made on a commercial scale.

11.63 A representative sample should be taken for the purpose of performing a retest.

11.7 Reserve/Retention Samples

11.70 The packaging and holding of reserve samples is for the purpose of potential future evaluation of the quality of batches of API and not for future stability testing purposes.

11.71 Appropriately identified reserve samples of each API batch should be retained for one year after the expiry date of the batch assigned by the manufacturer, or for three years after distribution of the batch, whichever is the longer. For APIs with retest dates, similar reserve samples should be retained for three years after the batch is completely distributed by the manufacturer.

11.72 The reserve sample should be stored in the same packaging system in which the API is stored or in one that is equivalent to or more protective than the marketed packaging system. Sufficient quantities should be retained to conduct at least two full compendial analyses or, when there is no pharmacopoeial monograph, two full specification analyses.

12. VALIDATION

12.1 Validation Policy

12.10 The company's overall policy, intentions, and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, in-process control test procedures, computerized systems, and persons responsible for design, review, approval and documentation of each validation phase, should be documented.

12.11 The critical parameters/attributes should normally be identified during the development stage or from historical data, and the ranges necessary for the reproducible operation should be defined. This should include:

- Defining the API in terms of its critical product attributes;
- Identifying process parameters that could affect the critical quality attributes of the API;
- Determining the range for each critical process parameter expected to be used during routine manufacturing and process control.

12.12 Validation should extend to those operations determined to be critical to the quality and purity of the API.

12.2 Validation Documentation

12.20 A written validation protocol should be established that specifies how validation of a particular process will be conducted. The protocol should be reviewed and approved by the quality unit(s) and other designated units.

12.21 The validation protocol should specify critical process steps and acceptance criteria as well as the type of validation to be conducted (e.g. retrospective, prospective, concurrent) and the number of process runs.

12.22 A validation report that cross-references the validation protocol should be prepared, summarising the results obtained, commenting on any deviations observed, and drawing the appropriate conclusions, including recommending changes to correct deficiencies.

12.23 Any variations from the validation protocol should be documented with appropriate justification.

12.3 Qualification

12.30 Before starting process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed. Qualification is usually carried out by conducting the following activities, individually or combined:

- Design Qualification (DQ): documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose.

- Installation Qualification (IQ): documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements.

- Operational Qualification (OQ): documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated

operating ranges.

- Performance Qualification (PQ): documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications.

12.4 Approaches to Process Validation

12.40 Process Validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.

12.41 There are three approaches to validation. Prospective validation is the preferred approach, but there are exceptions where the other approaches can be used. These approaches and their applicability are listed below.

12.42 Prospective validation should normally be performed for all API processes as defined in 12.12. Prospective validation performed on an API process should be completed before the commercial distribution of the final drug product manufactured from that API.

12.43 Concurrent validation can be conducted when data from replicate production runs are unavailable because only a limited number of API batches have been produced, API batches are produced infrequently, or API batches are produced by a validated process that has been modified. Prior to the completion of concurrent validation, batches can be released and used in final drug product for commercial distribution based on thorough monitoring and testing of the API batches.

12.44 An exception can be made for retrospective validation for well established processes that have been used without significant changes to API quality due to changes in raw materials, equipment, systems, facilities, or the production process. This validation approach may be used where:

1) Critical quality attributes and critical process parameters have been identified;
2) Appropriate in-process acceptance criteria and controls have been established;
3) There have not been significant process/product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability; and
4) Impurity profiles have been established for the existing API.

12.45 Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications, and

should be sufficient in number to demonstrate process consistency. Retained samples can be tested to obtain data to retrospectively validate the process.

12.5 Process Validation Program

12.50 The number of process runs for validation should depend on the complexity of the process or the magnitude of the process change being considered. For prospective and concurrent validation, three consecutive successful production batches should be used as a guide, but there may be situations where additional process runs are warranted to prove consistency of the process (e.g., complex API processes or API processes with prolonged completion times). For retrospective validation, generally data from ten to thirty consecutive batches should be examined to assess process consistency, but fewer batches can be examined if justified.

12.51 Critical process parameters should be controlled and monitored during process validation studies. Process parameters unrelated to quality, such as variables controlled to minimize energy consumption or equipment use, need not be included in the process validation.

12.52 Process validation should confirm that the impurity profile for each API is within the limits specified. The impurity profile should be comparable to or better than historical data and, where applicable, the profile determined during process development or for batches used for pivotal clinical and toxicological studies.

12.6 Periodic Review of Validated Systems

12.60 Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.

12.7 Cleaning Validation

12.70 Cleaning procedures should normally be validated. In general, cleaning validation should be directed to situations or process steps where contamination or carryover of materials poses the greatest risk to API quality. For example, in early production it may be unnecessary to validate equipment cleaning procedures where residues are removed by subsequent purification steps.

12.71 Validation of cleaning procedures should reflect actual equipment usage patterns. If various APIs or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a representative intermediate or API can be selected for

cleaning validation. This selection should be based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity, and stability.

12.72 The cleaning validation protocol should describe the equipment to be cleaned, procedures, materials, acceptable cleaning levels, parameters to be monitored and controlled, and analytical methods. The protocol should also indicate the type of samples to be obtained and how they are collected and labelled.

12.73 Sampling should include swabbing, rinsing, or alternative methods (e.g., direct extraction), as appropriate, to detect both insoluble and soluble residues. The sampling methods used should be capable of quantitatively measuring levels of residues remaining on the equipment surfaces after cleaning. Swab sampling may be impractical when product contact surfaces are not easily accessible due to equipment design and/or process limitations (e.g., inner surfaces of hoses, transfer pipes, reactor tanks with small ports or handling toxic materials, and small intricate equipment such as micronizers and microfluidizers).

12.74 Validated analytical methods having sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant. The method's attainable recovery level should be established. Residue limits should be practical, achievable, verifiable and based on the most deleterious residue. Limits can be established based on the minimum known pharmacological, toxicological, or physiological activity of the API or its most deleterious component.

12.75 Equipment cleaning/sanitization studies should address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the API, or other processes where such contamination could be of concern (e.g., non-sterile APIs used to manufacture sterile products).

12.76 Cleaning procedures should be monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production. Equipment cleanliness can be monitored by analytical testing and visual examination, where feasible. Visual inspection can allow detection of gross contamination concentrated in small areas that could otherwise go undetected by sampling and/or analysis.

12.8 Validation of Analytical Methods

12.80 Analytical methods should be validated unless the method employed is included in the relevant pharmacopoeia or other recognised standard reference. The suitability of all testing methods used should nonetheless be verified under actual conditions of use and documented.

12.81 Methods should be validated to include consideration of characteristics included within the ICH guidances on validation of analytical methods. The degree of analytical validation performed should reflect the purpose of the analysis and the stage of the API production process.

12.82 Appropriate qualification of analytical equipment should be considered before starting validation of analytical methods.

12.83 Complete records should be maintained of any modification of a validated analytical method. Such records should include the reason for the modification and appropriate data to verify that the modification produces results that are as accurate and reliable as the established method.

13. CHANGE CONTROL

13.10 A formal change control system should be established to evaluate all changes that may affect the production and control of the intermediate or API.

13.11 Written procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labelling and packaging materials, and computer software.

13.12 Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organisational units, and reviewed and approved by the quality unit(s).

13.13 The potential impact of the proposed change on the quality of the intermediate or API should be evaluated. A classification procedure may help in determining the level of testing, validation, and documentation needed to justify changes to a validated process. Changes can be classified (e.g. as minor or major) depending on the nature and extent of the changes, and the effects these changes may impart on the process. Scientific judgement should determine what additional testing and validation studies are appropriate to justify a change in a validated process.

13.14 When implementing approved changes, measures should be taken to ensure that all documents affected by the changes are revised.

13.15 After the change has been implemented, there should be an evaluation of the first batches produced or tested under the change.

13.16 The potential for critical changes to affect established retest or expiry dates should be

evaluated. If necessary, samples of the intermediate or API produced by the modified process can be placed on an accelerated stability program and/or can be added to the stability monitoring program.

13.17 Current dosage form manufacturers should be notified of changes from established production and process control procedures that can impact the quality of the API.

14. REJECTION AND RE-USE OF MATERIALS

14.1 Rejection

14.10 Intermediates and APIs failing to meet established specifications should be identified as such and quarantined. These intermediates or APIs can be reprocessed or reworked as described below. The final disposition of rejected materials should be recorded.

14.2 Reprocessing

14.20 Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and reprocessing by repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process is generally considered acceptable. However, if such reprocessing is used for a majority of batches, such reprocessing should be included as part of the standard manufacturing process.

14.21 Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process. This is not considered to be reprocessing.

14.22 Introducing unreacted material back into a process and repeating a chemical reaction is considered to be reprocessing unless it is part of the established process. Such reprocessing should be preceded by careful evaluation to ensure that the quality of the intermediate or API is not adversely impacted due to the potential formation of by-products and over-reacted materials.

14.3 Reworking

14.30 Before a decision is taken to rework batches that do not conform to established standards or specifications, an investigation into the reason for non-conformance should be performed.

14.31 Batches that have been reworked should be subjected to appropriate evaluation, testing,

stability testing if warranted, and documentation to show that the reworked product is of equivalent quality to that produced by the original process. Concurrent validation is often the appropriate validation approach for rework procedures. This allows a protocol to define the rework procedure, how it will be carried out, and the expected results. If there is only one batch to be reworked, then a report can be written and the batch released once it is found to be acceptable.

14.32 Procedures should provide for comparing the impurity profile of each reworked batch against batches manufactured by the established process. Where routine analytical methods are inadequate to characterize the reworked batch, additional methods should be used.

14.4 Recovery of Materials and Solvents

14.40 Recovery (e.g. from mother liquor or filtrates) of reactants, intermediates, or the API is considered acceptable, provided that approved procedures exist for the recovery and the recovered materials meet specifications suitable for their intended use.

14.41 Solvents can be recovered and reused in the same processes or in different processes, provided that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards before reuse or co-mingling with other approved materials.

14.42 Fresh and recovered solvents and reagents can be combined if adequate testing has shown their suitability for all manufacturing processes in which they may be used.

14.43 The use of recovered solvents, mother liquors, and other recovered materials should be adequately documented.

14.5 Returns

14.50 Returned intermediates or APIs should be identified as such and quarantined.

14.51 If the conditions under which returned intermediates or APIs have been stored or shipped before or during their return or the condition of their containers casts doubt on their quality, the returned intermediates or APIs should be reprocessed, reworked, or destroyed, as appropriate.

14.52 Records of returned intermediates or APIs should be maintained. For each return, documentation should include:

- Name and address of the consignee
- Intermediate or API, batch number, and quantity returned

- Reason for return
- Use or disposal of the returned intermediate or API

15. COMPLAINTS AND RECALLS

15.10 All quality related complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure.

15.11 Complaint records should include:

- Name and address of complainant;
- Name (and, where appropriate, title) and phone number of person submitting the complaint;
- Complaint nature (including name and batch number of the API);
- Date complaint is received;
- Action initially taken (including dates and identity of person taking the action);
- Any follow-up action taken;
- Response provided to the originator of complaint (including date response sent); and
- Final decision on intermediate or API batch or lot.

15.12 Records of complaints should be retained in order to evaluate trends, product-related frequencies, and severity with a view to taking additional, and if appropriate, immediate corrective action.

15.13 There should be a written procedure that defines the circumstances under which a recall of an intermediate or API should be considered.

15.14 The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall, and how the recalled material should be treated.

15.15 In the event of a serious or potentially life-threatening situation, local, national, and/or international authorities should be informed and their advice sought.

16. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

16.10 All contract manufacturers (including laboratories) should comply with the GMP defined in this guidance document. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.

16.11 Contract manufacturers (including laboratories) should be evaluated by the contract giver to ensure GMP compliance of the specific operations occurring at the contract sites.

16.12 There should be a written and approved contract or formal agreement between the contract giver and the contract acceptor that defines in detail the GMP responsibilities, including the quality measures, of each party.

16.13 The contract should permit the contract giver to audit the contract acceptor's facilities for compliance with GMP.

16.14 Where subcontracting is allowed, the contract acceptor should not pass to a third party any of the work entrusted to him under the contract without the contract giver's prior evaluation and approval of the arrangements.

16.15 Manufacturing and laboratory records should be kept at the site where the activity occurs and be readily available.

16.16 Changes in the process, equipment, test methods, specifications, or other contractual requirements should not be made unless the contract giver is informed and approves the changes.

17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS

17.1 Applicability

17.10 This section applies to any party other than the original manufacturer who may trade and/or take possession, repack, relabel, manipulate, distribute or store an API or intermediate.

17.11 All agents, brokers, traders, distributors, repackers, and relabellers should comply with GMP as defined in this guidance document.

17.2 Traceability of Distributed APIs and Intermediates

17.20 Agents, brokers, traders, distributors, repackers, or relabellers should maintain complete traceability of APIs and intermediates that they distribute. Documents that should be retained and available include:

- Identity of original manufacturer
- Address of original manufacturer
- Purchase orders

- Bills of lading (transportation documentation)
- Receipt documents
- Name or designation of API or intermediate
- Manufacturer's batch number
- Transportation and distribution records
- All authentic Certificates of Analysis, including those of the original manufacturer
- Retest or expiry date

17.3 Quality Management

17.30 Agents, brokers, traders, distributors, repackers, or relabellers should establish, document and implement an effective system of managing quality, as specified in Section 2.

17.4 Repackaging, Relabelling and Holding of APIs and Intermediates

17.40 Repackaging, relabelling and holding of APIs and intermediates should be performed under appropriate GMP controls, as stipulated in this guidance document, to avoid mix-ups and loss of API or intermediate identity or purity.

17.41 Repackaging should be conducted under appropriate environmental conditions to avoid contamination and cross-contamination.

17.5 Stability

17.50 Stability studies to justify assigned expiration or retest dates should be conducted if the API or intermediate is repackaged in a different type of container than that used by the API or intermediate manufacturer.

17.6 Transfer of Information

17.60 Agents, brokers, distributors, repackers, or relabellers should transfer all quality or regulatory information received from an API or intermediate manufacturer to the customer, and from the customer to the API or intermediate manufacturer.

17.61 The agent, broker, trader, distributor, repacker, or relabeller who supplies the API or intermediate to the customer should provide the name of the original API or intermediate manufacturer and the batch number(s) supplied.

17.62 The agent should also provide the identity of the original API or intermediate manufacturer to regulatory authorities upon request. The original manufacturer can respond to the regulatory authority directly or through its authorized agents, depending on the legal

relationship between the authorized agents and the original API or intermediate manufacturer. (In this context "authorized" refers to authorized by the manufacturer.)

17.63 The specific guidance for Certificates of Analysis included in Section 11.4 should be met.

17.7 Handling of Complaints and Recalls

17.70 Agents, brokers, traders, distributors, repackers, or relabellers should maintain records of complaints and recalls, as specified in Section 15, for all complaints and recalls that come to their attention.

17.71 If the situation warrants, the agents, brokers, traders, distributors, repackers, or relabellers should review the complaint with the original API or intermediate manufacturer in order to determine whether any further action, either with other customers who may have received this API or intermediate or with the regulatory authority, or both, should be initiated. The investigation into the cause for the complaint or recall should be conducted and documented by the appropriate party.

17.72 Where a complaint is referred to the original API or intermediate manufacturer, the record maintained by the agents, brokers, traders, distributors, repackers, or relabellers should include any response received from the original API or intermediate manufacturer (including date and information provided).

17.8 Handling of Returns

17.80 Returns should be handled as specified in Section 14.52. The agents, brokers, traders, distributors, repackers, or relabellers should maintain documentation of returned APIs and intermediates.

18. SPECIFIC GUIDANCE FOR APIs MANUFACTURED BY CELL CULTURE/FERMENTATION

18.1 General

18.10 Section 18 is intended to address specific controls for APIs or intermediates manufactured by cell culture or fermentation using natural or recombinant organisms and that have not been covered adequately in the previous sections. It is not intended to be a stand-alone Section. In general, the GMP principles in the other sections of this document apply. Note that the principles of fermentation for "classical" processes for production of small molecules and for processes using recombinant and non-recombinant organisms for production of proteins and/or polypeptides are the same, although the degree of control

will differ. Where practical, this section will address these differences. In general, the degree of control for biotechnological processes used to produce proteins and polypeptides is greater than that for classical fermentation processes.

18.11 The term "biotechnological process" (biotech) refers to the use of cells or organisms that have been generated or modified by recombinant DNA, hybridoma or other technology to produce APIs. The APIs produced by biotechnological processes normally consist of high molecular weight substances, such as proteins and polypeptides, for which specific guidance is given in this Section. Certain APIs of low molecular weight, such as antibiotics, amino acids, vitamins, and carbohydrates, can also be produced by recombinant DNA technology.The level of control for these types of APIs is similar to that employed for classical fermentation.

18.12 The term "classical fermentation" refers to processes that use microorganisms existing in nature and/or modified by conventional methods (e.g. irradiation or chemical mutagenesis) to produce APIs. APIs produced by "classical fermentation" are normally low molecular weight products such as antibiotics, amino acids, vitamins, and carbohydrates.

18.13 Production of APIs or intermediates from cell culture or fermentation involves biological processes such as cultivation of cells or extraction and purification of material from living organisms. Note that there may be additional process steps, such as physicochemical modification, that are part of the manufacturing process. The raw materials used (media, buffer components) may provide the potential for growth of microbiological contaminants. Depending on the source, method of preparation, and the intended use of the API or intermediate, control of bioburden, viral contamination, and/or endotoxins during manufacturing and monitoring of the process at appropriate stages may be necessary.

18.14 Appropriate controls should be established at all stages of manufacturing to assure intermediate and/or API quality. While this guidance document starts at the cell culture/fermentation step, prior steps (e.g. cell banking) should be performed under appropriate process controls. This guidance document covers cell culture/fermentation from the point at which a vial of the cell bank is retrieved for use in manufacturing.

18.15 Appropriate equipment and environmental controls should be used to minimize the risk of contamination. The acceptance criteria for quality of the environment and the frequency of monitoring should depend on the step in production and the production conditions (open, closed, or contained systems).

18.16 In general, process controls should take into account:

- Maintenance of the Working Cell Bank (where appropriate);

- Proper inoculation and expansion of the culture;
- Control of the critical operating parameters during fermentation/cell culture;
- Monitoring of the process for cell growth, viability (for most cell culture processes) and productivity where appropriate;
- Harvest and purification procedures that remove cells, cellular debris and media components while protecting the intermediate or API from contamination (particularly of a microbiological nature) and from loss of quality;
- Monitoring of bioburden and, where needed, endotoxin levels at appropriate stages of production; and
- Viral safety concerns as described in ICH Guidance Q5A *Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin.*

18.17 Where appropriate, the removal of media components, host cell proteins, other process-related impurities, product-related impurities and contaminants should be demonstrated.

18.2 Cell Bank Maintenance and Record Keeping

18.20 Access to cell banks should be limited to authorized personnel.

18.21 Cell banks should be maintained under storage conditions designed to maintain viability and prevent contamination.

18.22 Records of the use of the vials from the cell banks and storage conditions should be maintained.

18.23 Where appropriate, cell banks should be periodically monitored to determine suitability for use.

18.24 See ICH Guidance Q5D *Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products* for a more complete discussion of cell banking.

18.3 Cell Culture/Fermentation

18.30 Where aseptic addition of cell substrates, media, buffers, and gases is needed, closed or contained systems should be used where possible. If the inoculation of the initial vessel or subsequent transfers or additions (media, buffers) are performed in open vessels, there should be controls and procedures in place to minimize the risk of contamination.

18.31 Where the quality of the API can be affected by microbial contamination, manipulations

using open vessels should be performed in a biosafety cabinet or similarly controlled environment.

18.32 Personnel should be appropriately gowned and take special precautions handling the cultures.

18.33 Critical operating parameters (for example temperature, pH, agitation rates, addition of gases, pressure) should be monitored to ensure consistency with the established process. Cell growth, viability (for most cell culture processes), and, where appropriate, productivity should also be monitored. Critical parameters will vary from one process to another, and for classical fermentation, certain parameters (cell viability, for example) may not need to be monitored.

18.34 Cell culture equipment should be cleaned and sterilized after use. As appropriate, fermentation equipment should be cleaned, and sanitized or sterilized.

18.35 Culture media should be sterilized before use when appropriate to protect the quality of the API.

18.36 There should be appropriate procedures in place to detect contamination and determine the course of action to be taken. This should include procedures to determine the impact of the contamination on the product and those to decontaminate the equipment and return it to a condition to be used in subsequent batches. Foreign organisms observed during fermentation processes should be identified as appropriate and the effect of their presence on product quality should be assessed, if necessary. The results of such assessments should be taken into consideration in the disposition of the material produced.

18.37 Records of contamination events should be maintained.

18.38 Shared (multi-product) equipment may warrant additional testing after cleaning between product campaigns, as appropriate, to minimize the risk of cross-contamination.

18.4 Harvesting, Isolation and Purification

18.40 Harvesting steps, either to remove cells or cellular components or to collect cellular components after disruption, should be performed in equipment and areas designed to minimize the risk of contamination.

18.41 Harvest and purification procedures that remove or inactivate the producing organism, cellular debris and media components (while minimizing degradation, contamination, and loss of quality) should be adequate to ensure that the intermediate or API is recovered with

consistent quality.

18.42 All equipment should be properly cleaned and, as appropriate, sanitized after use. Multiple successive batching without cleaning can be used if intermediate or API quality is not compromised.

18.43 If open systems are used, purification should be performed under environmental conditions appropriate for the preservation of product quality.

18.44 Additional controls, such as the use of dedicated chromatography resins or additional testing, may be appropriate if equipment is to be used for multiple products.

18.5 Viral Removal/Inactivation steps

18.50 See the ICH Guidance Q5A *Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin* for more specific information.

18.51 Viral removal and viral inactivation steps are critical processing steps for some processes and should be performed within their validated parameters.

18.52 Appropriate precautions should be taken to prevent potential viral contamination from pre-viral to post-viral removal/inactivation steps. Therefore, open processing should be performed in areas that are separate from other processing activities and have separate air handling units.

18.53 The same equipment is not normally used for different purification steps. However, if the same equipment is to be used, the equipment should be appropriately cleaned and sanitized before reuse. Appropriate precautions should be taken to prevent potential virus carry-over (e.g. through equipment or environment) from previous steps.

19. APIs FOR USE IN CLINICAL TRIALS

19.1 General

19.10 Not all the controls in the previous sections of this guidance document are appropriate for the manufacture of a new API for investigational use during its development. Section 19 provides specific guidance unique to these circumstances.

19.11 The controls used in the manufacture of APIs for use in clinical trials should be consistent with the stage of development of the drug product incorporating the API. Process and test

procedures should be flexible to provide for changes as knowledge of the process increases and clinical testing of a drug product progresses from pre-clinical stages through clinical stages. Once drug development reaches the stage where the API is produced for use in drug products intended for clinical trials, manufacturers should ensure that APIs are manufactured in suitable facilities using appropriate production and control procedures to ensure the quality of the API.

19.2 Quality

19.20 Appropriate GMP concepts should be applied in the production of APIs for use in clinical trials with a suitable mechanism of approval of each batch.

19.21 A quality unit(s) independent from production should be established for the approval or rejection of each batch of API for use in clinical trials.

19.22 Some of the testing functions commonly performed by the quality unit(s) can be performed within other organizational units.

19.23 Quality measures should include a system for testing of raw materials, packaging materials, intermediates, and APIs.

19.24 Process and quality problems should be evaluated.

19.25 Labelling for APIs intended for use in clinical trials should be appropriately controlled and should identify the material as being for investigational use.

19.3 Equipment and Facilities

19.30 During all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean and suitable for its intended use.

19.31 Procedures for the use of facilities should ensure that materials are handled in a manner that minimizes the risk of contamination and cross-contamination.

19.4 Control of Raw Materials

19.40 Raw materials used in production of APIs for use in clinical trials should be evaluated by testing, or received with a supplier's analysis and subjected to identity testing. When a material is considered hazardous, a supplier's analysis should suffice.

19.41 In some instances, the suitability of a raw material can be determined before use based on acceptability in small-scale reactions (i.e., use testing) rather than on analytical testing alone.

19.5 Production

19.50 The production of APIs for use in clinical trials should be documented in laboratory notebooks, batch records, or by other appropriate means. These documents should include information on the use of production materials, equipment, processing, and scientific observations.

19.51 Expected yields can be more variable and less defined than the expected yields used in commercial processes. Investigations into yield variations are not expected.

19.6 Validation

19.60 Process validation for the production of APIs for use in clinical trials is normally inappropriate, where a single API batch is produced or where process changes during API development make batch replication difficult or inexact. The combination of controls, calibration, and, where appropriate, equipment qualification assures API quality during this development phase.

19.61 Process validation should be conducted in accordance with Section 12 when batches are produced for commercial use, even when such batches are produced on a pilot or small scale.

19.7 Changes

19.70 Changes are expected during development, as knowledge is gained and the production is scaled up. Every change in the production, specifications, or test procedures should be adequately recorded.

19.8 Laboratory Controls

19.80 While analytical methods performed to evaluate a batch of API for clinical trials may not yet be validated, they should be scientifically sound.

19.81 A system for retaining reserve samples of all batches should be in place. This system should ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time after approval, termination, or discontinuation of an application.

19.82 Expiry and retest dating as defined in Section 11.6 applies to existing APIs used in clinical trials. For new APIs, Section 11.6 does not normally apply in early stages of clinical trials.

19.9 Documentation

19.90 A system should be in place to ensure that information gained during the development and the manufacture of APIs for use in clinical trials is documented and available.

19.91 The development and implementation of the analytical methods used to support the release of a batch of API for use in clinical trials should be appropriately documented.

19.92 A system for retaining production and control records and documents should be used. This system should ensure that records and documents are retained for an appropriate length of time after the approval, termination, or discontinuation of an application.

20. GLOSSARY

Acceptance Criteria
Numerical limits, ranges, or other suitable measures for acceptance of test results.

Active Pharmaceutical Ingredient (API) (or Drug Substance)
Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

API Starting Material
A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials are normally of defined chemical properties and structure.

Batch (or Lot)
A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

Batch Number (or Lot Number)
A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined.

Bioburden
The level and type (e.g. objectionable or not) of micro-organisms that can be present in raw materials, API starting materials, intermediates or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

Calibration
The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements.

Computer System
A group of hardware components and associated software, designed and assembled to perform a specific function or group of functions.

Computerized System
A process or operation integrated with a computer system.

Contamination
The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging or repackaging, storage or transport.

Contract Manufacturer
A manufacturer performing some aspect of manufacturing on behalf of the original manufacturer.

Critical
Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.

Cross-Contamination
Contamination of a material or product with another material or product.

Deviation
Departure from an approved instruction or established standard.

Drug (Medicinal) Product
The dosage form in the final immediate packaging intended for marketing. (Reference Q1A)

Drug Substance
See Active Pharmaceutical Ingredient

Expiry Date (or Expiration Date)
The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.

Impurity
Any component present in the intermediate or API that is not the desired entity.

Impurity Profile
A description of the identified and unidentified impurities present in an API.

In-Process Control (or Process Control)
Checks performed during production in order to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or API conforms to its specifications.

Intermediate
A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. (Note: this guidance document only addresses those intermediates produced after the point that the company has defined as the point at which the production of the API begins.)

Lot
See Batch

Lot Number
See Batch Number

Manufacture
All operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage, and distribution of APIs and related controls.

Material
A general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs and packaging and labelling materials.

Mother Liquor
The residual liquid which remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API and/or impurities. It may be used for further processing.

Packaging Material
Any material intended to protect an intermediate or API during storage and transport.

Procedure
A documented description of the operations to be performed, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of an intermediate or API.

Process Aids
Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g. filter aid, activated carbon, etc).

Process Control
See In-Process Control

Production
All operations involved in the preparation of an API from receipt of materials through processing and packaging of the API.

Qualification
Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Quality Assurance (QA)
The sum total of the organised arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

Quality Control (QC)
Checking or testing that specifications are met.

Quality Unit(s)
An organizational unit independent of production which fulfills both Quality Assurance and Quality Control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Quarantine
The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

Raw Material
A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs.

Reference Standard, Primary
A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard can be: (1) obtained from an officially recognised source, or (2) prepared by independent synthesis, or (3) obtained from existing production material of high purity, or (4) prepared by further purification of existing production material.

Reference Standard, Secondary
A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.

Reprocessing
Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process. Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process, and not reprocessing.

Retest Date
The date when a material should be re-examined to ensure that it is still suitable for use.

Reworking
Subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API (e.g., recrystallizing with a different solvent).

Signature (signed)
See definition for signed

Signed (signature)
The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature.

Solvent
An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.

Specification
A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. "Conformance to specification" means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

Validation
A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria.

Validation Protocol

A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters/operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results.

Yield, Expected

The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data.

Yield, Theoretical

The quantity that would be produced at any appropriate phase of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production

This is **Exhibit "E"** 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

PRODUCT MONOGRAPH

^{N}SATIVEX®

delta-9-tetrahydrocannabinol 27mg/ml (from Tetranabinex® - *Cannabis sativa* L. extract) and cannabidiol 25mg/ml (from Nabidiolex® - *Cannabis sativa* L. extract)

Buccal spray

Cannabinoid Analgesic

Standard marketing authorization:
SATIVEX® is useful as adjunctive treatment for symptomatic relief of spasticity in adult patients with multiple sclerosis (MS) who have not responded adequately to other therapy and who demonstrate meaningful improvement during an initial trial of therapy.
Marketing authorization with conditions:
SATIVEX® may be useful as adjunctive treatment for the symptomatic relief of neuropathic pain in adult patients with multiple sclerosis.
Marketing authorization with conditions:
SATIVEX® may be useful as adjunctive analgesic treatment in adult patients with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain.

Marketing authorisations with conditions reflect the promising nature of the clinical evidence and the need for confirmatory studies to verify the clinical benefit. Patients should be advised of the conditional nature of the authorizations with conditions.

GW Pharma Ltd.
Salisbury, Wiltshire
U.K. SP4 0JQ
Control No: 132251

Distributed in Canada by:
Bayer Inc.,
Toronto, Ontario
M9W 1G6

Date of Revision:
August 11, 2010

This product has been approved under the Notice of Compliance with Conditions (NOC/c) Policy for its uses in adult patients with MS neuropathic pain and with cancer pain.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications and Clinical Uses;
- Mechanism of Action;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Health Product Safety Information Division at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

Table of Contents

[N]SATIVEX®

delta-9-tetrahydrocannabinol 27mg/ml (from Tetranabinex® - *Cannabis sativa* L. extract) and cannabidiol 25mg/ml (from Nabidiolex® - *Cannabis sativa* L. extract)

PART I: HEALTH PROFESSIONAL INFORMATION

NOC

SATIVEX® is useful as adjunctive treatment for symptomatic relief of spasticity in adult patients with multiple sclerosis (MS) who have not responded adequately to other therapy and who demonstrate meaningful improvement during an initial trial of therapy.

NOC/c

SATIVEX® may be useful as adjunctive treatment for the symptomatic relief of neuropathic pain in adult patients with multiple sclerosis.

SATIVEX® may be useful as adjunctive analgesic treatment in adult patients with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain.

Marketing authorisations with conditions reflect the promising nature of the clinical evidence and the need for confirmatory studies to verify the clinical benefit. Patients should be advised of the conditional nature of the authorizations with conditions.

SUMMARY PRODUCT INFORMATION

Route of Administration	Pharmaceutical Form/Strength	All Nonmedicinal Ingredients
Buccal	Buccal spray delta-9-tetrahydrocannabinol 27mg/ml (from Tetranabinex® - *Cannabis sativa* L. extract) and cannabidiol 25mg/ml (from Nabidiolex® - *Cannabis sativa* L. extract)	Ethanol anhydrous Propylene glycol Peppermint oil *This is a full listing of all nonmedicinal ingredients.*

INDICATIONS AND CLINICAL USE

NOC SATIVEX® is useful as adjunctive treatment for symptomatic relief of spasticity in patients with multiple sclerosis (MS) who have not responded adequately to other therapy and who demonstrate meaningful improvement during an initial trial of therapy.

NOC/c SATIVEX® may be useful as adjunctive treatment for the symptomatic relief of neuropathic pain in adult patients with multiple sclerosis (MS).

The physician who elects to use SATIVEX® for extended periods should periodically re-evaluate the long-term usefulness of SATIVEX® for the individual patient.

NOC/c SATIVEX® may be useful as adjunctive analgesic treatment in adult patients with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain.

Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the principal active components in SATIVEX®. THC is a psychotropic agent which may produce physical and psychological dependence and has the potential to be abused. Both active components, THC and CBD, are scheduled under the Controlled Drugs and Substances Act.

Geriatrics: There are limited data available on the use of SATIVEX® in elderly patients, therefore, the drug should be prescribed cautiously and carefully monitored in this patient population.

Paediatrics (<18 years of age): The safety and efficacy of SATIVEX® have not been established in adolescents or children under 18 years of age, therefore SATIVEX® should not be used in adolescents or children.

CONTRAINDICATIONS

SATIVEX® is contraindicated in:

- patients with known or suspected allergy to cannabinoids, propylene glycol, ethanol or peppermint oil
- patients with serious cardiovascular disease, such as ischaemic heart disease, arrhythmias, poorly controlled hypertension or severe heart failure
- patients with a history of schizophrenia or any other psychotic disorder
- children under 18 years of age
- women of child-bearing potential not on a reliable contraceptive or men intending to start a family (see "Use in Women of Child-Bearing Potential")
- pregnant or nursing women (see "Use in Women of Child-Bearing Potential").

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

THC and CBD are the principal active components in SATIVEX®. THC can produce physical and psychological dependence and has the potential for being abused.

THC has complex effects on the central nervous system (CNS). These can result in changes of mood, decrease in cognitive performances and memory, decrease in ability to control drives and impulses, and alteration of the perception of reality, particularly altered time sense. Fainting episodes have been observed with use of SATIVEX®. CNS effects, with dizziness being the most frequent (see Table 2), appear to be dose-related, increasing in frequency with higher dosages, and subject to great inter-patient variability. They usually resolve on reduction of doses, increasing the interval between doses or interruption of SATIVEX® (see "OVERDOSAGE"). Because of the potential of THC to alter the mental state, SATIVEX® should be used only as indicated and prescriptions should be limited to the amount necessary for the period between clinic visits. Drug administration should be discontinued in patients experiencing a psychotic reaction or a suicidal ideation and the patient should be closely observed in an appropriate setting until his/her mental state returns to normal. Patients should stop taking SATIVEX® if they become confused or disorientated. Patients should be warned not to drive or engage in activities requiring unimpaired judgement and coordination.

Cannabinoids have cardiovascular effects that include tachycardia, and transient changes in blood pressure, including episodes of postural hypotension. Use of SATIVEX® is not recommended in patients with pre-existing cardiovascular disease, such as ischaemic heart disease, arrhythmias, poorly controlled hypertension or severe heart failure.

Published reports on cannabinoids are equivocal with regard to the effects of THC on seizure threshold. Until further information is available, caution should be used when treating patients with a history of epilepsy or recurrent seizures.

General

During the initial self-titration period, patients may experience unacceptable adverse events, including dizziness. These should resolve with down-titration or interruption of treatment (see "OVERDOSAGE, Signs and Symptoms").

Careful dose titration and monitoring are advised if SATIVEX® is used in patients on a drug product containing fentanyl, or its analogues such as alfentanil and sufentanil (see DRUG INTERACTIONS).

Care should be taken with sedatives, drugs with sedating or psychotropic effects and hypnotics as co-administration with SATIVEX® may have an additive effect.

Buccal Mucosa

Regular inspection of the oral mucosa is advised. Patients should be advised not to continue spraying on to sore or inflamed mucosa.

Administration site irritation was common both during short-term and long-term use of SATIVEX®.

Carcinogenesis and Mutagenesis

See Part II – TOXICOLOGY.

Cardiovascular

See "Serious Warnings and Precautions".

CNS Effects

See "Serious Warnings and Precautions", "OVERDOSAGE" and "ADVERSE REACTIONS".

Driving and Operating Machinery

SATIVEX® may impair the mental and/or physical abilities required for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be warned not to drive or engage in activities requiring unimpaired judgement and coordination. Patients should also be cautioned about the additive/synergistic effects of SATIVEX® with other CNS depressants, including opioids, GABA inhibitors, sedative/hypnotics, and alcohol.

Genitourinary

See "Use in Women of Child-Bearing Potential" section below.

Haematologic

Clinical laboratory investigations did not reveal any trends of clinical significance in haematological parameters.

Hepatic/Biliary/Pancreatic

No consistent effect of SATIVEX® on clinical chemistry parameters has been observed.

No specific studies have been carried out in patients with significant hepatic or renal impairment, therefore SATIVEX® should be used with caution in such patients. Frequent review by the clinician is recommended.

SATIVEX® contains approximately 50% v/v of ethanol. Each dose contains up to 0.04 g of ethanol. The median daily dose of 5 sprays would be up to 0.2 g ethanol. Ethanol may be harmful for those suffering from alcoholism. This should also be taken into account in high-risk

groups such as patients with liver disease.

Immune

No clinically significant abnormalities of immune function have been observed in clinical trials with SATIVEX®.

Neurologic

In clinical studies with SATIVEX®, an increase in the number of falls has been observed. Whether this is due to dizziness, orthostatic hypotension or reduced spasticity has not been established. Patients should be made aware that care should be taken to avoid falls.

There is not sufficient information to characterize the effect of SATIVEX® on the seizure threshold. Caution should be used in treating patients with a history of epilepsy or recurrent seizures.

Peri-Operative Considerations

SATIVEX® may produce transient minor changes in blood pressure and heart rate. The central and peripheral effects of SATIVEX® should be taken into consideration in peri-operative situations.

Psychiatric

SATIVEX® should not be used in patients with a personal or strong family history of psychosis (including schizophrenia and affective psychosis) as symptoms may be aggravated by cannabinoids. SATIVEX® should be used with caution, if at all, in patients receiving other psychoactive drugs because of the potential for additive or synergistic CNS effects. In cases of disorientation (or confusion), hallucinations, delusional beliefs, or psychotic reaction, SATIVEX® should be stopped immediately and the patient monitored until the symptom has completely resolved (see "CONTRAINDICATIONS").

Suicidal ideations and other symptoms associated with depression have been reported. A causal association between SATIVEX® administration and suicidal ideation cannot be ruled out. The reported incidences of depression symptoms are consistent with that observed in populations of MS patients followed for a prolonged period of time. In case of a suicidal ideation, SATIVEX should be stopped immediately and the patient monitored until the symptom has completely resolved.

In acute studies with SATIVEX®, in people with multiple sclerosis, disorientation (4.1%), depression including depressed mood (2.9%), dissociation (1.7%), euphoric mood (2.2%), hallucination (0.9%), hallucination (auditory) (0.2%), hallucination (visual) (0.2%), illusion (0.1%), paranoia (0.5%) and suicidal ideation (0.5%) have been reported. In long-term Phase III extension studies (n=1016), the following additional adverse event, with a plausible causal relationship to SATIVEX®, has also been reported by patients with multiple sclerosis: delusional perception (0.1%).

Sensitivity/Resistance

SATIVEX® is contraindicated in patients with known or suspected allergy to cannabinoids, propylene glycol, ethanol or peppermint oil (see "CONTRAINDICATIONS").

Use in Women of Child-Bearing Potential

Independent research in laboratory species has found that cannabinoids have been associated with evidence of reproductive toxicity in early gestation and have been found to affect spermatogenesis. Therefore, women of child-bearing potential should take reliable contraceptive precautions for the duration of treatment and for three months after discontinuation of therapy. Male patients with a partner of childbearing potential should ensure that reliable contraceptive precautions are maintained for the duration of therapy and for three months after discontinuation of therapy.

Special Populations

Pregnant Women: Animal studies have indicated that cannabinoids may have detrimental effects on foetal development. SATIVEX® is contraindicated in pregnant women. SATIVEX® should not be used in women who intend to start a family.

In clinical trials with SATIVEX®, all female participants had to use a reliable contraceptive and all male participants had to ensure contraception with their partner. If a female participant became pregnant, she had to discontinue from the trial.

Nursing Women: In studies in laboratory species, due to the lipophilic nature of cannabinoids, considerable levels of cannabinoids were found in the maternal breast milk. Even at 1mg/kg/day there were 40-60 times the plasma level of cannabinoids in the breast milk.

SATIVEX® is contraindicated in nursing women.

Paediatrics (<18 years of age): Animal data have indicated that cannabinoids interfere with the development of neonatal and adolescent rodents. SATIVEX® is contraindicated in children under 18 years of age.

Geriatrics: There are limited data available on the use of SATIVEX® in elderly patients, therefore, the drug should be prescribed cautiously and carefully monitored in this patient population.

Hepatic and Renal Impairment: No specific studies have been carried out in patients with significant hepatic or renal impairment. (See "WARNINGS AND PRECAUTIONS".)

Monitoring and Laboratory Tests

Routine laboratory monitoring, appropriate for the patient's disease condition and concomitant medication, is recommended. Due to accumulation of cannabinoids in the body fat, trace amount of cannabinoids may be detected in the blood and urine for some weeks after SATIVEX® is discontinued.

DRUG DEPENDENCE/ABUSE LIABILITY

Recreational cannabis is known to produce dependence in some users. THC is a psychotropic agent which may produce physical and psychological dependence and has the potential to be abused.

SATIVEX® contains THC and should be used with caution in patients with a history of substance abuse, including alcohol abuse or dependence. Multiple substance abuse is common and marijuana, which contains the same active compounds, is a frequently abused substance. Therefore, SATIVEX® is not recommended in patients with addiction and drug abuse liability.

In a study designed to identify its liability for abuse, SATIVEX® at a dose of 4 sprays taken at one time, showed no more liability for abuse than placebo. Higher doses of SATIVEX® of 8 to 16 sprays taken at one time showed a greater liability for abuse than placebo.

In long-term open-label studies with SATIVEX®, no increase in the dosing level of SATIVEX® was observed.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

SATIVEX® has been administered to 805 multiple sclerosis patients in placebo-controlled studies and to 1016 patients during long-term open-extension studies. Over 300 subjects with MS have more than six months exposure, and 231 subjects with MS have been exposed to SATIVEX® for over one year.

In addition to the adverse events (all-causality) reported in the placebo-controlled acute studies (refer to Tables 1 and 2) the following adverse events observed in patients with MS (n=1016) on long-term treatment with SATIVEX® were considered to have a plausible causal relationship to SATIVEX®: palpitations (1.2%), tooth discolouration (2.1%), oral mucosal disorder (2.2%), oral mucosal discolouration (0.7%), oral mucosal exfoliation (0.7%), stomatitis (0.6%), hypertension (0.3%), delusional perception (0.1%) and syncope (0.9%).

Clinical Trial Adverse Drug Reactions

The following data summarise the adverse events in patients in clinical trials with various neurological conditions. Patients in clinical trials for relief of pain in cancer are described separately.

In all placebo-controlled trials in MS, adverse events have usually been mild or moderate in severity with discontinuation rates from treatment due to undesirable effects of 9.8% of patients on SATIVEX® compared to 4.7% on placebo. In most patients, adverse events have resolved without treatment, and some on a reduction of dosage of SATIVEX®. The studies from which these figures are derived incorporate a period of titration to optimal therapeutic and/or maximum tolerated dose during which unwanted effects are likely to be maximal. Because SATIVEX® is self-titrated to effect, patients are likely to experience a higher incidence of adverse events during the titration period than when the optimal dose is established.

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Treatment-emergent adverse events that occurred in 1% or more of patients treated with SATIVEX®, and at an incidence greater than (or equal to) 1% more frequently than placebo, in the acute phase in all Phase III trials, are given below in Tables 1 and 2. Table 1 includes all adverse events related to the application site, as the placebo used in studies contained the same excipients (ethanol and propylene glycol) as used in SATIVEX®.

Table 1 excludes CNS effects, while Table 2 lists only CNS effects.

Table 1: Treatment-Emergent Adverse Events for SATIVEX® in placebo-controlled studies in patients with multiple sclerosis occurring at 1% or above and at ≥ ≧1% more frequently than in placebo (excluding CNS effects)

	SATIVEX® n = 805 (%)	Placebo n = 741 (%)
Cardiac disorders		
Tachycardia	1.0	0.4
Ear and labyrinth disorders		
Vertigo	6.5	2.0
Eye disorders		
Vision blurred	1.9	0.4
Gastrointestinal disorders		
Abdominal pain upper	1.4	0.3
Constipation	2.4	0.5
Diarrhoea	5.5	3.9
Dry mouth	6.1	3.1
Glossodynia*	1.1	1.3
Mouth ulceration*	1.5	0.8
Nausea	9.6	5.7
Oral discomfort*	1.9	1.9
Oral pain*	2.1	2.2
Vomiting	3.5	2.2
General disorders and administration site conditions		
Application site irritation*	0.7	1.1
Application site pain*	2.0	2.3
Asthenia	5.6	3.1
Fatigue	12.5	8.4
Malaise	1.0	0.4
Infections and infestations		
Pharyngitis*	1.2	1.1
Injury, poisoning and procedural complications		
Fall	1.5	0.5
Metabolism and nutrition disorders		
Anorexia (includes appetite decreased)	2.1	0.7
Appetite increased	1.4	0.4
Nervous system disorders		

Table 1: Treatment-Emergent Adverse Events for SATIVEX® in placebo-controlled studies in patients with multiple sclerosis occurring at 1% or above and at ≥ ≧1% more frequently than in placebo (excluding CNS effects)

	SATIVEX® n = 805 (%)	**Placebo n = 741 (%)**
Dysgeusia (abnormal taste)*	3.1	0.8
Respiratory, thoracic and mediastinal disorders		
Throat irritation*	0.5	0.1

* application site reaction

Table 2: Treatment-Emergent CNS adverse events for SATIVEX® in placebo-controlled studies in patients with multiple sclerosis occurring at 1% or above and at ≥1% more frequently than in placebo

	SATIVEX® n =805 (%)	Placebo n =741 (%)
General disorders and administration site conditions		
Feeling abnormal	2.4	0.5
Feeling drunk	3.0	0.4
Nervous system disorders		
Amnesia (includes short term memory loss)	1.1	0.3
Balance disorder (balance impaired)	2.9	1.8
Disturbance in attention	3.9	0.1
Dizziness	25.0	8.2
Dysarthria	2.0	0.4
Lethargy	1.5	0.7
Memory impairment	1.4	0.1
Somnolence	8.2	2.3
Psychiatric disorders		
Anxiety*	0.9	0.9
Depression (includes depressed mood)	2.9	2.0
Disorientation (includes confusion)	4.1	0.8
Dissociation	1.7	0.1
Euphoric mood	2.2	0.9
Hallucination*	0.9	0.1
Hallucination, auditory*	0.2	0
Hallucination, visual*	0.2	0
Illusion*	0.1	0
Paranoia*	0.5	0.1
Suicidal ideation*	0.5	0.1

* included as there is a plausible relationship with SATIVEX®

Application Site

Application site type events were reported by approximately 14% of patients receiving SATIVEX® or placebo. These included glossodynia, mouth ulceration, oral discomfort, oral pain, application site irritation, application site pain, pharyngitis, throat irritation and dysgeusia. The incidences were similar for SATIVEX® treated patients and placebo appearing to indicate that some application site type reactions may be due to the excipients (50% ethanol and 50% propylene glycol). The majority of these reactions consisted of mild to moderate stinging at the time of application. Mouth ulceration was observed in 1.5% of patients using SATIVEX®, and

0.8% in placebo. Two cases of possible leukoplakia were reported as related to SATIVEX®, but neither was confirmed histologically; a third case was unrelated.

Patients who complain of discomfort should be advised to vary the site of application within the mouth, and should not continue spraying onto sore or inflamed mucus membranes. Regular inspection of the oral mucosa is strongly recommended in long-term administration. If lesions are observed or persistent soreness reported, treatment should be interrupted until complete resolution occurs.

Cardiovascular

THC may cause tachycardia. Its effects on blood pressure are inconsistent, but occasionally patients may experience orthostatic hypotension and/or syncope upon abrupt standing, particularly during initial dose titration when caution is essential. SATIVEX® is not recommended in patients with pre-existing cardiovascular disease, such as ischaemic heart disease, arrhythmias, poorly controlled hypertension or severe heart failure. In a thorough QT study, there were no clinically relevant changes in QTc, PR or QRS interval duration, heart rate, or blood pressure, following five days of dosing in healthy volunteers with SATIVEX® up to 18 sprays twice daily.

Adverse events in patients with pain in cancer

Treatment-emergent adverse events that occurred in 3% or more of patients given SATIVEX® or placebo in a trial for patients with pain in cancer are given below in Table 3.

Table 3: Treatment Emergent Adverse Events for SATIVEX® in a placebo-controlled study in patients with pain in cancer

	SATIVEX® n = 60 (%)	Placebo n = 59 (%)
Blood and Lymphatic System Disorders		
Anaemia Nos	0	5
Cardiac Disorders		
Cardio-Respiratory Arrest	0	3
Ear and Labyrinth Disorders		
Vertigo	5	2
Gastrointestinal Disorders		
Nausea	12	10
Vomiting	8	7
Constipation	5	10
Oral Pain	2	5
Diarrhoea	7	3
Glossodynia	3	0
Abdominal pain upper	2	3
Dry mouth	0	3
Stomatitis	2	3

Table 3: Treatment Emergent Adverse Events for SATIVEX® in a placebo-controlled study in patients with pain in cancer

	SATIVEX® n = 60 (%)	Placebo n = 59 (%)
General Disorders and Administration Site Conditions		
Pain exacerbated	0	3
Pyrexia	0	3
Weakness	5	0
Disease Progression	3	0
Hepatobiliary Disorders		
Hepatic cytolysis	0	3
Infections and Infestations		
Oral Candidiasis	3	2
Urinary Tract Infection	0	7
Lower Respiratory Tract Infection	0	5
Investigations		
GGT Increased	3	5
Blood Urea Increased	2	5
Liver Function Tests Abnormal	5	3
Blood Creatinine Increased	2	3
Blood Calcium Increased	0	5
Musculoskeletal and Connective Tissue Disorders		
Pain in Limb	2	3
Buttock Pain	0	3
Neoplasms Benign, Malignant and Unspecified (incl.Cysts and Polyps)		
Neoplasm Progression	10	5
Malignant Neoplasm Progression	2	5
Nervous System Disorders		
Somnolence	15	14
Dizziness	12	5
Disturbance in Attention	3	0
Dysgeusia	3	0
Headache	3	0
Psychiatric Disorders		
Confusion	7	3
Hallucination	3	2
Insomnia	3	2
Panic Attack	3	0
Euphoric Mood	3	0

Table 3: Treatment Emergent Adverse Events for SATIVEX® in a placebo-controlled study in patients with pain in cancer

	SATIVEX® n = 60 (%)	Placebo n = 59 (%)
Renal and Urinary Disorders		
Urinary Retention	5	0
Haematuria	3	0
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnoea	2	3
Vascular Disorders		
Hypotension	5	0

Urinary Retention and Infections

The combined incidence of urinary retention and urinary infections appear to be increased in the cancer patients taking SATIVEX® over those on placebo. Caution is advised in the urinary care of the cancer patients who are using SATIVEX®.

Abnormal Haematologic and Clinical Chemistry Findings

No consistent effect of SATIVEX® on haematologic and clinical chemistry parameters has been observed.

Post-Market Adverse Drug Reactions

Adverse event profile, based on post-market spontaneous reports, is consistent with those observed in clinical trials.

DRUG INTERACTIONS

Serious Drug Interactions

- Care should be taken with sedatives, drugs with sedating or psychotropic effects and hypnotics as co-administration with SATIVEX® may have an additive effect.
- Alcohol may interact with SATIVEX®, particularly in affecting coordination, concentration and ability to respond quickly.

Overview

The two main components of SATIVEX®, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), are metabolized by the Cytochrome P450 enzyme system, including CYP1A2, CYP2C9, CYP2D6, CYP2C19 and CYP3A4. The inhibitory effects *in vitro* and in animal models were only seen at exposures significantly higher than the maximum observed in clinical trials. [In clinical trials where SATIVEX® has been taken concomitantly with other drugs metabolized by the Cytochrome P450 enzyme system, no clinically apparent drug-drug interactions have been seen in these trials at clinical doses.

In an *in vitro* study with 1:1% (v/v) THC botanical drug substance (BDS) and CBD BDS, no relevant induction of Cytochrome P450 enzymes was seen for human CYP1A2, CYP2C9, CYP2C19 and CYP3A4 enzymes in human hepatocytes, at doses of up to 1μM (314 ng/mL).

Drug-Drug Interactions

There may be a potential risk of drug-drug interactions due to CYP450 inhibition by SATIVEX®. Caution should be exercised in patients taking drugs known to be substrates for CYP450 3A4 or CYP450 2C19, such as amitriptyline, fentanyl and the related opioids sufentanil and alfentanil.

Concomitant treatment with the CYP 3A4 inhibitor ketoconazole produced an increase in C_{max} and AUC of THC, 11-OH-THC (its primary metabolite) and CBD. The extent of this increase was less than the between subject variability. Following treatment with the CYP3A4 inducer rifampicin, a reduction in the C_{max} and AUC of THC, 11-OH-THC, and CBD was observed. The magnitude of this reduction for THC and CBD was less than the between subject variability.

Concomitant treatment with the CYP2C19 inhibitor omeprazole resulted in no notable change in any of the pharmacokinetic parameters.

Protein Binding

THC is highly bound to plasma proteins, and therefore might displace other protein-bound drugs. Although this displacement has not been confirmed *in vivo*, practitioners should monitor patients for a change in dosage requirements when administering SATIVEX® to patients who are receiving other drugs which are tightly protein-bound.

Drug-Food Interactions

No clinically relevant food interaction has been observed.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

No laboratory interactions have been established. Cannabinoids may be detected in the plasma and urine several weeks after SATIVEX® is discontinued (see "Monitoring and Laboratory Tests").

Drug-Lifestyle Interactions

Effects of smoked or other forms of cannabis would be additive to those of SATIVEX® with a likelihood of producing intoxication or other unwanted effects and are not recommended while using this product.

DOSAGE AND ADMINISTRATION

Adults

Dosing Considerations

SATIVEX® is for buccal use only. The spray should be directed to below the tongue, or towards the inside of the cheeks. The site should be varied. The patient should be advised not to direct the spray towards the pharynx and not to inhale the spray. It must not be sprayed into the nose.

Treatment initiation and stabilization

- On day one of treatment, patients should take one spray during the morning and one spray during the afternoon/evening. The morning dose can be taken at any time between waking up and 12 noon and the afternoon dose can be taken at any time between 4 pm and bedtime.
- On subsequent days the patient may gradually increase the total number of sprays, by one spray each day, as needed and tolerated. There should be at least a 15 minute gap between sprays. During initial titration, sprays should be evenly spread out over the day.
- If unacceptable adverse reactions such as dizziness or other CNS-type reactions develop at any time, dosing should be suspended until they have resolved. Some patients may be able to continue therapy at the dose reached by increasing the interval between doses; others may require their subsequent doses reduced. Patients should then carefully re-titrate to a tolerated dosage regimen that gives acceptable pain relief.

Following the titration period, patients are advised to maintain the optimal dose achieved. Re-titration upwards or downwards may be appropriate if there are any changes in the severity of the patient's conditions, changes in his/her concomitant medication or if unacceptable side effects develop.

The usual dose ranges between 4 – 8 sprays daily. The majority of patients require 12 sprays or less; dosage should be adjusted as needed and tolerated. There is limited experience with doses higher than 12 sprays per day. Some patients may require and may tolerate a higher number of sprays.

Missed Dose

SATIVEX® is a self-titration regime to be used "as required" for relief of pain, therefore "missed dose" is not applicable.

Administration

Priming

1. Shake the vial gently before use.
2. Remove the protective cap.
3. Holding the vial in an upright position, prime the SATIVEX® vial by pressing on the actuator two or three times firmly and quickly, directing into a tissue until a fine spray appears.

Important

Point the spray safely away when priming it into a tissue. Do not prime it near children, pets or an open flame.

Normal use

1. Shake the vial gently before use.
2. Remove the protective cap.
3. Hold the vial in the upright position and direct into the mouth. Press firmly and quickly towards the buccal surface in the following regions: below the tongue or towards the inside of the cheeks. The site should be varied. Never aim at the throat, as SATIVEX® can cause irritation.
4. Replace the protective cap.
5. Keep away from sources of heat and direct sunlight.

OVERDOSAGE

SATIVEX®

Signs and Symptoms

There is no experience of deliberate overdose with SATIVEX®. Signs and symptoms of overdose were reported from a thorough QT study conducted according to international standards. After receiving 18 sprays in 20 minutes, some subjects showed serious psychiatric signs and symptoms. The initial adverse reactions appeared within one to two hours and were consistent with the intoxication effects of cannabis and THC. In four patients out of 257, the intoxication symptoms developed into major psychiatric symptoms such as depression, anxiety, paranoia, delusions, hallucinations, and / or psychosis. These serious symptoms reached a plateau after two to three hours and lasted for nine to 24 hours.

Management

Recommended treatments include counselling and interventions to prevent injury. Additional treatments should be symptomatic and supportive. Benzodiazepines may be used in patients with severe agitation. The recovering patient must be followed up until all clinical symptoms dissipate. The possibility of multiple drug involvement should be considered. The nearest local Poison Control Centre must be contacted for current information.

Experience with oral THC overdose is as follows:

Signs and Symptoms

Following MILD THC intoxication, symptoms include drowsiness, euphoria, heightened sensory awareness, altered time perception, reddened conjunctiva, dry mouth and tachycardia; following MODERATE THC intoxication, symptoms include memory impairment, depersonalization, mood alteration, urinary retention, and reduced bowel motility; and following SEVERE THC intoxication, symptoms include decreased motor coordination, lethargy, slurred speech, and postural hypotension. Apprehensive patients may experience panic reactions and seizures may occur in patients with existing seizure disorders.

The estimated lethal human dose of intravenous THC is 30 mg/kg (2100 mg/70 kg).

Management

An overdose severe enough to cause depression of consciousness should be treated with the normal precautions for dealing with an unconscious patient by securing the airway and monitoring vital signs. Patients experiencing depressive, hallucinatory or psychotic reactions should be placed in a quiet area and offered reassurance. Benzodiazepines (5 to 10 mg diazepam *per oral)* may be used for treatment of extreme agitation. In the case of hypotension, patients should be placed in the Trendelenburg position (head lower than feet) or modified Trendelenburg position (only the legs elevated) until the condition remits. Intravenous fluids or pressors are rarely required.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Mammalian tissues contain at least two types of cannabinoid (CB) receptor, CB_1 and CB_2. CB_1 receptors are present at nerve terminals in the CNS and also in some peripheral tissues including dorsal root ganglia, sympathetic ganglia, adrenal gland, heart, lung, reproductive tissues, urinary bladder, gastrointestinal tissues, and immune cells. Within the brain, the distribution of CB_1 receptors is heterogeneous, with a pattern consistent with the demonstrated effects of cannabinoids on motor function, cognition and memory. Relevant for pain modulation, CB_1 receptors are found on pain pathways in the brain and spinal cord, as well as on terminals of peripheral nervous system primary afferent neurons where they may mediate cannabinoid-induced analgesia. CB_2 receptors are present primarily on peripheral and central immune cells, where they may modulate immune function through release of cytokines. Cannabidiol (CBD) is an agonist of TRPV-1 (vanilloid) receptor with an inhibitory action on adenosine uptake.

Pharmacodynamics: animal data

The principal pharmacological effects of THC include analgesic, muscle relaxant, antiemetic, appetite stimulant and psychoactive effects. CBD has analgesic, anticonvulsant, muscle relaxant, anxiolytic, neuroprotective, anti-oxidant and anti-psychotic activity. THC is metabolised to 11-hydroxy-tetrahydrocannabinol (11-OH-THC), a psycho-active metabolite. The main primary metabolite of CBD is 7-hydroxy-cannabidiol.

Pharmacokinetics: human data

Summary of Pharmacokinetic Parameters for SATIVEX® in healthy volunteers – Single dose PK in two studies. The differences seen in the PK data may reflect the inter-subject variability and the conduct of the study.

Table 4: Mean Pharmacokinetic Parameters (GWPK0112)**

Treatment	Analyte	T_{max} (hrs) (n=12)	Cmax (ng/ml) (n=12)	$t_{1/2}$ (hrs) (n=12)	AUC_{0-t} (min*ng/ml) (n=12)	AUC_{inf} (min*ng/ml) (n=12)
SATIVEX® * (Under the tongue)	CBD	1.63	2.50	1.44	408.53	427.33
	THC	1.63	5.54	1.76	808.78	837.25
	11-OH-THC	1.58	6.24	2.15	1522.09	1632.46
SATIVEX® * (Inside the cheek)	CBD	2.80	3.02	1.81	384.13	407.79
	THC	2.40	6.14	1.34	751.23	770.62
	11-OH-THC	2.40	6.13	1.91	1293.14	1362.12

* 4 sprays (total 10.8 mg THC + 10 mg CBD)

** The pharmacokinetic data show great inter-subject variability. THC, CBD, and 11-OH-THC appear in the plasma from about 30 minutes after dosing.

Table 5: Mean Pharmacokinetic Parameters (GWPK0215)

Treatment	Analyte	T_{max}** (hrs) (n=24)	C_{max} (ng/ml) (n=24)	$t_{1/2}$ (hrs) (n=24)	AUC_{0-t} (min*ng/ml) (n=24)	AUC_{inf} (min*ng/ml) (n=24)
SATIVEX®* (Under the tongue)	CBD	4.22	3.33	1.81	680.61	718.46
	THC	4.38	4.90	1.40	894.80	918.81
	11-OH-THC	3.83	4.49	2.17	1423.20	1463.67

* 4 sprays (total 10.8 mg THC + 10 mg CBD)

** As the data here represent more than one peak, T_{max} may represent an early buccal absorption and later gastrointestinal absorption.

Individual subject plasma concentration data and pharmacokinetic parameters show a high degree of inter-subject variability.

Table 6: Summary of Pharmacokinetic Parameters for SATIVEX® in MS Patients – Steady-state PK

Parameters	Cannabinoid (Analyte)	Visit A (n = 13)	Visit B (n = 7)
Pre-dose trough (ng/ml)	CBD	0.12 – 4.41	0.75 – 4.19
	THC	0.16 – 4.64	0.47 – 5.67
	11-OH-THC	0.05 – 5.41	1.02 – 5.67
C_{max} (ng/ml)	CBD	1.09 – 16.97	3.83 – 13.69
	THC	2.30 – 28.66	2.86 – 33.63
	11-OH-THC	2.76 – 20.45	3.74 – 14.22
T_{max} (hours)	CBD	1 – 6	3.0 – 6
	THC	1 – 6	2.5 – 6
	11-OH-THC	1 – 6	1.5 – 6

Note: Visit A took place after at least 20 weeks on SATIVEX®. Visit B occurred 8 weeks after Visit A. All patients were using at least 5 sprays daily.

Plasma levels have been studied in a limited number of patients on stable self-titrated doses during chronic therapy in the extension phase of study GWMS0001EXT. Most patients apparently had self-titrated their dosing to a level at which plasma concentrations for both THC and CBD were generally in the range of 5-10 ng/ml or less. Sampling of plasma concentration levels during chronic dosing suggests that significant accumulation of cannabinoids does not occur.

Absorption: Following a single buccal administration, maximum plasma concentrations of both CBD and THC typically occur within two to four hours. When administered buccally, blood levels of THC and other cannabinoids are lower compared with inhalation of smoked cannabis. The resultant concentrations in the blood are lower than those obtained by inhaling the same dose because absorption is slower, redistribution into fatty tissues is rapid and additionally some of the THC undergoes hepatic first pass metabolism to 11-OH-THC, a psycho-active metabolite.

Distribution: Cannabinoids are distributed throughout the body; they are highly lipid soluble and accumulate in fatty tissue. The release of cannabinoids from fatty tissue is responsible for the prolonged terminal elimination half-life.

Metabolism: THC and CBD are metabolized in the liver by a number of cytochrome P_{450} isoenzymes, including CYP2C9, CYP2C19, CYP2D6 and CYP3A4. They may be stored for as long as four weeks in the fatty tissues from which they are slowly released at sub-therapeutic levels back into the blood stream and metabolized via the renal and biliary systems.

Excretion: Elimination from plasma is bi-exponential with an initial half-life of one to two hours. The terminal elimination half-lives are of the order of 24 to 36 hours or longer. SATIVEX® is excreted in the urine and faeces.

Special Populations and Conditions:

No pharmacokinetic studies were done in any special population.

STORAGE AND STABILITY

SATIVEX® should not be used beyond its expiry date, and should be used within 28 days once it has been opened and is in use.

Prior to opening, SATIVEX® should be stored upright in a refrigerator (2-8°C). Do not freeze. Once opened, the spray may be stored at room temperature (15-25°C) and should be used within 28 days. Return unused portion of Sativex to the pharmacy for safe disposal or dispose of according to local regulations.

Keep away from sources of heat and direct sunlight. Keep out of reach and sight of children.

SPECIAL HANDLING INSTRUCTIONS

None.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Buccal spray

delta-9-tetrahydrocannabinol 27mg/ml (from Tetranabinex® - *Cannabis sativa* L. extract) and cannabidiol 25mg/ml (from Nabidiolex® - *Cannabis sativa* L. extract)

SATIVEX® is contained in an amber glass vial fitted with a metering pump possessing a polypropylene dip tube and elastomer neck, covered with a polyethylene cap. The metering pump delivers 100 microlitres per actuation (spray).

Non-medicinal ingredients:
Ethanol anhydrous
Propylene glycol
Peppermint oil

Pack Sizes: 5.5 ml or 10 ml.
The 5.5 ml vial contains up to 51 metered sprays.
The 10 ml vial contains up to 84 metered sprays.
1, 2, 3, 4, 5, 6, 8, 10 or 12 amber glass vials per carton.
(Not all presentations may be available in Canada).

PART II: SCIENTIFIC INFORMATION

NOC

SATIVEX® is useful as adjunctive treatment for symptomatic relief of spasticity in adult patients with multiple sclerosis (MS) who have not responded adequately to other therapy and who demonstrate meaningful improvement during an initial trial of therapy.

NOC/c

SATIVEX® may be useful as adjunctive treatment for the symptomatic relief of neuropathic pain in adult patients with multiple sclerosis.

SATIVEX® may be useful as adjunctive analgesic treatment in adult patients with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain.

Marketing authorisations with conditions reflect the promising nature of the clinical evidence and the need for confirmatory studies to verify the clinical benefit. Patients should be advised of the conditional nature of the authorizations with conditions.

PHARMACEUTICAL INFORMATION

Drug Substance

Common name:

delta-9-tetrahydrocannabinol 27mg/ml (from Tetranabinex® - *Cannabis sativa* L. extract) and cannabidiol 25mg/ml (from Nabidiolex® - *Cannabis sativa* L. extract)

Tetranabinex® is an extract of a chemically and genetically characterised cannabis plant, containing delta-9-tetrahydrocannabinol as the principal cannabinoid (delta-9-tetrahydrocannabinol Botanical Drug Substance (THC BDS)).

Nabidiolex® is an extract of a chemically and genetically characterised cannabis plant, containing cannabidiol as the principal cannabinoid (cannabidiol Botanical Drug Substance (CBD BDS)).

Chemical name:

THC:

3-pentyl-6,6,9-trimethyl-6A,7,8,10A-tetrahydro-6H-dibenzo(B,D)pyran-1-ol

or
6,6,9-trimethyl-3-pentyl-7,8,9,10-tetrahydro-6H-dibenzo(B,D)pyran-1-ol

CBD:
Based on numbering system related to monoterpenes:
2-[1-methyl-4-isopropenyl-cyclohexen-3-yl]-5-pentyl-1,3-benzenediol
Based on standard IUPAC numbering:
2-[3-methyl-6-isopropenyl-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol

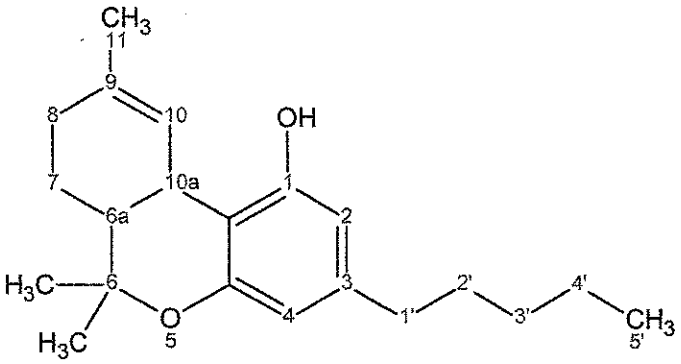
Molecular formula and molecular mass:

THC: $C_{21}H_{30}O_2$
molecular mass: 314.47

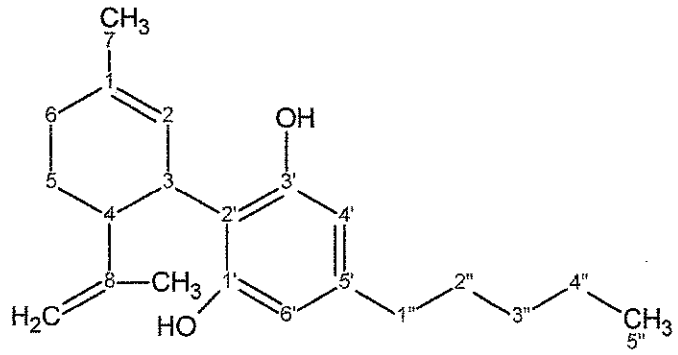
CBD: $C_{21}H_{30}O_2$
molecular mass: 314.47

Structural formula:

THC:



CBD (numbering system related to monoterpenes):



Physicochemical properties:

The THC BDS (Tetranabinex®) is a brown viscous semi-solid with an absence of immiscible liquid. It has a characteristic smell of decarboxylated cannabis. Typically it contains not less than 64% THC with the remainder being co-extracted plant extract.

Soluble in:

Methanol
Ethanol
Acetone
Dichloromethane

Insoluble in:

Water

The CBD BDS (Nabidiolex®) is a brown viscous semi-solid with an absence of immiscible liquid. It has a characteristic smell of decarboxylated cannabis. Typically it contains not less than 60% CBD with the remainder being co-extracted plant extract.

Soluble in:

Methanol
Ethanol
Acetone
Dichloromethane

Insoluble in:

Water

CLINICAL TRIALS

NOC Adjunctive treatment for the symptomatic relief of spasticity in adult patients with multiple sclerosis (MS) who have not responded adequately to other medication and who demonstrate worthwhile improvement during an initial trial of therapy.

The efficacy of SATIVEX® in relieving spasticity in adult patients with MS was demonstrated with Study GWSP0604. This study was a 12-week placebo-controlled, double-blind, randomized withdrawal study in identified responders. The responders those who showed at least a 20% reduction in mean 11-point spasticity numerical rating scale (NRS) score during a 4-week period immediately prior to the withdrawal period. The patients were required to have at least moderate spasticity as defined by a score of ≥4 using a single spasticity severity NRS. Patients were required to have had spasticity due to MS of at least 3 months duration which was not wholly relieved with current anti-spasticity therapy and which was expected to remain stable for the duration of the study. Patients had to be either currently established on a regular dose of anti-spasticity therapy or to have previously tried and failed or could not tolerate suitable anti-spasticity therapy. A total of 241 patients, out of 572, qualified as responders (42%), 124 received SATIVEX® and 117 received placebo. The primary efficacy variable was the change in the mean Numerical Rating Scale (NRS) for spasticity from responder baseline to the last week of treatment. SATIVEX® was self-titrated to symptom resolution or maximum tolerated dose, though with a limit of 12 sprays per day. The change from responder baseline was -0.19 ± 1.35 standard deviation for those on SATIVEX vs. +0.64 ± 2.14 standard deviation for those on placebo. The adjusted difference between the two groups (0.84) were statistically significant ($p = 0.0002$). Some of the secondary efficacy parameters, such as the responder rate at 30% and global impressions, were also statistically significant.

Supportive evidence of efficacy was found in Studies GWMS0106 and GWSP0702. Study GWMS0106 was a 6-week, placebo controlled, randomized parallel group study in MS patients with spasticity which was not adequately relieved with their existing therapy. Study GWSP0702 was 4-week placebo controlled, parallel group, randomized withdrawal study in MS patients with spasticity who had received beneficial effects of SATIVEX as an add-on therapy for at least 12 weeks prior to the randomized withdrawal phase.

NOC/c Adjunctive treatment for the symptomatic relief of neuropathic pain in adult patients with multiple sclerosis.

The potential efficacy of SATIVEX® as an adjunct treatment for the symptomatic relief of neuropathic pain in multiple sclerosis was demonstrated by the results of a randomized, double-blind, placebo-controlled, parallel group, 4-week clinical study in multiple sclerosis patients with neuropathic pain (Study GWMS0107). There were 66 patients (14 male, 52 female) ranging in age from 27 to 51 (mean 49 ± 8.3 standard deviation). The primary efficacy measure was the change from baseline of the mean BS-11, 11-box Numerical Rating Scale (NRS). To enter the study, the patient was required to have a pain severity score ≥4 on the 11-box NRS on at least four occasions during the 7-10 day baseline period. Regular medication for neuropathic pain had to have been stable for at least two weeks prior to entry and was maintained during the

study. SATIVEX® was self-titrated to symptom resolution or maximum tolerated dose. Secondary efficacy measures included the Neuropathic Pain Scale (NPS) and sleep disturbance (also on an 11 point NRS). Completing patients from this study had the opportunity to enter an open-label extension study.

The baseline pain severity was 6.5 in the SATIVEX® group and 6.4 in the placebo group. Analysis of the change from baseline of the mean 11-box NRS pain score showed a statistically significant treatment difference of -1.25 in favour of SATIVEX® (p=0.005; 95% CI: -2.11, -0.39 units).

Efficacy was also observed in the following secondary outcome measures. A pain reduction on the 11-box NRS of at least 50% was seen in 48% of the patients treated with SATIVEX®, compared with 12% of the placebo group. Analysis of the change from baseline of the mean NPS showed a statistically significant treatment difference of -6.82 in favour of SATIVEX® (p=0.039; 95% CI: -13.28, -0.37). The NRS score for sleep improved by 2.73 from a baseline in the SATIVEX® group, and by 1.41 in the placebo group. The treatment difference of -1.39 was significantly in favour of SATIVEX® (p=0.003; 95% CI: -2.27, -0.50).

The study medication was well tolerated. There were no serious adverse events during the study, and only one patient on SATIVEX® discontinued due to an adverse event. Sixty-three of 66 (95%) eligible patients completing study GWMS0107 entered the long-term extension study.

NOC/c Adjunctive treatment for the relief of pain in adult patients with advanced cancer who experience inadequate analgesia during the highest tolerated dose of strong opioid therapy for persistent background pain

The efficacy of SATIVEX® was investigated in a two-week placebo-controlled, three-arm study in patients who reported moderate to severe pain despite already taking a strong opioid for persistent pain. The three groups were SATIVEX® (n=53), placebo (n=52), and THC cannabis extract (n=56). Some of the patients took high dose tramadol.

The primary comparison was between the SATIVEX® group and the placebo group. There were two co-primary outcome endpoints: reduction from baseline at the last observation on the 11-point Numerical Rating Scale (NRS) and the use of escape medication at the last observation. The analysis was based on the intent-to-treat (ITT) population.

Baseline NRS scores were 5.68 in the SATIVEX® group and 6.05 in the placebo group. The study outcomes showed a reduction from baseline on the NRS of 1.37 points on SATIVEX® compared with 0.69 points on placebo. The difference between the two primary comparison groups was significant in favour of SATIVEX® (p=0.024). An improvement of greater than 30% in pain score was reported by 43% of patients on SATIVEX® compared with 21% on placebo (Odds Ratio = 2.81; 95% CI: 1.22, 6.50). There was no difference in the use of escape medication between the two groups.

DETAILED PHARMACOLOGY

Pharmacokinetics

The therapeutic dose of THC is highly variable between patients, and therefore it is important that patients can accurately control their dose to get an adequate therapeutic response whilst avoiding intolerable side effects.

The oral mucosa is relatively permeable, well vascularised, and the blood supply permits systemic absorption. Therefore the oromucosal (oral cavity) route, including sublingual and buccal, offers a delivery route that allows patients to administer small, discrete increments as and when required to optimise individual dosing regimes. Thus, this route allows for greater precision in self-titration.

The high levels of 11-OH-THC following SATIVEX® administration is consistent with a proportion of the dose being swallowed, undergoing alimentary tract absorption and hepatic first pass metabolism.

Individual subject plasma concentration data and pharmacokinetic parameters show a high degree of inter-subject variability.

Following administration of SATIVEX®, T_{max} occurs later (98-253 minutes) than may be expected of a medicine administered via the oral mucosa. This almost certainly reflects alimentary tract absorption of the proportion of the administered dose that is swallowed. The locally absorbed proportion of the dose is not easily discernable from the plasma concentration data from these studies. This is not surprising as redistribution of cannabinoids from plasma is very rapid with an early phase half-life of 5-10 minutes, as has been shown following smoked marijuana and rapid automated blood sampling.

By 12-24 hours after dosing, CBD, THC and 11-OH-THC are usually at or below the limit of quantification in plasma. This is thought to be due to a combination of renal and hepatic clearance and re-distribution of the cannabinoids and their metabolites to adipose tissue.

The terminal half-lives of the principal cannabinoids in SATIVEX® have not been measured in man because of the slow release of cannabinoids from adipose tissue. Half-lives described in the published literature are of the order of 20 to 30 hours. In the clinical trials the plasma half-lives of CBD, THC and 11-OH-THC have been calculated to be of the order of 100 minutes, 85 minutes and 130 minutes respectively. (Study GWPK0112 and GWPK0215 – see Part 1, ACTION AND CLINICAL PHARMACOLOGY.)

Plasma levels have, however, been studied in patients on stable self-titrated doses during chronic therapy in the extension phase of study GWMS0001. Most patients seemed to have self-titrated their dosing to a level at which plasma concentrations were generally in the range of 5-10 ng/ml or less. Sampling of plasma concentration levels during chronic dosing suggests that significant accumulation of cannabinoids does not occur.

Pharmacodynamics

At present, two distinct cannabinoid receptors, CB_1 and CB_2, have been characterised by the use of specific agonists and antagonists and each has been cloned. In addition, two endogenous ligands, arachidonoylethanolamide (anandamide) and 2-arachidonoyl glycerol (2-AG), have been thus far investigated. Other endogenous ligands for cannabinoid receptors have been discovered but have not yet been fully investigated. It is likely that other subtypes of cannabinoid receptors also exist.

Mammalian tissues contain at least two types of cannabinoid receptor, CB_1 and CB_2. These are both coupled to $G_{i/o}$ protein that inhibit adenylate cyclase but stimulate mitogen-activated protein kinase. The CB_1 receptor is also coupled to G protein that modulates certain types of calcium and potassium channel. CB_1 receptors are present in the central nervous system and also in some peripheral tissues including dorsal root ganglia, sympathetic ganglia, adrenal gland, heart, lung, reproductive tissues, urinary bladder, gastrointestinal tissues, and immune cells. Central and peripheral neuronal CB_1 receptors are found mainly at nerve terminals and one function of these receptors is to inhibit neurotransmitter release. CB_2 receptors are present primarily on peripheral and central immune cells. Their roles are proving more difficult to establish but seem to include the modulation of cytokine release. Thus whilst the CB_1 receptor has a neuromodulatory role, the CB_2 receptor appears to be immunomodulatory.

Within the brain, the distribution of CB_1 receptors is heterogeneous, accounting for several well-documented pharmacological properties of CB_1 receptor agonists. For example, the cerebral cortex, hippocampus, lateral caudate-putamen, substantia nigra pars reticulata, globus pallidus, entopeduncular nucleus and the molecular layer of the cerebellum are all populated with particularly high concentrations of CB_1 receptors, a distribution pattern that is consistent with the well-established ability of cannabinoids to alter motor function and to impair cognition and memory. Additionally, CB_1 receptors are found on pain pathways in the brain and spinal cord and also outside the CNS at the peripheral terminals of primary afferent neurons and it is thought these CB_1 receptors mediate cannabinoid-induced analgesia.

The principal pharmacological effects of THC include analgesic, muscle relaxant, antiemetic, appetite stimulant and psychoactive effects (e.g. feeling drunk, disturbance in attention, dizziness, somnolence, disorientation, dissociation and euphoric mood). CBD has analgesic, anticonvulsant, muscle relaxant, anxiolytic, neuroprotective, anti-oxidant and anti-psychotic activity.

It has been hypothesised that endogenous cannabinoids function in the CNS as "retrograde synaptic messengers" being released from postsynaptic neurons and travelling backwards across synapses to activate presynaptic CB_1 receptors and to suppress neurotransmitter release. The mechanisms by which the biological actions of endogenous cannabinoids are terminated, have not been fully evaluated. However, it appears likely that they are removed from the extracellular space by tissue uptake and that intracellular metabolism via an enzyme system, fatty acid amide hydrolase (FAAH), is also involved.

Onset of Action (PK/PD Relationships)

The pharmacokinetic studies have shown that following buccal administration of SATIVEX®, THC, CBD and 11-OH-THC (the main metabolite of THC) appear in the plasma almost simultaneously from about 30 minutes post-dose although there is wide inter-subject variability. (GWPK0112 and GWPK0215 - see Part 1, ACTION AND CLINICAL PHARMACOLOGY.) For those subjects who reported intoxication following dosing, this generally occurred between 30 and 150 minutes after dose administration but there was large inter-subject variability.

MICROBIOLOGY

Not applicable.

TOXICOLOGY

Single and Repeat Dose Toxicology Studies – THC and CBD

Table 7: Overview of Acute Dose Toxicology Studies with THC[1] Identified in the Published Literature

Species	Test Article	THC Dose Range (mg/kg/day)	Duration	Route	Observed Maximum Non-Lethal Dose (mg/kg/day)	LD_{50} (mg/kg)
Rat	THC	225 – 3600	Acute	PO (gavage)	Not stated	Fischer: 1015 M; 800 F (for 96% pure THC); 1910 M; 1040 F (for 90% pure THC) Wistar-Lewis: 1160 M; 860 F
Rat	Synthetic THC	Not stated	Acute	IV	Not stated	15 - 20
Dog	THC	65.6 – 3000	Acute	PO (gavage)	3000	No deaths
Dog	Synthetic THC	3.9 – 210	Acute	IV	25	100
Monkey	THC	131 – 9000	Acute	PO (gavage)	9000	No deaths
Monkey	Synthetic THC	3.9 – 1050	Acute	IV	3.9	62.5

[1] Other than smoked or inhalation routes of administration.

Table 8: Overview of Repeat Dose Toxicology Studies with THC Identified in the Published Literature

Species	Test Article	THC Dose Range (mg/kg/ day)	Duration	Route	Observed Maximum Non-Lethal Dose (mg/kg/day)	Mortalities
Mouse	THC	5 – 500	13 weeks (dosed 5 days/week)	PO (gavage)	500	No deaths attributable to THC
Rat	THC	0.025 – 1.25	28 days	PO (gavage)	No deaths	No deaths
Rat	THC	3.75 – 30	30 days	IP	No deaths	No deaths
Rat	THC	5 – 500	13 weeks (dosed 5 days/week)	PO	150	2/10 M died at 50 mg/kg/day and 1/10 F at 15 mg/kg/day
			13 weeks followed by 9 week recovery (dosed 5 days/week)		15	1/10 M died at 50 mg/kg/day and 7/10 F at 500 mg/kg/day
Rat	9 & 8–THC	50 – 500	17 weeks	PO (gavage)	250	23% M and 27% F died at 400 mg/kg/day
Rat	THC	2 – 50	14, 28, 90 or 180 days and 180 days plus 30-day recovery	PO (gavage)	2	7% death in M in 10 mg/kg group; 22% M and 28% F death in 50 mg/kg group by Day 173
Guinea pig	THC	3	6 months	IP	No deaths	No deaths
Rabbit	THC	3 – 100	13 days	SC	No deaths	No deaths

Table 9: Overview of Single and Repeat Dose Toxicology Studies on CBD Identified in the Published Literature or Sponsored by GW Pharmaceuticals

Species	Test Article	CBD Dose Range (mg/kg/day)	Duration	Route	Observed Maximum Non-Lethal Dose (mg/kg/day)	LD_{50} (mg/kg)[2]
Rat (Fischer)	CBD (98%)	110 – 310	Acute	IV	160 (M) 210 (F)	232 (M) 252 (F)
Monkey	CBD (98%)	150 – 320	Acute	IV	200	212
Rat (Fischer)	CBD	30 – 300	90 days (with 30 days recovery)	PO (gavage)	300	No Deaths
Rat	CBD[3]	5 – 75	14 days	IV	5 NOAEL	75 mg/kg/day
Rat	CBD[3]	1 – 25	28 days	IV	1	5
Rat	CBD[3]	25 – 225	90 days	PO (diet)	225	No deaths
Monkey	CBD	30 – 300	90 days (with 30 days recovery)	PO (gavage)	300	No Deaths

[2] or lowest group in which deaths occurred for repeat dose toxicity studies
[3] CBD content 69% (doses stated in terms of CBD)

Overall, the toxicological data suggest that both THC and CBD have very low acute toxicity after single doses, suggesting a likely good margin of safety for SATIVEX® in humans. There is some evidence, from repeat dose studies, for cumulative toxicity for THC in rodents which may be due to metabolic overload. Both THC and CBD appear to have similar pharmaco-toxicological profiles in laboratory species, although at dose levels up to 300 mg/kg/day in repeat-dosing studies, in rats and monkeys, CBD produced no evidence to suggest significant effects on behaviour or on CNS function generally. Both THC and CBD reduced the weight of sex organs, an effect that is more pronounced for THC and which appears to be due to change in the functional status of the organs probably mediated via inhibitory effects on the release of sex hormones. These effects are reversible for both compounds. Both compounds caused increases in weight of the liver and adrenal glands but these effects are not associated with any histopathological changes.

Repeat Dose Toxicology Studies (1:1 THC BDS:CBD BDS)

Two repeat dose studies have been carried out using the THC BDS and CBD BDS in the same 1:1 ratio as used in SATIVEX® buccal spray.

Table 10: Overview of Repeat Dose Toxicology Studies with 1:1 THC BDS: CBD BDS

Species	Drug	Doses THC+CBD (mg/kg/day)	Duration	Route	No Observed Adverse Effect Level NOAEL) (mg/kg/day)
Rat	1:1 THC BDS: CBD BDS	50, 100, 200	6 weeks	Dietary	50 (M) 100 (F)
Dog	1:1 THC BDS: CBD BDS	10, 60, 100	4 weeks (5 weeks exposure)	Dietary	10

Repeat Dose Toxicology in Rats

In the 6-week rat study, there were no deaths during the study and no treatment-related clinical observations or ophthalmoscopic findings. Food consumption and bodyweight gain were markedly reduced at all dose levels, though not in a dosage-related manner. Although treatment-related changes were noted in a few haematology and blood chemistry parameters and in urinary pH, these were not considered to be toxicologically significant. There were notable changes in the weight of several organs, all of which correlated with histopathological findings.

Histopathological changes considered to be related to treatment were seen in the adrenal glands, liver, seminal vesicles, bone marrow, thymus, ovaries and uterus. Although some changes were generally confined to the high and intermediate dosages, the hypertrophy of the zona glomerulosa in the adrenal glands was seen in all groups. The changes seen in the bone marrow at the low dose were considered equivocal.

It was not possible to determine a No Observed Effect Level (NOEL) under the conditions of this study. However based on the pathology, the No Observed Adverse Effect Level (NOAEL) was 50 mg/kg/day for males and 100 mg/kg/day for females.

The extent of systemic exposure (AUC 0-last) for CBD and THC was similar in male and female rats and generally increased approximately in proportion with increasing dose level. The toxicokinetic parameters are presented below.

Table 11: Toxicokinetic Parameters for 6 week Exposure in Male Rats

Week 4 (Day 1 of Steady State)						
	THC	THC	THC	CBD	CBD	CBD
Dose	50	100	200	50	100	200
C_{max} (ng/ml)	509.19	1130.36	1498.45	87.12	224.61	491.17
T_{max} (hours)	24:00	04:00	08:00	24:00	04:00	08:00
AUC (0 - last) (hr*ng/ml)	7253.53	16127.18	22517.08	1120.15	3136.49	7073.30

The C_{max} for THC and CBD are far in excess of the plasma levels achieved by repeat dosing with SATIVEX® in human patients gaining therapeutic benefit (5-30ng/ml, Study GWMS0001EXT). The C_{max} plasma levels achieved in this study at the top dose are 50 times

the anticipated plasma exposure in humans for THC and 50 times the anticipated plasma exposure in humans for CBD.

Repeat Dose Toxicology in Dogs

The intended maximum dose level was 200 mg/kg/day. In order to dose the animals up to this level, dose titration is necessary. During the ascending dose phase of the study a spectrum of clinical observations was noted in the high dose animals that were directly related to the drug administration, thus the maximum dose was reduced during the steady state period to 100 mg/kg/day. The corresponding toxicokinetic parameters are presented in the table below.

Table 12: Toxicokinetic Parameters for 9 week Exposure in Male Dogs

Week 4 (Day 1 of Steady State)						
	THC	THC	THC	CBD	CBD	CBD
Dose	10	45	200	10	45	200
C_{max} (ng/ml)	545.01	1011.76	8648.41	385.07	863.52	8341.80
T_{max} (hours)	6.67	4.67	4.00	6.67	4.67	4.00
AUC (0 - last) (hr*ng/ml)	6980.78	12830.38	76127.19	5053.85	11803.53	89098.66
Week 9 (Day 25 of Steady State)						
Dose	10	45	100	10	45	100
C_{max} (ng/ml)	434.46	1179.00	2937.10	362.16	1440.16	3280.48
T_{max} (hours)	4.67	6.00	3.00	4.67	6.67	3.00
AUC (0 - last) (hr ng/ml)	6325.67	17238.66	32903.15	5402.50	23102.60	44380.32

In conclusion, a spectrum of transient but severe clinical observations, some of which were CNS related, led to reduced food consumption and body weight gain and accounted for the reduction of the repeat high dose level from 200 to 100 mg/kg/day. However other changes were limited to elevated liver weight and a possibly adaptive hepatocellular hypertrophy at dose levels of 45 mg/kg/day and above. In addition, the elevated alkaline phosphatase activation noted in these animals was probably associated with this liver change. Therefore, the NOAEL for 1:1 CBD BDS: THC BDS could be considered as 10 mg/kg/day when administered orally to the dog over 30 days.

The C_{max} for THC and CBD are far in excess of the plasma levels achieved by repeat dosing with SATIVEX® in human patients gaining therapeutic benefit (5-30ng/ml, Study GWMS0001EXT). The C_{max} plasma levels achieved in this study at the top dose are 98 times the anticipated plasma exposure in humans for THC and 110 times the anticipated plasma exposure in humans for CBD.

Repeat Dose Toxicology Studies - SATIVEX®

Repeat Dose Toxicology in Rats

SATIVEX® was administered by daily oral gavage Sprague-Dawley rats in a 26-week repeated dose toxicology study. The study included three active treatment groups, one vehicle (placebo) group and one sham (purified water) group. The doses for the active treatment groups were 5.4:5.0, 13.5:12.5 and 40.5:37.5 THC:CBD mg/kg/day. The high dose was reduced to 27:25 THC:CBD mg/kg/day with a reduction of dosage volume from 1.5 to 1.0 mL/kg/day because of continued mortality. Three subsets of animals were included to study recovery (4-week), toxicokinetics and immunotoxicity.

A high mortality rate (33 – 38%) was observed in the two upper dose groups and the placebo group. Clinical signs and pathological examinations indicated that the mortalities were caused by accidental delivery of the test items into the trachea. The survivors showed dose dependent toxicities attributable to the excipients and cannabinoids. The excipient-related toxicities included loud breathing, abdominal breathing, pallor of extremities, etc. The cannabinoid-related toxicities included ptyalism, ataxia, body tremors, scabs, etc. The adverse effects were more frequent in the female rats.

Table 13: Toxicokinetic Parameters for 6 month Exposure in Male Rats

	Week 26 (of Steady State)					
	THC	THC	THC	CBD	CBD	CBD
Dose	5.4	12.5	27	5.0	13.5	25
C_{max} (ng/ml)	245	952	1243	53.1	155	255
T_{max} (hours)	2	9	9	2	9	9
AUC (0 - last) (hr*ng/ml)	1938	8366	12575	295	1246	2650

The plasma THC/CBD levels indicated that exposure increased near/supra-linearly with dose level. Gender effect for THC (levels generally higher in females) and accumulation for both THC and CBD were also observed. Abnormalities in biochemistry, haematology and immunology were observed, but their significance in toxicology was unclear. The NOAEL seemed to be lower than 5.4:5.0 THC:CBD mg/kg/day.

Implications of the animal toxicity studies with regard to patients

At the maximum dosage levels used in humans of about 1 mg/kg/day for each, it is considered that SATIVEX® is unlikely to produce any significant target organ toxicity in humans. However, detrimental effects on reproductive function cannot be ruled out at this dosage level.

Genotoxicity

A full battery of four genotoxicity assays, (the AMES test (bacterial mutation assay), the mouse mammalian cell mutation assay (mouse lymphoma), the mouse micronucleus assay and the unscheduled DNA synthesis assay), have been conducted using 1:1 THC BDS:CBD BDS or

with CBD BDS. They all produced negative results and have shown that at the concentrations tested, there were no genotoxic effects.

Three genotoxicity tests were carried out with SATIVEX®. SATIVEX® did not show any mutagenic activity in the bacterial reverse mutation test with *Salmonella typhimurium* (AMES test). In a mouse lymphoma assay, no mutagenic activity was noted in the presence of SATIVEX® with the exogenous metabolic activation system (S-9 mix). However, there was a slight increase in mutation frequency without S-9 mix. In order to evaluate and confirm the biological significance of the positive results obtained in the mouse lymphoma test with SATIVEX®, an *in vivo* rat micronucleus assay was conducted. Under the experimental conditions, SATIVEX® did not induce any damage to chromosomes or the mitotic apparatus of rat bone marrow cells after two oral administrations separated by a 24-hour interval at dose levels of 0.5, 1 or 2 mL/kg/day.

Carcinogenicity

Carcinogenicity - THC

THC has been fully evaluated for carcinogenic potential by well-documented and reported 2-year studies in mice and rats in the US National Toxicology Programme in 1996. The results obtained in both species were generally consistent in terms of clinical signs, body weight changes and incidences of non-neoplastic and neoplastic lesions. The results obtained in rats were clearly negative whilst in mice a non-dosage related increase in thyroid follicular cell tumours was seen at a single dosage level (125 mg/kg/day, which is 100 times the highest tested dose in humans, on a mg/kg basis). This effect is considered to be of doubtful toxicological significance in view of the lack of a dose-response relationship and the lack of evidence to suggest that hyperplasia of thyroid follicular cells progressed to adenomas or carcinomas. This evidence, taken together with the lack of structural relationship of THC to any known carcinogen and to its negative responses in most genotoxicity tests, suggests that it is likely to have a very low carcinogenic potential in humans. Positive carcinogenic effects reported for THC after subcutaneous administration in mice are considered of doubtful scientific validity since the results have not been published in full or confirmed by other workers.

Carcinogenicity - CBD

The carcinogenic potential of CBD BDS was evaluated in a 2-year carcinogenicity study in rats (GW Study No JJG003). No apparent effects on survival were noted. There was no increased incidence of any factor contributory to death when treated animals were compared with Controls. Clinical signs observed were those expected for rats of this age and strain and were considered to be unaffected by administration of CBD BDS. There was no evidence of an adverse effect of the drug on the incidence or time of onset of palpable masses.

A clear treatment and dose related reduction in overall bodyweight gain (Weeks 1 – 104) was seen for males and females given 15 or 50 mg/kg/day; at 50 mg/kg/day, males had a 26 % reduction and females had a 35 % reduction in bodyweight gain compared with Controls. A dosage related reduction in food consumption and food conversion efficiency was present for both sexes throughout the study.

There were no effects of treatment with CBD BDS on haematological parameters in males or females during Weeks 52 or 78. During Week 103 only, the white blood cell counts were statistically significantly lower than those of Controls for males given 15 or 50 mg/kg/day; however individual values were within the background ranges found in this laboratory and the differences from Controls were considered to be of no toxicological significance. There was no evidence of an increased incidence of leukaemia in the CBD BDS treated groups.

There was an apparent increase in the incidence of abnormal size of the thyroid glands in CBD BDS-treated males. There was a reduction in the number of skin masses recorded in both males and females of the 50 mg/kg/day group and in the number of findings recorded in the pituitary gland and mammary tissue in the females of this group. In association with the reduced number of findings in the pituitary gland there was a reduction in the number of ventral depressions in the brain that are generally caused by pituitary enlargement.

There was no indication of carcinogenic potential. Indeed, there was, in animals given 50 mg/kg/day, an apparent reduction in the incidence of tumours generally associated with hormonally-mediated neoplasia in ageing animals. Non-neoplastic findings considered to be associated with treatment included an increased incidence of centrilobular hypertrophy in the liver of males in the 15 mg/kg/day and the 50 mg/kg/day groups and females in the 50 mg/kg/day group. There was an increase in focal follicular hyperplasia in the thyroid glands of males given 50 mg/kg/day.

It was concluded that administration of both 15 and 50 mg/kg/day of CBD BDS in the diet resulted in a greater than 10 % reduction in overall bodyweight gain in both sexes and there was good survival in all groups over 104 weeks of treatment. There was no evidence that administration of CBD BDS at dose levels of up to 50 mg/kg/day to the HsdBrlHan:WIST rat influenced tumour formation. There was no apparent increase in the incidence of neoplasia, alteration in the time of tumour onset or induction of rare tumours. There was some evidence of reduction in some of the commonly seen hormone mediated ageing changes, especially those seen in ageing females.

Reproductive and Developmental Toxicity

Four reproductive toxicology studies have been completed using 1:1 THC BDS: CBD BDS, comprising:

- Embryo-foetal developmental toxicity (teratology) in rats
- Embryo-foetal developmental toxicity (teratology) in rabbits
- Pre- & Post-natal developmental toxicity in rats
- Fertility and early embryonic developmental toxicity in rats

Table 14: Reproductive Toxicology Studies with 1:1 THC BDS: CBD BDS

Study	Species	Dose 1:1 THC BDS:CBD BDS mg/kg/day	Route	Findings
Embryo-foetal developmental toxicity (teratology)	Rat	1,5,25	Oral (gavage)	NOEL of 1 mg/kg/day for foetal development

Table 14: Reproductive Toxicology Studies with 1:1 THC BDS: CBD BDS

Study	Species	Dose 1:1 THC BDS:CBD BDS mg/kg/day	Route	Findings
Embryo-foetal developmental toxicity (teratology)	Rabbit	5,10,25	Oral (gavage)	NOEL less than 5 mg/kg/day for maternal toxicity. NOEL of 25 mg/kg/day for developmental toxicity
Pre-and post-natal developmental toxicity	Rat	1,2,4 mg/kg/day	Oral (gavage)	NOAEL 1 mg/kg/day for maternal toxicity
Fertility and early embryonic developmental toxicity	Rat	1,5,25 mg/kg/day	Oral (gavage)	NOAEL for male fertility was 25 mg/kg/day. NOAEL for female fertility and embryonic development was 25 mg/kg/day

Embryo-foetal Developmental Toxicity (Teratology) in Rats

The doses selected for this study were taken from a dose range finding study. Three groups of 24 timed-mated, sexually mature female rats of the Crl:CD (SD) IGS BR VAF PLUS strain were dosed once daily, by oral (gavage), with 1:1 THC BDS: CBD BDS at dose levels of 1, 5 and 25 mg/kg/day on Day 6 to Day 17 of gestation, inclusive.

At 5 and 25 mg/kg/day dose-related significant losses in bodyweight and lower food consumption were observed along with persistent clinical observations in the period after dosing. Therefore the NOEL for maternal toxicity was considered to be 1 mg/kg/day. At this dose level, maternal systemic exposure for the three analytes were as follows: for CBD AUC 0-last: 4.74-15.81 hr*ng/ml, for THC AUC 0-last: 22.28-68.00 hr*ng/ml and for 11-hydroxy THC AUC 0-last 14.31-22.53 hr*ng/ml.

At 1 mg/kg/day values for foetal abnormalities were comparable with the control animals and were therefore considered to be within the normal range for rat foetuses. It is therefore considered that 1 mg/kg/day is the NOEL for foetal development. Increased incidences of minor abnormalities and variants at 5 or 25 mg/kg/day were generally related to a slight delay of ossification of the foetal skeleton. These findings were not considered to have an adverse effect on foetal development.

Embryo-foetal Developmental Toxicity (Teratology) in Rabbits

Three groups of twenty time-mated female New Zealand White Rabbits were dosed once daily, via the oral (gavage) route, from Day 6 to Day 18 of gestation (total of 13 days inclusive), with 1:1 THC BDS: CBD BDS. The dose levels used were 5, 10, and 25 mg/kg/day.

Two females (10 mg/kg/day) aborted or started to abort on Days 25 and 28 of gestation, and 2 females (25 mg/kg/day) aborted on Days 27 and 24, respectively. Clinical signs of unsteady gait and changes in activity were recorded at 10 and 25 mg/kg/day. Reductions in group mean bodyweight were noted, especially at 10 and 25 mg/kg/day. Bodyweight performance improved after cessation of dosing, but the absolute group mean bodyweight on Day 28 of

gestation was lower than controls and there was an overall loss in bodyweight over the treatment period.

Over Days 6 to 9 of gestation, dosage-related reductions in food consumption were observed at 10 and 25 mg/kg/day. Dosage-related reductions in food consumption were observed in all groups treated with 1:1 THC BDS: CBD BDS over Days 9-19 of gestation. Two females from each of the groups dosed at 10 and 25 mg/kg/day aborted. There were no other findings recorded at necropsy considered to be related to treatment.

Pregnancy Data: There were 18 (90%), 17 (85%), 16 (80%) and 14 (70%) of females with live foetuses on the scheduled day of necropsy at 0, 5, 10 and 25 mg/kg/day. There was a slightly lower number of pregnant females in the groups treated with 5, 10 and 25 mg/kg/day THC BDS: CBD BDS, however, values were within the background data range. There was no effect of treatment with 1:1 THC BDS: CBD BDS on any pregnancy parameter.

There were marginal reductions in group mean litter weight and reductions in group mean foetal weight were observed at 10 and 25 mg/kg/day. Higher incidences of minor abnormalities and variants in the groups treated with 1:1 THC BDS: CBD BDS were generally associated with the incomplete or non-ossification of the skeleton and were considered to be indicative of slightly delayed foetal development as a result of an indirect effect of maternal treatment.

Based on the results of this study the NOEL was considered to be less than 5 mg/kg/day with regard to maternal toxicity and 25 mg/kg/day with regard to developmental toxicity.

Pre- & Post-natal Developmental Toxicity in Rats

The objective of this study was to investigate the effects of 1:1 THC BDS: CBD BDS on embryonic, foetal and post-natal development of the rat following administration to mated females from Day 6 of gestation throughout lactation to Day 20 of lactation inclusive. The F1 generation was allowed to mature, untreated and the effects on growth, development, behaviour and reproductive performance were assessed.

Three groups of 25 time-mated female rats were dosed, once daily by oral (gavage), from Day 6 of gestation to Day 20 of lactation, inclusive, with the drug (1:1 THC BDS: CBD BDS). The dose levels used were 1, 2 and 4 mg/kg/day.

Maternal treatment with 1:1 THC BDS: CBD BDS at 2 and 4 mg/kg/day during gestation and at 4 mg/kg/day during lactation resulted in a reduction in food consumption and corresponding lower mean gains in bodyweight. At 1 mg/kg/day lower bodyweight gain was observed at the start of treatment on Day 6 of gestation until Day 7 of gestation. Therefore the NOAEL for maternal treatment with the drug was considered to be 1 mg/kg/day.

Table 15: Comparison of Plasma & Breast Milk Levels

	Plasma Levels (8hrs Post Dose)		Breast Milk Levels (6hrs Post Dose)	
Dose Level	THC (ng/ml)	CBD (ng/ml)	THC (ng/ml)	CBD (ng/ml)
1 mg/kg/day	1.99*	<1.00*	356.76	97.71
	<1.00*	<1.00*	464.97	171.65
	<1.00*	<1.00*	547.27	185.23
2 mg/kg/day	13.36	3.36	1251.41	482.38

Table 15: Comparison of Plasma & Breast Milk Levels

	Plasma Levels (8hrs Post Dose)		Breast Milk Levels (6hrs Post Dose)	
	87.71	25.47	657.11	199.86
	16.07	2.86	883.14	302.23
4 mg/kg/day	131.69	37.06	2030.03	769.43
	110.67	26.16	1407.65	445.00
	388.98	108.52	1227.75	487.25

*Data from Embryo-foetal toxicity study in rats

Pup Growth and Pup/F1 Development:

Maternal administration of drug at 4 mg/kg/day resulted in a slightly lower lactation index. Lower mean pup bodyweights were recorded throughout lactation for males and females so that at selection to the F1 generation group mean bodyweights were lower than those of the controls and remained marginally lower through the maturation period. Associated with this finding there was a lower percentage of pups with the righting reflex on Day 5 of lactation. Additionally, there was marginally less mean time spent on the Rotarod (assessment of locomotion) for F1 males following maternal administration of the drug at 4 mg/kg/day.

Therefore the NOEL was considered to be 2 mg/kg/day. As expected, due to the lipophilic nature of the molecules, there were considerable levels of cannabinoids in the maternal breast milk. Even at 1mg/kg/day there were 40-60 times the plasma level of cannabinoids in the breast milk.

F1 Reproductive Performance:

There was no adverse effect of maternal treatment with 1:1 THC BDS: CBD BDS on fertility or mating performance for F1 males and females or on gestation of the F1 females. Therefore the NOAEL was considered to be 4 mg/kg/day.

Fertility and Early Embryonic Developmental Toxicity in Rats

The aim of the study was to investigate the effects of the drug on the fertility and early embryonic development of the rat following administration to males for 28 days prior to pairing and during pairing until necropsy, and to females for 14 days prior to pairing, during pairing and then to Day 6 of gestation. Three groups of 25 male and 25 female Sprague-Dawley derived rats were dosed once daily, by oral (gavage), with 1:1 THC BDS: CBD BDS at dose levels of 1, 5 and 25 mg/kg/day. The males were dosed for 28 days prior to pairing, during pairing and for at least two weeks after the end of the pairing period. The females were dosed for 14 days prior to pairing, during pairing and up to and including Day 6 of gestation.

Dosing was associated initially with clinical signs of decreased activity, reduced bodyweight and food consumption. There was no effect of treatment on fertility, therefore the NOAEL for male fertility was considered to be 25 mg/kg/day.

Oral (gavage) administration of the test article to female rats at 5 or 25 mg/kg/day for 14 days prior to pairing, during pairing and until Day 6 of gestation was associated with lower gains in mean bodyweight and reduced food consumption. Additionally, at 25 mg/kg/day clinical signs of decreased activity were seen during the initial dosing period. At 5 or 25 mg/kg/day there was

no effect of treatment on the number of females that became pregnant. There was a treatment-related effect on the mean number of corpora lutea resulting in a statistically significant reduction in the number of implants and live embryos per female compared with the controls, however, values were within background ranges and were therefore considered not to be of toxicological significance. The NOAEL for female fertility and early embryonic development was considered to be 25 mg/kg/day.

Based on these data, it would be inadvisable to use the preparation in human females either during pregnancy or nursing. Adequate contraceptive precautions should be taken in all females of child-bearing potential treated with SATIVEX® and the preparation is unsuitable for use in pre-pubertal children.

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PART III: CONSUMER INFORMATION

[N]SATIVEX®

delta-9-tetrahydrocannabinol 27 mg/ml (from Tetranabinex® - *Cannabis sativa* L. extract) and cannabidiol 25 mg/ml (from Nabidiolex® - *Cannabis sativa* L. extract)

SATIVEX® is indicated, as add-on treatment, for symptomatic relief of muscle stiffness in adult patients with multiple sclerosis (MS) who have not responded adequately to other medication and who demonstrate worthwhile improvement during an initial trial of therapy.

SATIVEX® may be useful, as add-on treatment, for the symptomatic relief of pain caused by damage to the nerves in adult patients with multiple sclerosis (MS).

SATIVEX® may be useful, as add-on pain control treatment, in adult patients with advanced cancer who continue to experience moderate to severe pain even after receiving the highest tolerated dose of a strong opioid pain medication.

SATIVEX® has been approved with conditions for the second and third indications above, pending the results of studies to verify its clinical benefit. For more information, patients are advised to contact their health care provider.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

This leaflet is part III of a three-part "Product Monograph" published when SATIVEX® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SATIVEX®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

SATIVEX® is used to relieve muscle stiffness in people with multiple sclerosis who do not get enough relief from other drugs they are using and who find additional relief with SATIVEX®.

SATIVEX® is used to relieve neuropathic pain (pain caused by damage to the nerves), in people with multiple sclerosis (MS). It is also used to relieve pain in patients with advanced cancer who are not getting enough pain relief even at the highest tolerated dose of a strong opioid pain medication.

What it does:

SATIVEX® helps to relieve your pain.

When it should not be used:

You should **not** use this product if you:

- Have a known or suspected allergy to any cannabis-based products, propylene glycol, ethanol or peppermint oil.
- Have serious heart disease.
- Have a history of schizophrenia or any other psychotic disorder.
- Are a child or adolescent under 18 years of age.
- Are pregnant or nursing.
- Are female at risk of pregnancy and not using a reliable contraceptive.
- Are male and intending to start a family while on treatment with SATIVEX®.

Medicinal ingredients:

SATIVEX® contains *Cannabis sativa* L. extracts Tetranabinex® and Nabidiolex® equivalent to 27 mg/ml delta-9-tetrahydrocannabinol (THC) and 25 mg/ml cannabidiol (CBD).

What the nonmedicinal ingredients are:

Ethanol
Propylene glycol
Peppermint oil (flavouring)
This is a full listing of all nonmedicinal ingredients.

Dosage forms:

SATIVEX® is provided as a solution in a spray pump. It is contained in an amber glass vial fitted with a metering pump delivering 100 microlitres per actuation (spray). The pump is protected with a plastic cap.

SATIVEX® is for buccal use. This means SATIVEX® is to be sprayed into the mouth, under the tongue or on to the inside of the cheek. Each 100 microlitre spray contains 2.7 mg delta-9-tetrahydrocannabinol and 2.5 mg cannabidiol.

SATIVEX® is available in 5.5 ml and 10 ml amber glass vials.
(Not all presentations may be available in Canada)

The 5.5 ml vial contains up to 51 metered sprays.
The 10 ml vial contains up to 84 metered sprays.
(Not all presentations may be available in Canada)

SATIVEX® is packed as individual, two, three, four, five, six, eight, ten or 12 vials in each carton.
(Not all presentations may be available in Canada)

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

THC, one of the principal active components of SATIVEX®, has numerous effects on the central nervous system such as changes in mood, decreased mental performance and memory and altered perceptions of reality. Symptoms such as fainting and interference in the physical ability to carry out complicated tasks have been seen in patients taking SATIVEX®. Therefore you should not drive, operate machinery or engage in activities that require unimpaired judgement and coordination.

While taking SATIVEX® you should not drink alcohol or take other drugs which may have an effect on the central nervous system such as sedatives or hypnotics, without consulting your doctor, as these products have a further additive effect on some of the symptoms listed above.

BEFORE you use SATIVEX® talk to your doctor or pharmacist if you:

- suffer from any allergic reactions
- suffer from epilepsy
- suffer from any liver, kidney or heart disease
- suffer from schizophrenia or depression
- have an irregular heart beat/rhythm, including a fast or slow pulse
- have high blood pressure
- are addicted to drugs or alcohol
- are taking other medicines.

You and your partner must ensure reliable contraceptive precautions are taken during your treatment and for at least three months after you stop taking SATIVEX®.

There may be a potential for abuse or development of dependence in some individuals with long-term use. Discuss with your doctor.

If you see another doctor or go into hospital, let them know what medicines you are taking.

This product contains approximately 50% v/v ethanol. Each spray contains approximately 0.04 g of alcohol. The usual daily dose will be greater than one spray. It may be harmful for those suffering from alcoholism. The alcohol content should be taken into account when the product is to be used in high-risk groups such as patients with liver disease or epilepsy.

INTERACTIONS WITH THIS MEDICATION

Some drugs may interact with SATIVEX®. Therefore, it is important to talk to your doctor or pharmacist about any other medicines you are taking such as but not limited to:

- sedatives
- hypnotics
- fentanyl and the related opioid drugs sufenatil and alfenatil
- amitriptyline
- cannabis (marijuana, pot). Do not smoke marijuana while using SATIVEX®.
- Alcohol may interact with SATIVEX®, particularly in affecting coordination, concentration and the ability to respond quickly.

PROPER USE OF THIS MEDICATION

Usual dose:

SATIVEX® is to be sprayed into your mouth, under your tongue or on to the inside of your cheek. Do not spray the back of the throat to avoid inhaling and to avoid throat irritation. Vary the location in the mouth into which you spray SATIVEX®, in order to avoid stinging and discomfort in the mouth. **Do not spray into the nose.**

The dose you require is determined by you. You can determine the dose that best suits you according to the pain relief you experience from taking SATIVEX®. Your regular daily dose is determined by increasing your dose gradually over the first few weeks of taking SATIVEX®.

- On day one, you should take one spray during the morning and one spray during the afternoon/evening. The morning dose can be taken at any time between waking up and 12 noon, and the afternoon/evening dose can be taken at any time between 4 pm and bedtime.

- After the first day you may gradually and carefully increase your intake by **one spray each day**, as needed and tolerated until you experience improved relief of your pain.

- There should be at least a 15 minute gap between sprays.
- When you have found a daily number of sprays that controls your pain, you may adjust the timing between them, depending on how you feel.
- Once you establish the timing and number of sprays that controls your pain, maintain that schedule.
- The best dosing schedule of sprays varies from person to person.

The average dose of SATIVEX® is 4 - 8 sprays per day. The majority of patients need 12 sprays a day or less; there is limited experience with doses higher than 12 sprays a day but you may need a higher number of sprays.

If you experience any bothersome side effects reduce your number of sprays or increase the time between each dose.

Follow these instructions unless your doctor gives you different advice. If there is something you do not understand, ask your doctor or pharmacist. Continue to take this medicine for as long as your doctor prescribes.

HOW TO USE YOUR SPRAY

On first opening of a new vial:

Shake the vial gently and remove the protective cap. Place the vial between the thumb and second finger with the first finger placed on the actuator. Press two or three times firmly and quickly into a tissue until a fine spray appears. See Diagram 1.

The medicine is now ready for use.

On normal use:

1. Shake the vial gently before use.
2. Remove the protective cap.
3. Place the vial between the thumb and second finger with the first finger placed on the actuator.
4. Hold the vial in the upright position and direct the spray into your mouth under the tongue or onto the inside of the cheek. Hold your breath and press firmly and quickly. See Diagram 2.

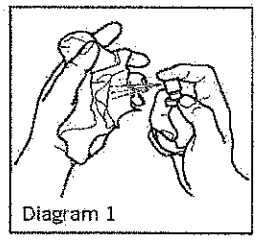


Diagram 1

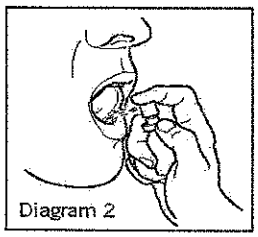


Diagram 2

5. Replace the protective cap.

Important:

If you take 5 sprays each day you will notice after about 10 days (for the 5.5 ml vial; 16 days for the 10 ml vial) that the noise of the spray action may change. You may also become aware of a different feeling in your mouth. This is indicating your medicine container is nearly empty. At this point start a new container of medicine.

Keep spray away from eyes. If the spray comes into contact with your eyes or skin it should be washed away immediately with lots of water.

Do not spray near children or pets.

Do not use the spray near an open flame or heat source.

Overdose:

If you accidentally take more than you normally do and you experience severe intoxication reactions, contact your nearest hospital emergency department, regional Poison Control Centre or tell your doctor immediately. Symptoms of intoxication reactions include hallucinations (seeing/hearing things that are not there), delusions (believing things that are not true), anxiety or paranoia (excessive anxiety or fear), increased or decreased heart rate with postural hypotension (feeling dizzy upon standing up). Bring any remaining medicine and the container with you.

The day following an overdose, you should make a follow-up appointment with your usual doctor.

Missed Dose:

If you forget to take a dose, do not worry. SATIVEX® is a medicine that is taken as required. Just take another as soon as you feel you need to.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, SATIVEX® may cause side effects in some patients. They may include dry or sore mouth, feeling or being sick, discomfort and stinging in the mouth or mouth ulcers, tiredness, drowsiness, confusion, dizziness or faintness, disorientation, poor concentration, impaired memory or poor recall, strange ideas, a feeling of unreality, feeling abnormal or drunk, poor balance, slurred speech, feeling people are against you and a feeling of general happiness or a "high" (easy laughing, heightened awareness). Other side effects may include palpitations (rapid heartbeat), vertigo, blurred vision, constipation, diarrhoea, weakness, feeling ill, tooth or mouth discolouration, throat infection, upset stomach, increase or decrease in appetite, abnormal taste, cough or throat irritation. You may also have side effects of stomach pain or disturbance in attention.

Stinging or discomfort in the mouth may be experienced if SATIVEX® is sprayed in the same place in the mouth on repeated occasions. This is usually overcome by varying the area in the mouth where SATIVEX® is sprayed. Do not continue spraying SATIVEX® onto sore or inflamed areas. If soreness persists inform your doctor.

If unacceptable and unwanted effects occur, stop taking SATIVEX®. These effects can be expected to wear off within a few hours. When returning to your medicine the dose should be reduced or the time between doses increased.

If you suffer any of these side effects and they become troublesome or continue, or you feel unwell in any other way, seek advice from your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom /Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Common	fatigue	✓		
	dizziness	✓		
Common	fainting			✓
	high or low blood pressure		✓	
	rapid heartbeat			✓
	panic attacks (suddenly being afraid)	✓		
	disorientation/confusion			✓
	depression (sad or low mood)		✓	
	paranoia (excessive fear and anxiety)			✓
	anorexia (decreased appetite)		✓	
	feeling drunk	✓		
	difficulty passing urine	✓		
	falls		✓	
Uncommon	hallucinations (seeing or hearing things that are not there)			✓
	thoughts about suicide			✓
	transient toxic psychosis (losing a sense of reality and not behaving normally)			✓

This is not a complete list of side effects. For any unexpected effects while taking SATIVEX®, contact your doctor or pharmacist.

HOW TO STORE IT

Store upright.

This product is flammable. Replace cap after use.

Store your unopened medicine in a refrigerator (2-8°C). Do not freeze.

Once SATIVEX® is opened, use within 28 days. Opened vials of SATIVEX® may be stored at room temperature (15-25°C).

Shake the vial gently before use.

Do not leave your medicine in a hot place such as in direct sunlight or near a heat source.

Store in a secure place. Do not give your medicine to anyone else.

Do not use SATIVEX® after the expiry date shown on the product packaging.

Return unused portion of SATIVEX® to the pharmacy for safe disposal or dispose of according to local regulations.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

1. Report online at www.healthcanada.gc.ca/medeffect
2. Call toll-free at 1-866-234-2345
3. Complete a Canada Vigilance Reporting Form and:
   - Fax toll-free to 1-866-678-6789, or
   - Mail to: Canada Vigilance Program
     Health Canada
     Postal Locator 0701D
     Ottawa, Ontario
     K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health care professionals can be obtained by contacting the importer, Bayer Inc., at: 1-800-265-7382.

E-mail: canada.medinfo@bayer.com
Bayer Canada web address: www.bayer.ca

Manufactured by: GW Pharma Ltd., Salisbury, Wiltshire UK, SP4 0JQ

Distributed in Canada by: Bayer Inc., Toronto, Ontario M9W 1G6

This leaflet was prepared by GW Pharma Ltd.
Last revised: August 11, 2010.

PRODUCT MONOGRAPH

^{N} CESAMET®

Nabilone

Capsules; 1mg, 0.5 mg, 0.25 mg

Antiemetic

Valeant Canada limitée/Limited
4787 Levy Street,
Montreal, Quebec H4R 2P9

Date of Revision:
March 17, 2009

Submission Control No: 124406

NAME OF DRUG

^{N}CESAMET® capsules

(nabilone)

THERAPEUTIC CLASSIFICATION

Antiemetic Agent

ACTION

^{N}CESAMET® (nabilone) is a synthetic cannabinoid with antiemetic properties which have been found to be of value in the management of some patients with nausea and vomiting associated with cancer chemotherapy. It also has sedative and psychotropic effects.

After oral administration, comparable peak plasma levels of nabilone and of its carbinol metabolite were attained within 2 hours. The combined plasma concentrations of nabilone and of its carbinol metabolite accounted for, at most, 10 to 20% of the total radiocarbon concentration in plasma. The plasma half-life of nabilone was approximately 2 hours, while that of the total radiocarbon was of the order of 35 hours.

Of the two major possible metabolic pathways, stereo-specific enzymatic reduction and direct enzymatic oxidation, the latter appears to be the more important in man.

The drug and its metabolites are eliminated mainly in the feces (approximately 65%) and to a lesser extent in the urine (approximately 20%). The major excretory pathway is the bilary system.

INDICATIONS

Adults: > 18 years

^{N}CESAMET® (nabilone) is indicated for the management of severe nausea and vomiting associated with cancer chemotherapy.

Pediatrics: < 18 years

The safety and efficacy of ^{N}CESAMET® in the pediatric population have not been established and its use is not recommended in this patient population.

Geriatrics: > 65 years

^{N}CESAMET® should be used with caution in the elderly. (See PRECAUTIONS).

CONTRAINDICATIONS

^{N}CESAMET® (nabilone) is contraindicated in patients with known sensitivity to marijuana or other cannabinoid agents, and in those with a history of psychotic reactions.

WARNINGS

^{N}CESAMET® (nabilone) should be used with extreme caution in patients with severe liver dysfunction and in those with a history of non-psychotic emotional disorders.

^{N}CESAMET® should not be taken with alcohol, sedatives, hypnotics, or other psychotomimetic substances.

^{N}CESAMET® should not be used during pregnancy, in nursing mothers, or pediatric patients since its safety under these conditions has not been established.

PRECAUTIONS

Since ^{N}CESAMET® (nabilone) will often impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car and operating machinery, the patient should be warned accordingly and should not be permitted to drive or engage in dangerous tasks until the effects of nabilone are no longer present.

Adverse psychotropic reactions can persist for 48 to 72 hours following cessation of treatment.

Since ^{N}CESAMET® elevates supine and standing heart rates and causes postural hypotension, it should be used with caution in the elderly and in patients with hypertension or heart disease.

Drug Interactions: Potential interactions between ^{N}CESAMET®, and diazepam; sodium secobarbital; alcohol; or codeine, were evaluated. The depressant effects of the combinations were additive. Psychomotor function was particularly impaired with concurrent use of diazepam.

Pediatric Use: The safety and efficacy in children under the age of 18 has not been established. Therefore the use of ^{N}CESAMET® in this patient population is not recommended.

ADVERSE REACTIONS

The most frequently observed adverse reactions to nabilone and their incidences reported in the course of clinical trials were as follows: drowsiness (66.0%), vertigo (58.8%), psychological high (38.8%), dry mouth (21.6%), depression (14.0%), ataxia (12.8%), blurred vision (12.8%), sensation disturbance (12.4%), anorexia (7.6%), asthenia (7.6%), headache (7.2%), orthostatic hypotension (5.2%), euphoria (4.0%) and hallucinations (2.0%).

The following adverse reactions were observed in less than 1% of the patients who were administered nabilone in the course of the clinical trials: tachycardia, tremors, syncope,

nightmares, distortion in the perception of time, confusion, dissociation, dysphoria, psychotic reactions and seizures.

Spontaneously Reported Adverse Reactions: The following adverse reactions listed in order of decreasing frequency by body system have been reported since ^{N}CESAMET® has been marketed. All events are listed regardless of causality assessment.

Blood and Hematopoetic: Leukopenia

Cardiovascular: Hypotension and tachycardia

Eye and Ear: Visual disturbances

Gastrointestinal: Dry mouth, nausea, vomiting, and constipation

Nervous System: Hallucinations, CNS depression, CNS stimulation, ataxia, stupor, vertigo, convulsion, and circumoral paresthesia

Psychiatric: Somnolence, confusion, euphoria, depression, dysphoria, depersonalization, anxiety, psychosis, and emotional lability

Miscellaneous and Ill-Defined Conditions: Dizziness, headache, insomnia, abnormal thinking, chest pain, lack of effect, and face edema

SYMPTOMS AND TREATMENT OF OVERDOSE

Signs and Symptoms: Signs and symptoms which might be expected to occur are psychotic episodes including hallucinations, anxiety reactions, respiratory depression and coma (experience with cases of overdosage of more than 10 mg/day has not yet been reported).

Treatment: Overdosage may be considered to have occurred, even at prescribed dosages, if disturbing psychiatric symptoms are present. In these cases, the patient should be observed in a quiet environment and supportive measures, including reassurance, should be used. Subsequent doses should be withheld until patients have returned to their baseline mental status; routine dosing may then be resumed if clinically indicated. In such instances, a lower initiating dose is suggested.

If psychotic episodes occur, the patient should be managed conservatively, if possible. For moderate psychotic episodes and anxiety reactions, verbal support and comforting may be sufficient. In more severe cases, antipsychotic drugs may be useful; however, the utility of antipsychotic drugs in cannabinoid psychosis has not been systematically evaluated. Support for their use is drawn from limited experience using antipsychotic agents to manage cannabis overdoses. Because of the potential for drug-drug interactions (eg, additive CNS depressant effects due to nabilone and chlorpromazine), such patients should be closely monitored.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

The use of forced diuresis, peritoneal dialysis, hemodialysis, charcoal hemoperfusion, or cholestyramine has not been reported. In the presence of normal renal function, most of a dose of nabilone is eliminated through the biliary system.

Treatment for respiratory depression and comatose state consists in symptomatic and supportive therapy. Particular attention should be paid to the occurrence of hypothermia. If the patient becomes hypotensive, consider fluids, inotropes, and/or vasopressors.

DOSAGE AND ADMINISTRATION

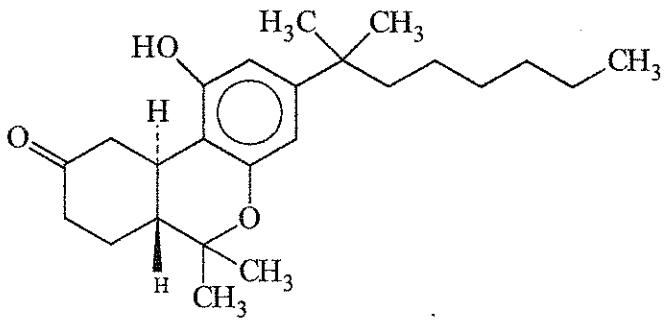
Adults:

The usual dosage of ^{N}CESAMET® (nabilone) is 1 mg or 2 mg twice a day. The first dose should be given the night before initiating administration of chemotherapeutic medication. The second dose is usually administered 1 to 3 hours before chemotherapy. If required, administration of ^{N}CESAMET® can be continued up to 24 hours after the chemotherapeutic agent is given. The maximum recommended daily dose is 6 mg in divided doses.

^{N}CESAMET® is available in 0.25 mg and 0.5 mg strengths for dose adjustment within the therapeutic range. Dose adjustment may be required for the purposes of response and tolerance in individual patients. Overdosage may occur even at prescribed dosages, if disturbing psychiatric symptoms are present. In these cases, the patient should be observed in a quiet environment and supportive measures, including reassurance, should be used. Subsequent doses should be withheld until patients have returned to their baseline mental status; routine dosing may then be resumed if clinically indicated. In such instances, a lower initiating dose is suggested.

^{N}CESAMET® contains nabilone in a capsule dosage form and is intended only for oral administration.

STRUCTURAL FORMULA AND CHEMISTRY



Molecular Formula: $C_{24}H_{36}O_3$

Molecular Weight: 372

U.S.A.N: Nabilone

Chemical Name: trans(+)-3-(1,1-dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9H-dibenzo(b,d),pyran-9-one

Description: White crystalline powder

Composition:

Each 1 mg ^{N}CESAMET® capsule contains 1 mg of nabilone, starch, povidone, gelatin, FD&C blue #2 (indigo carmine), red iron oxide, and titanium dioxide.

Each 0.5 mg ^{N}CESAMET® capsule contains: 0.5 mg of nabilone, starch, povidone, gelatin, titanium dioxide, D&C red # 33, D&C yellow # 10, FD&C red # 40.

Each 0.25 mg ^{N}CESAMET® capsule contains: 0.25 mg of nabilone, starch, povidone, gelatin, titanium dioxide, D&C yellow # 10, FD&C blue #1, FD&C red # 40.

Stability and Storage Recommendations:

Store at controlled room temperature at 15-30°C.

AVAILABILITY

^{N}CESAMET® 1 mg capsule: each No. 2 hard gelatin capsule, opaque blue cap and white body, imprinted ICN logo on the cap and 3101 on the body, contains 1 mg of nabilone and are available in bottles of 50 capsules.

^{N}CESAMET® 0.5 mg capsule: each No. 4 hard gelatin capsule, opaque red cap and white body, imprinted ICN logo on the cap and 3102 on the body, contains 0.5 mg of nabilone and are available in bottles of 50 capsules.

^{N}CESAMET® 0.25 mg capsule: each No. 4 hard gelatin capsule, opaque green cap and white body, imprinted ICN logo on the cap and 3103 on the body, contains 0.25 mg of nabilone and are available in bottles of 50 capsules.

^{N}CESAMET® (nabilone) legally is considered to be a narcotic and is subject to the controls which apply to those drugs.

PHARMACOLOGY

Nabilone has neurologic, endocrinologic and cardiovascular activity in animals although these may not be valid predictors of effects in a clinical setting.

Nabilone produces ataxia and hypoactivity; by the oral route, it is twice as active as Δ^{9} THC. In rabbits and in rhesus monkeys, doses of 0.064 and 0.01 mg/kg, respectively, caused a modest decrease in blood pressure. Massive doses of 3 mg/kg caused sustained, alternating periods of hypotension and hypertension in rhesus monkeys. Doses of 0.064 mg/kg in dogs caused a modest, delayed increase in blood pressure.

Standard behavioural assays were used to evaluate psychoactive effects. Nabilone slowed muricidal activity in rats, reduced reactivity of septal-lesioned rats, slowed self-stimulation, reduced food consumption and increased reactivity to touch. In most operant conditioning studies nabilone depressed responding.

Nabilone effectively antagonized emetic doses of carmustine and of mechlorethamine in cats. Naloxone antagonized the anti-emetic effect of nabilone in apomorphine or deslanoside-induced emesis in cats.

Nabilone is rapidly absorbed and extensively metabolized in rats, dogs, monkeys and man.

Two major metabolic pathways appear to be involved in the bio-transformation of nabilone. One is the stereo-specific enzymatic reduction of nabilone to two metabolites, the RRS and the SSS carbinols. A second possible metabolic pathway is the direct enzymatic oxidation of the aliphatic side-chain of nabilone, without prior reduction of the 9-keto moiety, to produce hydroxylic and carboxylic analogs.

In the dog, the stereo-specific reduction pathway appears to be the more important, and possibly the only, pathway involved. This probability is supported by the high concentrations of the SSS carbinol metabolite found in dog plasma and brain tissue, as compared to those concentrations found in monkeys.

In the dog, peak plasma concentrations of nabilone and of the SSS metabolite occurred two hours after an oral dose. Carbinol levels were 3 to 4 times greater than those of nabilone, and the combined concentrations accounted for essentially all of the plasma radiocarbon. The concentration of the SSS carbinol in brain tissue was 2 to 4 times greater than that found in plasma. The plasma half-life of nabilone was approximately 2 hours, while that of the radiocarbon and of the metabolite was over 30 hours. Furthermore, after repeated dosing, the SSS carbinol accumulated in brain tissue in the dog, but not in the monkey. It is thought that the presence of these high concentrations of metabolite in plasma and brain over time may have played a role in the toxicity of nabilone observed in the long-term canine study.

In the monkey, the kinetics of nabilone are different from the dog but similar to those in man (see ACTION section). Furthermore, in the monkey and in man, the two metabolic pathways appear to be involved, the more important one also being direct enzymatic oxidation.

Antiemetic Effects of Nabilone in Animals:

The antiemetic activity of nabilone was evaluated in cats against carmustine (BCNU) and mechlorethamine (HN2). Without pretreatment, BCNU at 10 to 20 mg/kg evoked vomiting with an incidence of 50 percent (11 of 22 trials) and an average latency of 145 minutes. In contrast, after pretreatment with nabilone, BCNU failed to cause vomiting in any of 14 trials. HN2 at 5 mg/kg proved to elicit vomiting uniformly and promptly, with an average latency of 15 minutes. In the presence of nabilone, HN2 elicited vomiting in only 2 of 8 trials after the prolonged average latency of 209 minutes.

Nabilone is effective in reducing cis-platinin induced emesis of pigeons. Doses as low as 0.02 mg/kg, I.M., decreased the emetic episodes induced by a dose of 8 mg/kg, I.V., of cis-platinin. Nabilone is approximately 80 to 160 times more potent than prochlorperazine in this test system. Prochlorperazine effectively blocks apomorphine-induced emesis at doses of 0.125, 0.25 and 0.5 mg/kg, I.V. Nabilone, on the other hand, was totally ineffective in blocking apomorphine-induced emesis at doses of 0.008, 0.016 and 0.032 mg/kg, I.V.

HUMAN PHARMACOLOGY

Radiolabeled ^{14}C-nabilone formulated with PVP was administered orally to two fasted subjects in a 2 mg dose containing 48 μCi of radioactivity. The plasma concentration of ^{14}C-nabilone equivalence reached approximately 10 ng/mL at 1 to 2 hours and then disappeared exponentially with time. After the oral administration of the ^{14}C-nabilone-PVP formulation, 60 percent of the radioactivity was recovered in feces and 24 percent was recovered in urine for a total recovery of 84 percent.

Intravenous studies were conducted with a solution obtained by dissolving nabilone in ethanol. A 0.5 mg intravenous dose of ^{14}C-labeled nabilone administered to 5 normal subjects resulted in a mean area under the plasma concentration curve of 90 ng/hr/mL. Approximately 22 percent of

the radioactivity was recovered in urine and approximately 67 percent was recovered in feces. Less than 1 percent was recovered as expired CO_2.

The mean area under the plasma concentration curve after a 2 mg oral dose in two subjects was 345 ng/hr/mL. The percentages of radioactivity excreted in urine and feces after the oral and intravenous administration of nabilone are in good agreement.

This supports the view that most of the oral dose was absorbed. The results further indicate that within the dose range studied, the elimination of the drug was independent of the route of administration and the size of the dose.

^{14}C-nabilone (0.5 mg, 12 μCi) was administered by the intravenous route to 5 subjects. Plasma concentration of total radioactivity disappeared after dosing in at least a biphasic manner with the initial phase representing uptake and distribution into tissues, while the latter phase presumably represented metabolism and subsequent excretion of the drug.

The alcoholic metabolite forms rapidly and disappears at a slower rate than the parent compound. The mean plasma half life of total radioactivity for the five subjects was 20.6 ±1.3 hours over a range of 17 to 25 hours.

Chronic oral administration of nabilone 1 mg t.i.d. for 14 days resulted in no significant accumulation of nabilone or carbinol.

TOXICOLOGY

Acute Toxicity:

The oral LD_{50} of nabilone was >1000 mg/kg in mice, >2000 mg/kg in rats, >1 mg/kg in cats and >5 mg/kg in monkeys. The oral and intravenous LD_{50} in dogs was higher than 1 mg/kg. Signs

of toxicity included hypoactivity, ataxia and respiratory depression in all species. Dogs given singly intravenous doses of 1 mg/kg promptly became ataxic and lost consciousness for about 48 hours.

Subacute Toxicity:

Rats: Nabilone was administered to rats for 14 consecutive days, at a dose of 0.8 mg/kg, by the intravenous route. Two animals died during the study. Effects seen after dosing included loss of righting reflex, intermittent tonic convulsions, hypnosis, vocalization, Straub tail and hypothermia.

Nabilone was administered in the diet to rats for 92 days, at dosage levels of 6.25, 12.50 and 25.00 mg/kg. Hypothermia was observed in all treated animals during the first 24 hours. During the first week, catatonia and hyperirritability to touch occurred in the high-dose group. Slight to moderate decreases in body weight gains occurred in all treated groups.

Dogs: Intravenous doses of 0.4 mg/kg/day were administered to dogs for 14 days. Effects observed after dosing included hyperirritability to touch, sedation, respiratory depression, fine tremors, ataxia and anorexia. All dogs developed thrombophlebitis at the injection site.

Nabilone also was administered orally for 3 months at dose levels of 0.25, 0.5, and 1.0 mg/kg/day. During the first week, ataxia was seen in the mid and high-dose group and anorexia in the high-dose group.

Chronic Toxicity:

A year-long study in dogs was initiated, but terminiated after 7 months due to high mortality. Nabilone was administered orally at dose levels of 0.5, 1.0 and 2.0 mg/kg/day. Eight dogs per dose were treated. Most deaths were preceded by convulsions. No histopathologic lesions were found in the brain or other tissues. The occurrence of convulsions and death in these dogs was believed to be due to the accumulation of a toxic metabolite in the plasma and the brain.

A subacute study in which the toxicity of nabilone was compared to that of SSS carbinol was conducted in dogs. Nabilone and the SSS carbinol were administered daily for five days, intravenously, to 1 male and 1 female per drug, at the dose of 2 mg/kg. One nabilone-treated dog became moribund and was sacrificed on the second day. Anorexia, ataxia, hypoactivity, emesis and shivering were observed in both treated groups. Plasma levels of the SSS carbinol were 27 - 37 times higher than the levels of nabilone. No convulsions occurred. Tissue levels of the SSS carbinol or of nabilone in the brain were not determined.

Doses of 0.0, 0.1, 0.5, and 2.0 mg/kg/day of nabilone were administered by the nasogastric route to Rhesus monkeys for one year. An additional group was given 2.0 mg/kg/day on an intermittent schedule: two-week periods of treatment each followed by an interval of two weeks of treatment. The only changes noted were hypoactivity and sedation which occurred the first two days at the mid- and high-dose levels. Transient periods of anorexia and isolated instances of ataxia and emesis also were noted at the high-dose level.

Teratogenic Studies:

Nabilone was administered orally to pregnant rats on gestation days 6 through 15 at doses of 1, 4 and 12 mg/kg. Hypoactivity and, when handled, hyperirritability and hypertonia were observed during the first three days of treatment. Anorexia and weight loss occurred in all treated groups. Litter size was decreased and resorption incidences increased. The body weights of fetuses from treated animals were slightly reduced.

Nabilone was administered orally to gravid rabbits on gestation days 6 through 18 of 0.7, 1.6 and 3.3 mg/kg. Anorexia and decreased body weight occurred in the mid- and high-dose groups. One rabbit each in the low- and mid-dose groups. and three rabbits in the high-dose, aborted and resorption incidences were increased at the mid- and high-dose levels.

Reproduction Studies:

Nabilone was administered in the diet to rats at dose levels of 1, 4 and 12 mg/kg. Male and female rats were treated, respectively, for 60 and 17 days prior to mating; in females, nabilone

administration continued through mating, gestation and lactation periods. Dose-related decrease in body weight and food consumption occurred in both male and female rats. The mean liveborn litter size in the high-dose group was decreased due to increased number of stillborn.

Perinatal and Postnatal Studies:

Nabilone was administered by gavage to pregnant rats at doses of 1, 4 and 12 mg/kg from gestation day 14 through post-partum day 21. Maternal food intake and body weight gain were decreased in treated dams. Mean litter size and survival values were significantly decreased in the high-dose group: only 4 litters survived through post-partum day 7 and the remainder of the study. Progeny survival in the mid-dose group was slightly decreased. The initial body weights of pups in the mid- and high-dose groups were depressed, and hypothermia was observed in pups from the high-dose group.

Dominant-Lethal Tests in Rats:

Two studies were conducted using the nabilone-PVP co-precipitate, the results were not indicative of a dominant- lethal effect.

Micronucleus Test:

There was no treatment-related effect on the incidence of micronuclei in rat bone marrow polychromatic erythrocytes.

Hypothermia in Rats:

Nabilone produced hypothermia in rats, the response was not significantly altered by differences in the age, sex, or nutritional status of the nabilone-treated rats.

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PART III: CONSUMER INFORMATION

N CESAMET®
nabilone

This leaflet is part III of a three-part "Product Monograph" published when CESAMET® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CESAMET®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
CESAMET® (nabilone) is indicated for the management of severe nausea and vomiting associated with cancer therapy.

What it does:
CESAMET® decreases nausea (sensation of feeling sick) and vomiting.

When it should not be used:
You should not take CESAMET® if:
- you have known sensitivity to marijuana or other cannabinoid agents
- you have a history of psychotic reactions
- you are under the age of 18 years
- you are breastfeeding
- you are pregnant

What the medicinal ingredient is:
The medicinal ingredient in Cesamet® is nabilone, a synthetic cannabinoid agent.

What the non-medicinal ingredients are:
Cesamet® contains the following non-medicinal ingredients: D&C red #33 (0.5 mg capsule), D&C yellow #10 (0.25 and 0.5 mg capsules), FD&C blue #1 (0.25 mg capsule), FD&C blue #2 (1 mg capsule), FD&D red #40 (0.25 and 0.5 mg capsules), gelatin, iron oxide red (1 mg capsule), povidone, starch, and titanium dioxide.

What dosage forms it comes in:
Cesamet® (nabilone) is formulated into capsules of 0.25 mg, 0.5 mg, or 1 mg strengths for oral administration.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
- Since CESAMET® will often impair the mental and/or physical abilities required for the performance of potentially hazardous task, you should not drive a car, operate machinery, or perform any activity that requires mental alertness until the effects of CESAMET are no longer present.
- While taking CESAMET®, do not drink alcohol or take other drugs such as sedatives, hypnotics or other substances that can affect the nervous system without consulting with your doctor.
- CESAMET® should be used with extreme caution if you have severe liver dysfunction or a history of non-psychotic emotional disorders.

BEFORE you use CESAMET® talk to your doctor or pharmacist if:
- you are taking any other prescription or non-prescription medicine, or natural/herbal remedies
- you are pregnant or breastfeeding
- you are allergic to nabilone, the main ingredient in CESAMET®, or any other ingredient in CESAMET® (see "What the non-medicinal ingredients are")
- you have hypertension or heart problems

INTERACTIONS WITH THIS MEDICATION

While you are taking CESAMET, do not start any new medicines, including natural or herbal medicines, without speaking to your doctor first. Tell your doctor about all the medicines that you are taking including those that you have bought yourself.

CESAMET can interact with:
- Diazepam
- Sodium secobarbital
- Alcohol
- Codeine
- Any medicine that affects your mental and psychomotor function (e.g., causes hallucinations, weird thoughts, etc).

PROPER USE OF THIS MEDICATION

The label on the container of your medicine should tell you how often to take your medicine and how many doses you should take each time. If not, or if you are not sure, ask your doctor or pharmacist.
Do not take more doses, or take them more often than your doctor prescribes.
Your doctor prescribed CESAMET® for your use only. You should not let anyone else use it.

Usual adult dose:
You will receive CESAMET prior to chemotherapy and, if necessary, after cancer treatment. Based on how likely you are to experience nausea and/or vomiting, caused by your cancer treatment, your doctor will tell you the amount you need to take and how frequently. Follow the directions provided by your doctor for using this medicine. Your doctor may also have to adjust your dose depending on how you react to CESAMET.

Overdose:
Some of the signs of overdose are psychotic episodes including hallucinations, anxiety reactions, respiratory depression, and coma.

Overdose may even occur at prescribed doses. If psychiatric symptoms (e.g., weird thoughts, hallucinations, etc.) are present, contact poison control centre immediately or go to the nearest emergency room.

Missed Dose:
If you forget a dose of CESAMET®, you should take it as soon as you remember. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. **Do not** double your dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Some patients may experience drowsiness, psychological high, vertigo, dry mouth, depression, ataxia, asthenia, blurred vision, sensation disturbance, anorexia, headache, orthostatic hypotension, euphoria, and hallucinations. You should tell your doctor or pharmacist about these symptoms.

If your nausea (feeling of sickness) or vomiting do not improve while taking CESAMET, consult your doctor for further advice.

If you feel unwell or have any symptoms that you do not understand, you should contact your doctor immediately.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek emergency medical assistance
		Only if severe	In all cases	
Common	Drowsiness		✓	
	Dry mouth	✓		
	Euphoria		✓	
	Hallucinations			✓
	Somnolence		✓	
	Vertigo		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek emergency medical assistance
		Only if severe	In all cases	
Uncommon	Confusion			✓
	Depression		✓	
	Dissociation			✓
	Headache	✓		
	Orthostatic hypotension		✓	
	Nightmares		✓	
	Seizure			✓
	Tachycardia		✓	
	Tremors		✓	

This is not a complete list of side effects. For any unexpected effects while taking CESAMET®, contact your doctor or pharmacist immediately.

HOW TO STORE IT

Keep CESAMET® out of reach of children. Store it at room temperature (15 to 30°C) in the package it came in.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345
By toll-free fax: 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Valeant Canada, at:
1-800-361-4261

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