

NOTICE

Our file number: 07-114023-876

Release of final Health Canada document: Clinical Assessment of Abuse Liability for Drugs with Central Nervous System Activity

The final version of the Health Canada guidance document *Clinical Assessment of Abuse Liability for Drugs with Central Nervous System Activity* is now available. This guidance document replaces the draft of the same title published for consultation on March 21, 2006. The effective date for this document is December 7, 2007.

This guidance document is intended to protect the health and well being of patients receiving pharmaceuticals and the general public by promoting a strategic approach to the assessment of abuse liability during the clinical drug development process and post-marketing. Sponsors are expected to consider these recommendations when designing clinical trial programmes for drugs which fall within the scope of the guidance document.

Comments and suggestions received from the consultation on the draft version of the guidance were reviewed and considered in the finalization of this document. A tabulation summarizing the comments received during the external consultation and the outcome of the Health Canada discussion of these comments is available on request.

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GUIDANCE DOCUMENT

Clinical Assessment of Abuse Liability for Drugs with Central Nervous System Activity

Published by authority of the
Minister of Health

Date Adopted	2007/05/16
Effective Date	2007/12/07

Health Products and Food Branch

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Également disponible en français sous le titre : Évaluation clinique du risque d'abus associé aux médicaments qui agissent sur le système nerveux central

FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document **may be** acceptable provided they are supported by adequate 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 document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

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1. BACKGROUND

The clinical assessment of abuse liability is an important element of the safety evaluation of many new drugs that possess central nervous system (CNS) activity, either as a component of their intended therapeutic action or as an undesired collateral effect.

In the context of psychoactive pharmaceutical products, abuse liability refers to the likelihood that a drug product could be subject to user-initiated, non-therapeutic self-administration. Drugs with primary or secondary central nervous system activity that have been subject to abuse encompass members of a wide range of therapeutic classes including, but not limited to, general, local, and dissociative anaesthetics; centrally-acting analgesics; sedative-hypnotics; anxiolytics; appetite suppressants; decongestants; antitussives; antihistamines; antiemetics; antidiarrheals; and drugs used to treat narcolepsy and Attention Deficit Hyperactivity Disorder. While products in all of these classes have CNS activity, the extent to which they have abuse liability varies substantially. There are examples of drugs within many of these classes that are not scheduled as controlled substances under the *Controlled Drugs and Substances Act* (CDSA) in Canada.

Structural and functional drug classes that have been associated with abuse syndromes include opioids, CNS depressants, CNS stimulants, cannabinoids, nicotine-like compounds, glutamate antagonists, and N-methyl-D-aspartate (NMDA) antagonists.

A clinical assessment of abuse liability plays an important role in providing information to guide decisions concerning the approvability, scheduling, and labelling of a new drug.

2. OBJECTIVES

This guidance document is intended to protect the health and well being of patients receiving pharmaceuticals and the general public by promoting a strategic approach to the assessment of abuse liability during the clinical drug development process and post-marketing. The results of the recommended studies and evaluations should be used to guide risk-benefit assessments and decisions relating to drug approval, scheduling, prescribing information, information for the consumer, and risk management programmes.

3. SCOPE

This guidance document is applicable to new pharmaceuticals that have central nervous system activity, either as a component of their therapeutic effect or as an undesired collateral effect. The recommendations contained herein may also be applicable to Supplemental New Drug Submissions when new administration routes, dose forms, or formulations are being developed that result in increased systemic exposure, alterations in the onset or duration of the effect (e.g., controlled or delayed release formulations), improved palatability, tamper resistance, or other differences that might either increase or decrease the abuse liability of the product.

Some of the recommendations contained in this guidance document might also be relevant to marketed drugs, if a re-evaluation of their abuse liability indicates the need for further clinical evaluation, such as a controlled post-market pharmacovigilance study (see section 6).

The abuse liability of drugs that do not act centrally, such as anabolic steroids, would be assessed by other approaches and is not the subject of this guidance document.

4. CLINICAL ABUSE LIABILITY STUDY

A clinical pharmacology study of abuse liability should be performed if indicated by an integrated review of the relevant available data, including the following considerations:

- **Physicochemical Characteristics/Formulation:** Concerns regarding abuse liability arise when a new chemical entity is related to a structural class of drugs that is associated with abuse liability. These concerns would be intensified if the new chemical entity is an immediate precursor, salt, or derivative of a substance that is already scheduled under the *Controlled Drugs and Substances Act* in Canada or if it has physicochemical characteristics that would increase the potential for abuse by means of intravenous injections or smoking (e.g., high aqueous solubility, stability at temperatures that produce a vapour). The results of *in vitro* extractability studies may be of assistance in judging whether the formulated product is amenable to tampering or extraction in clandestine laboratories for illicit use.
- **Non-clinical Pharmacology:** The possibility of abuse liability should be considered for any drug that penetrates the blood-brain barrier. Concern is justified if the new chemical entity belongs to or shares relevant CNS activity with a pharmacological class of drugs that is associated with abuse liability or if it exhibits a new mechanism of CNS action for which there is no clinical experience. Useful preliminary information on abuse liability can be gained from ligand binding studies, functional *in vitro/ex vivo* assays, safety pharmacology core battery studies (e.g., tests of sedation, excitation), as well as studies of primary or secondary pharmacodynamic effects. The occurrence of withdrawal reactions in spontaneous or precipitated withdrawal tests is informative regarding the potential of a test substance to produce physical dependence. Non-clinical safety pharmacology studies specifically designed to quantify various parameters of drug-seeking behaviour include self-administration tests and drug discrimination tests. Self-administration paradigms, in which laboratory animals are given the opportunity to self-administer the test substance by performing operant responses that are linked to drug delivery, are considered to provide the most direct non-clinical evidence of abuse liability.
- **Clinical Trials:** Suspicions concerning abuse liability might arise if a new chemical entity is associated with adverse events suggestive of abuse liability (e.g., euphoria), excessive use or diversion, physical dependence, or tolerance (see Section 5).

- **Post-Marketing Experience:** Evidence of drug abuse might emerge from post-marketing controlled clinical trials, spontaneous adverse event reports, surveys, or epidemiological studies (see Section 6).

The clinical abuse liability study should generally be performed at a time point in the drug development programme when the therapeutic dose range, final formulation, and adverse event profile have been established, although earlier scheduling should be considered, if warranted by clinical risk. Compliance with Good Clinical Practices (GCPs) is expected.

In cases where there is already compelling evidence of drug abuse from post-marketing experience, the clinical abuse liability study might be considered optional if the available data are sufficient to support appropriate decisions about approval, labelling, and scheduling.

4.1 Subjects

Human abuse liability studies are generally performed in experienced, recreational, non-therapeutic drug users. Volunteers should be selected who have experience with drugs from the same pharmacological class as the investigational drug and the selected positive control. If the investigational drug represents a new pharmacologic mechanism, volunteers should be selected who have experience with drugs of similar psychoactive properties (e.g., sedative, stimulant). Experienced drug users usually display better tolerability for the CNS effects of the test drugs than do healthy volunteers with no history of abuse of drugs of that class (see Section 4.3).

These subjects can use their experience with similar drugs as a basis upon which to compare the investigational drug (e.g., estimating its street value, categorizing it in relation to drugs of known abuse liability). Individuals with histories of polydrug abuse are particularly useful in this regard. The characteristics of the study population with respect to past and current drug use and abuse should be presented in detail (e.g., drugs abused, drug of choice, duration of abuse or abstinence). For ethical reasons, the selected volunteers should not meet any of the following criteria:

- history of or current *Diagnostic and Statistical Manual of Mental Disorders* Fourth Edition (*DSM-IV*) diagnosis of substance dependence
- currently seeking or participating in treatment for substance-related disorders
- history of participation in treatment for substance-related disorders, including successful completion of such treatment

Conduct of these studies in individuals with no history of abuse should usually be avoided, as the risk of false negative results is greater than in subjects with known vulnerability. An exception is the case of nicotine replacement products, which can be studied in cigarette smokers without histories of other drug abuse.

Prior to exposure to the drugs, subjects should be given an opportunity to perform the tests, use computer-based data collection devices, and demonstrate that they can follow directions and be co-operative.

Human abuse liability studies should be conducted in clinical pharmacology laboratory settings. If subjects are not confined to the laboratory during the washout periods separating consecutive treatments, they should be screened for drugs of abuse prior to each administration of study medication. Because high doses of the test drugs are often administered in these trials, equipment and expertise should be immediately available to deal with any severe or serious adverse events.

4.2 Design

4.2.1 General Considerations

The preferred design for clinical abuse liability studies is usually a double-blind, multiple arm, complete, balanced crossover, in which subjects are randomized to receive all treatments. In some cases, a complete crossover design study might be difficult to perform if there are many treatment arms, if the drug and/or its active metabolites have long half-life values, such that lengthy time periods would be required to achieve washout; or if carryover effects are anticipated for other reasons. An alternative to consider in these situations is a balanced incomplete crossover design, in which subjects are randomized to receive placebo and a subset of the active treatments, under crossover conditions. A fixed order nested design, whereby subjects are nested in a few fixed order sequences, might be useful when the investigational drug has a long half-life. To minimize problems with validity and generalizability, this alternative design must be carefully planned, taking into account possible period or learning effects and the potential for dropouts.

4.2.2 Treatments

Both placebo and positive control treatment arms should be included. The positive control for a study of a new chemical entity should be a drug of known abuse liability, preferably from the same pharmacological class as the investigational drug and having a similar time course. The ability of the positive control treatment to produce dose-dependent, statistically significant effects on the primary outcome measures will serve to establish validity and define sensitivity. Scheduling of the abuse liability assessments will be facilitated if the investigational drug and the positive control are similar in terms of the time course of their effects. In some cases, a separate reference agent might be useful in addition to the positive control to assist in the assessment of relative risk and scheduling determinations.

Formulations that are intended to mitigate abuse liability (e.g., altered absorption rate, long half-life, tamper resistance, combination products) should be studied for relative abuse liability in clinical pharmacology studies in which the new formulation is directly compared with the immediate-release formulation of the same compound. Study of an immediate-release formulation will be important, even for new drugs that are being developed as a controlled- or delayed-release formulation only, as addicts can be expected to endeavour to reduce any formulation to its immediate-release state. A larger sample size may be needed to detect differences between the new formulation and the immediate-release formulation or the new formulation and placebo.

If the investigational drug is a ‘prodrug’ that is metabolized to an active compound of known abuse liability, the positive control should be an approved dose form/formulation of the active compound in question.

If the investigational drug does not belong to an established pharmacological class or has atypical actions, a positive control should be selected from one or more pharmacological classes of abusable drugs that possess some properties in common with the investigational drug (e.g., CNS depression or stimulation).

In some cases, a negative control arm might also be appropriate. The negative control is typically a compound of the same or similar pharmacological class, which exerts effects on behaviour, but is not scheduled as a controlled substance (e.g., pseudoephedrine for stimulants). If the investigational drug does not belong to an established pharmacological class, a negative control can be chosen that possesses properties in common with the investigational drug. Use of a negative control can help to confirm appropriate specificity in the study and provide additional comparative information for interpretation of signal intensity.

4.2.3 Pre-Testing Qualification Phase

Testing of subjects who do not reliably exhibit a positive response to treatment with drugs of known abuse liability will result in false negative conclusions. Testing of subjects who will respond positively to any drug can lead to the conclusion that drugs of low abuse potential have an abuse liability similar to morphine or amphetamine.

For these reasons, a pre-testing qualification phase can be useful for enrichment of the subject pool. This qualifying session is typically of double-blind, crossover design in which subjects are randomized to receive placebo and a positive control, consisting of a drug of known abuse liability, usually from the same pharmacological class as the investigational drug. The primary goal of the qualification procedure is to identify subjects who report ‘liking’ the positive control, being willing to pay more for the positive control than for placebo, and/or experiencing pharmacological effects that are

consistent with the known pharmacology of the prototypical drug. Only subjects who demonstrate the ability to distinguish the positive control drug from placebo would qualify for eligibility in the main study. Although all tests would be practised during this phase, only a subset of relevant measures of interest would form the basis of the decision about qualification of the subject for the main study.

4.3 Dose Selection and Route of Administration

The administration route used in the abuse liability study should generally be the same as that intended for therapeutic use. Because parenteral dosing circumvents first pass metabolism, the metabolite profile following intravenous or intramuscular dosing may differ substantially from that following oral dosing, with important implications for subjective effects. Differences in the onset and duration of the drug effect between administration routes would also be expected to influence abuse liability. When multiple administration routes are being pursued in a particular drug submission, an abuse liability study may be needed for each. However, if there is no evidence of abuse using the route of administration with the fastest onset of action, evaluation of a slower onset route would generally not be needed, provided that the profile of major active metabolites was not different.

Oral products can often be altered by drug abusers to permit administration by other routes (e.g., parenteral, inhalational) to achieve a faster onset of action and a better ‘high’. In some cases, follow-up studies with a parenteral or inhalational administration route may be informative when previous studies with a new chemical entity intended for oral use suggest cause for concern. The conduct of such studies would be dependent on the availability of a parenteral/inhalational product that meets chemistry and manufacturing standards for clinical trial use and sufficient human pharmacokinetic, pharmacodynamic, safety, and tolerability data to support the use of this administration route in an abuse liability study.

Typically two or three doses of the test drug and the positive control drug should be compared with a placebo control. Study of a broad range of doses allows characterization of the shape and slope of the dose-effect relationship and minimizes the possibility of false negative conclusions for drugs with bell-shaped dose-effect curves or mixed agonist-antagonist properties.

The doses of the positive control drug should be selected to produce effects on the outcome measures ranging from weak to strong. The inclusion of a low dose allows exploration of the sensitivity limits of the assay.

The dose range of the investigational drug should be selected to include therapeutic and high supratherapeutic doses. The testing of supratherapeutic doses is important, as drug abusers can be expected to experiment with high doses. The high dose should be the maximal tolerated dose from healthy volunteer studies with the investigational drug, unless the dose-limiting effects are CNS in nature and expected to be better tolerated in experienced users. In such cases, the high dose should be determined in a dose-escalation pilot study conducted in experienced, recreational, non-therapeutic drug users under conditions of careful safety monitoring.

Single doses of each treatment are usually administered in the main study. To avoid confounding carryover effects or adverse events due to drug-drug interactions, each treatment should be followed by a washout period of a duration sufficient to ensure elimination of the study drugs and their metabolites.

4.4 Time Course

The time course of the drug effect should be fully characterized in terms of onset, peak, duration of activity, and offset. The choice of time points should generally be guided by the plasma concentration-time profile of the investigational drug and the reference agent(s), as well as the pharmacodynamic profile, if available. Care should be taken to schedule evaluations at time points that correspond to the expected time of peak plasma concentrations of the parent compound and any active metabolites. In instances where there is a delay in the pharmacodynamic or subjective effects of a drug relative to the pharmacokinetic effects, the anticipated time of the maximal pharmacodynamic effect should be the focus of characterization. End of day or next day questions may be included to assess the overall global experience of the drug.

Drugs that have a rapid onset are generally considered to have a higher abuse liability than drugs with a more delayed onset of action.

4.5 Outcome Measures

4.5.1 General Considerations

Subjective measures of the likelihood of abuse include a variety of instruments, specially constructed scales, and questionnaires. Self-reported measures are scored on graded scales to allow subjects more opportunity to make fine distinctions. Self-reported measures of drug value and subjective price value (i.e., drug versus money) are often included and should be linked to a behavioural consequence to assure their validity. Furthermore, a number of secondary dependent variables are usually included to assess the unpleasant or dysphoric effects of the drug, psychomotor or cognitive performance, mood effects, and similarity to other drugs.

4.5.2 Outcome Measures

The sponsor should identify one or two primary outcome measures for the study. Primary outcome measures should be appropriately validated. Standardized assessment instruments include the Addiction Research Center Inventory (ARCI). Outcome measures that have not been validated may also be used, but should be considered secondary or supportive variables. The evaluation of multiple subject-rated outcome measures is typical, including visual analogue scales such as ‘Good Effects’ and instruments for the assessment of drug liking, monetary value, drug identification, side effects and mood changes, and strength of effect.

Objective measures of drug effect (e.g., psychomotor or cognitive performance and physiological measures) may be useful as a validity check to ensure appropriate pharmacological effects within and between treatment arms, and allow for a comparison of side effect profiles that may affect abuse liability. Observer ratings may also be useful. The choice of outcome measures should be based on drug class (e.g., especially measures of drug identification, side effects, mood changes, and objective measures).

Before initiating the study, the subjects should undergo standardized training in the use of all assessment instruments to avoid changes related to the acquisition of performance skills during post-randomisation treatment. Direct computer terminal presentation of the tests using validated systems facilitates the collection of data from these measures, but non-computerized methods are also acceptable.

When feasible, pharmacokinetic determinations are encouraged to assist in the interpretation of outlier data. The pharmacokinetic sampling scheme may be sparse, primarily to capture onset, peak, and decline of plasma concentrations. In some cases, an assessment of pharmacokinetic/pharmacodynamic relationships may be informative.

Adverse events and safety measures (e.g., vital signs and ECGs) should also be assessed.

4.5.3 Interpretation of Data

Abuse potential is assessed on the basis of the evaluation and integrative interpretation of the pattern of results across several groups of measures. Important considerations include the steepness of the dose-response curves and the comparison of results between the investigational drug and the positive control, any unscheduled negative control, and the placebo treatment. The time course of effects should be assessed across the various measures, particularly the critical measures. For some drugs or formulations, effects may be perceived as pleasant or neutral at early time points, but assume adverse properties at later time points.

Interpretation of these studies may be difficult in cases where multiple assessment instruments detect conflicting results or when the investigational drug and the reference agents have dissimilar properties. The interpretation of the data collected from an abuse liability study can be facilitated by organizing the report into sections based on pharmacological effect. The following outline provides an example of the way in which the report should be organized:

- Measures of Positive Response (i.e., liking or enjoying acute effects of the drug)¹
- Measures of Negative Response (i.e., disliking or dysphoric reaction to drug effects)
- Measures of Other Pharmacologic Effects (e.g., psychomotor performance or cognitive tests)
- Measures of Perceived Drug Similarity

4.5.4 Statistical Considerations

Sample size estimates and power calculations should be based on historical data with the positive control drug on the primary outcome measure or measures. The 95% confidence intervals should be provided for comparisons between treatment arms. P-values may be informative as well.

Attention should be directed to results and patterns for individual subjects, as well as analyses of central tendency. Visual displays of individual subject data can be informative. Box plots are an effective means of illustrating the distribution of effects within a treatment arm. Evidence of outliers or subgroups of subjects affected by the drug should be discussed fully.

4.6 Limitations of Human Laboratory Studies of Abuse Liability

Human laboratory studies of abuse liability can be a useful and sensitive means of detecting signals suggestive of abuse liability; however, there are limitations associated with the information derived from these studies, which should be recognized:

- The results of these studies may be clearly indicative of abuse potential or may require qualitative interpretation, with the associated risk of subjective bias.

¹ Organize the measures of positive response such that the primary measure or measures are followed by the secondary measures.

- The use of multiple outcome measures of differing sensitivity and specificity, without correction for multiplicity, can lead to conflicting results across outcome measures, with the associated risk of false positive or negative conclusions. In many cases, the relative sensitivity and specificity of the various measures of abuse potential have not been characterized. Data interpretation may require the weighing of favourable and unfavourable subjective effects across multiple measures, or determining the margin between a dose giving a signal and the therapeutic dose, without established quantitative criteria for deciding how many bad effects (relative to good effects) or what degree of margin above the therapeutic dose is meaningful.
- The ability of these studies to make distinctions of relative abuse liability is limited, particularly when comparing drugs with different mechanisms of action, because of the inherent uncertainty associated with determining equivalent doses of the investigational drugs and reference agents and the fact that the abuse liability signal is a confound of mechanism and dose. Quantitative comparisons of relative abuse potential are therefore limited to the doses studied.

The recommendations made in earlier sections of this document, such as selecting one or two well-validated primary outcome measures, limiting the number of outcome measures, and including both positive and negative control drugs, will help to address these limitations. Sponsors are encouraged to develop and validate new methods and assessment instruments for evaluating abuse potential.

Results from human laboratory studies of abuse liability should be considered in the context of all of the data relevant to the scheduling decision.

5. ASSESSMENT OF ADVERSE EVENTS, ADHERENCE, PHYSICAL DEPENDENCE, AND DEVELOPMENT OF TOLERANCE IN OTHER CLINICAL TRIALS

When concerns exist about abuse liability, prospective collection of relevant adverse events should be incorporated into phase I, II, and III clinical trials. Adverse events suggestive of abuse liability should be carefully characterized. Furthermore, data should be presented for any events of diversion, tampering, loss, misuse, withdrawal/discontinuation signs and symptoms, and overdose.

5.1 Adverse Events

An increased incidence of the following adverse events in patients receiving an investigational drug may be suggestive of abuse liability:

- agitation
- amnesia
- anorexia
- anxiety
- ataxia
- cognitive impairment
- confusion
- craving
- depersonalization
- drug abuse
- emotional lability
- euphoria
- hallucinations
- insomnia
- paresthesia
- sedation/somnolence
- thinking abnormal
- withdrawal-emergent signs and symptoms

To characterize the profile of effects that may represent a signal of abuse, the list of terms used in a particular drug development programme should include those directly relevant to abuse (e.g., euphoria, drug abuse), as well as those relevant to the pharmacology of the investigational drug (e.g., miosis for opioids). When there is concern regarding possible abuse liability, adverse events suggestive of abuse should be subject to systematic follow-up, adjudication by a prespecified method to determine whether they represent abuse in the individual case, and prospective analysis. Detailed case narratives should be provided for reports of abuse.

5.2 Adherence

Suspicious should be raised if adherence assessments (e.g., pill counts) indicate that some subjects are taking more study drug than instructed. Reports of 'lost' medication might also prompt concerns about excessive use or diversion.

5.3 Physical Dependence

The ability of an investigational treatment to produce physical dependence is assessed by an evaluation of adverse events that emerge during the period following discontinuation of the drug. It should be noted that some drugs produce withdrawal/discontinuation phenomena, sometimes referred to as physical dependence, without being linked to abuse liability (e.g., beta blockers, selective serotonin reuptake inhibitors, corticosteroids).

If withdrawal/discontinuation effects are anticipated on the basis of pharmacological class (e.g., opioids, stimulants, sedative/hypnotics, antidepressants), non-clinical studies, or prior clinical trials with the investigational drug, these effects should be further evaluated in therapeutic clinical trials. Depending on the pharmacology and pharmacokinetics of the investigational drug, further evaluation might involve adding a blinded withdrawal phase to some or all subsequent clinical trials. Adverse events that are newly emergent or that worsen in severity during the withdrawal phase should be characterized. If a well-validated withdrawal instrument exists for a particular drug class, it should be included; however, the capture of withdrawal-related adverse events by these instruments is limited to the prospectively listed events. Characterization of all withdrawal-/discontinuation-emergent adverse events is important in ensuring that the syndrome is adequately characterized. Care should be taken to distinguish signs and symptoms of withdrawal from re-emergence of the symptoms of the underlying disease state that was being treated with the medication.

5.4 Tolerance

Tolerance refers to the need to continually escalate dose over time to maintain therapeutic effect or to attain a desirable subjective response. The potential for tolerance should be assessed whenever suspicions arise on the basis of non-clinical or clinical data or pharmacological class effects (e.g., opioids). The development of tolerance can be assessed by characterizing mean and modal doses used in flexible dose efficacy studies or long-term open-label trials following an adequate period for dose optimization and stabilization.

6. POST-MARKETING EVALUATION OF ABUSE LIABILITY

If the new drug has been approved for use in other regulatory jurisdictions, the post-marketing adverse event data should be examined for reports of abuse, dependence, and withdrawal/discontinuation syndromes. However, because the abuse of a new drug may develop slowly, a post-marketing signal may not become evident until sufficient time has elapsed for an illicit market to become established. Therefore, the absence of post-marketing evidence of abuse liability must be weighed together with non-clinical and clinical findings from the drug development programme. The value of the post-marketing experience will depend on the extent of exposure to the drug and whether active post-marketing surveillance has been in place for adverse events of abuse.

When a new drug with suspected abuse liability becomes commercially available, the sponsor should implement mechanisms whereby to monitor the emergence of abuse, using a variety of sources. Data acquisition should occur in a timely manner to allow prompt interventions when required. Controlled post-marketing studies may be needed to quantify rates of abuse. Whenever possible, these studies should provide comparative data for pharmacologically related compounds, which might include compounds with similar therapeutic indications and illicit drugs. Pertinent information can sometimes be derived from post-marketing epidemiology studies; surveys using questionnaires directed to health care providers, patients, or 'at risk' populations; quantitative internet surveillance; registry studies; case reports/series; or outcomes of product-specific drug abuse surveillance programmes. Likewise, statistics for emergency department admissions, admissions to substance abuse programmes, or analysed samples from regional forensic laboratories can be informative. All of the aforementioned approaches to monitoring post-marketing abuse will be most effective if abuse of the drug is frequent or results in serious medical consequences. Drugs with low population exposure, infrequent abuse, or non-serious medical consequences may elude detection by these mechanisms.

7. REGULATORY IMPLICATIONS AND RISK MANAGEMENT

Decisions regarding the approval of a drug with abuse liability and its scheduling under the *Controlled Drugs and Substances Act* will be based on an integrated assessment of the following factors:

- physicochemical characteristics (e.g., chemical and pharmacological similarity to other substances listed in the CDSA)
- non-clinical pharmacology (e.g., withdrawal tests, self-administration paradigms)
- clinical pharmacology (e.g., human laboratory study of abuse liability, pharmacokinetic characteristics)
- efficacy (e.g., evidence of a legitimate therapeutic use)
- risk to health and safety (e.g., adverse events and other data from clinical trials that are suggestive of abuse liability, diversion, physical dependence, or tolerance)
- when available, evidence of extent of actual abuse/misuse (e.g., post-marketing adverse event reports, epidemiology studies)
- international requirements and trends in control/scheduling

Clinical data will be given particular weight in this evaluation. Both likelihood of misuse and consequences of misuse should be considered in regulatory decision-making. For example, a higher intensity of concern would be generated by a drug that causes respiratory depression, seizures, or psychomotor impairment when used at supratherapeutic doses than one with a more favourable therapeutic index.

If a drug is considered to have abuse liability, the following issues should be considered when preparing the Product Monograph:

- contraindications or warnings and precautions regarding administration to individuals who abuse alcohol or substances or have histories of such abuse
- warnings and precautions concerning withdrawal/discontinuation syndromes, including a list of withdrawal-/discontinuation-emergent signs and symptoms
- limitations regarding the maximum dose and/or duration of treatment
- recommendations for the gradual downward titration of dosage prior to discontinuation

Manufacturers are encouraged to design and implement risk management strategies to decrease the likelihood of drug abuse. Consideration should be given to developing drug formulations that reduce abuse liability.

Because the current methods of evaluating abuse liability rely upon qualitative interpretation of results from multiple data sources, there may be instances when the actual level of abuse in the community differs from the predictions. When concerns exist regarding abuse liability, manufacturers are encouraged to monitor the frequency of abuse following introduction of the drug onto the market. Controlled post-marketing studies that assess the emergence of drug-seeking behaviour in treated patients may provide particularly useful information in this regard. In some cases, the approval of a drug with abuse liability might be dependent upon the sponsor making a commitment to perform post-marketing studies. Results from post-marketing studies and adverse event monitoring might serve as a basis for re-consideration of the original scheduling decision.