Health Canada Santé Canada

GUIDANCE DOCUMENT

Tamper-Resistance Formulations of Opioid Drug Products

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Health Products and Food Branch

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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's mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document ***may be*** acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant programme 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 INTRODUCTION

Opioids, which are regulated both under the *Food and Drugs Act* and the *Controlled Drugs and Substances Act*, are a type of medication used to treat pain and are an important component of pain management available to patients.

This guidance document is specific to the "tamper-resistance" feature of controlled-release opioid products. It is intended for the pre-market review of drug submissions when sponsors seek to obtain approval for controlled-release opioid drug formulations with tamper-resistant properties and wish to include, in product monographs, scientific statements and claims regarding tamper-resistance. Therefore, all Health Canada guidelines and policies designed to assist sponsors in the preparation and filing of drug submissions are applicable such as, the Management of Drug Submissions and the Clinical Assessment of Abuse Liability for Drugs with Central Nervous System Activity.

Although standards have yet to be developed for criteria and data requirements for the different possible approaches to abuse-deterrence, it is expected that the demonstration of tamper-resistance properties would be based on scientific methods and studies yielding evidence of sufficient quality. Health Canada will consider the *totality of the evidence* when evaluating the tamper-resistance claims. Such evidence informs Health Canada's consideration to include scientific statements and claims regarding tamper-resistance in product monographs. As data become available regarding the impact of tamper-resistance formulations of opioid drugs in deterring abuse, Health Canada may amend its current position and practices, as described in this guidance, in regards to tamper-resistance claims.

When submitting a drug submission in support of a drug product that is proposed to be tamper-resistant, it is Health Canada's expectation that sponsors seek early dialogue with Health Canada at the pre-submission stages. Seeking early input will allow discussions on labelling plans, labelling language, readiness of the application, Risk Management Plans (RMP) and risk monitoring/mitigation measures including design of supportive studies.

1.1 Policy Statements

- Current guidelines and requirements remain applicable to all tamper-resistance opioid drug products, as per the *Food and Drug Regulations*. Sponsors are responsible for providing the necessary evidence to support all aspects of an application for authorization.
- Authorization to include statements or claims of tamper-resistance in product monographs (PMs) of controlled-release opioid drug products will be based on evidence provided by the sponsor and available information at the time of the review of a submission.
- The issuance of a Notice of Compliance (NOC) for an opioid drug product, manufactured with tamper-resistance properties, is based on the requirements of the *Food and Drugs Act* and *Regulations* for the recommended conditions of use.

- Drug submissions for tamper-resistance formulations of opioid products that include direct or indirect comparison of the drug product to a reference drug, are subject to the laws, and patent and intellectual property principles of the *Food and Drug Regulations (Data Protection)* and the *Patented Medicines (Notice of Compliance) Regulations*.
- For new tamper-resistant opioids that are compared to marketed tamper-resistant opioid products, the non-clinical and clinical data to support a submission for a tamper-resistance formulation may vary and is determined by the similarity of safety, efficacy and quality between the product and the suitable reference drug.
- When tamper-resistance formulation changes are proposed, a sponsor is required to demonstrate that the tamper-resistance formulation does not change the safety and efficacy profile for the patient when used under the recommended conditions of use.
- Additional clinical efficacy and/or safety studies may be needed for tamper-resistance formulations that are novel or unique, and that could introduce new clinical or non-clinical concerns for the product in the intended population.
- The product monograph (PM) for a tamper-resistant opioid product is intended to provide the necessary information for safe and effective use of drugs and also to serve as a standard against which all promotion and advertising of the drug can be compared.
- Requests for the inclusion of scientific statements and claims of tamper-resistance in the PM for opioid products should be supported by well-designed studies.
- Health Canada recognizes that alternative criteria and/or data requirements for tamper-resistance formulations of opioid drug products may need to be considered as experience is gained with emerging approaches.

1.2 Scope and Application

This guidance applies to all drug submissions for sponsors seeking authorization to include tamper-resistance statements in product monographs (PMs) of controlled-release opioid drugs. As per Part C, Division 8 of the *Food and Drug Regulations (FDR)*, to seek a Notice of Compliance (NOC) for the product, a sponsor is required to file a submission with Health Canada for review of the safety, efficacy and quality of the controlled-release opioid under the recommended conditions of use.

This guidance sets out specific criteria and data requirements for demonstrating the tamper-resistance characteristics of a human drug product[1] for the purpose of reducing the likelihood of prescription opioid drug abuse.

Epidemiological studies do not fall within the scope of this document and are not reviewed in a submission for the purposes of obtaining an NOC. This is consistent with the pre-market review of drug products.

[1] For the purposes of this guidance document, veterinary drugs are excluded.

This guidance document should be used in conjunction with Health Canada's guidance document entitled "Clinical Assessment of Abuse Liability for Drugs with Central Nervous System Activity".

1.3 Definitions

Tamper-resistance formulation: A tamper-resistant product is formulated or manufactured with measures intended to reduce the likelihood of abuse by different routes of administration, as demonstrated by appropriate *in vitro* and clinical studies. Such formulations may contain the following:

- physical/chemical barriers rendering the product more difficult to manipulate and/or less rewarding if administered;
- an added opioid antagonist which would become active if the product is manipulated (tampered with) thereby interfering with, reducing or defeating the euphoric effect associated with abuse;
- an added aversive agent rendering an unpleasant effect if the product was manipulated;
- a delivery system in which drug release designs or the method of drug delivery can offer resistance to abuse; or
- a combination of the above noted types of formulations.

The above noted list is by no means exhaustive and therefore, tamper-resistance formulations may encompass novel and unique approaches or technologies that have not been captured above, such as, new molecular entities with different properties or prodrugs.

Abuse: For psychoactive pharmaceuticals with centrally-acting reinforcing properties, abuse is defined as use that is associated with increased risk for harm, as characterized by obtaining the drugs from illegitimate sources, or risky patterns of use (excluding under-use) that deviate from accepted medical practice and/or scientific knowledge, or taking the drugs for purposes which are non-therapeutic.

Addiction: A chronic relapsing disorder, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviours that include one or more of the following: impaired control over drug use, compulsive drug-seeking behaviour, continued use despite harm, and craving. Addiction may or may not include physical dependence.

2 GUIDANCE FOR IMPLEMENTATION

2.1 Applicable Regulations and Requirements for New Drug Submissions, Supplemental New Drug Submissions, Abbreviated New Drug Submissions or Supplemental Abbreviated New Drug Submissions

For the purposes of obtaining a Notice of Compliance, sponsors requesting approval of tamper-resistant products must file New Drug Submissions (NDS), Abbreviated New drug Submissions (ANDS), Supplemental New Drug Submissions (SNDS), or Supplemental Abbreviated New Drug Submissions (SANDS) and, subject to the *Food and Drug Regulations* a sponsor is required to satisfy the requirements in Part C, Division 8. Health Canada urges sponsors to come forward with potential submissions on new technologies early in development.

A change in formulation, to add a tamper-resistance feature to an already approved product, requires the filing of an SNDS or SANDS in accordance with the Health Canada guidance document entitled “Post-Notice of Compliance (NOC) Changes”. However, it is to be noted that a NDS may be required for post-NOC changes, such as submissions for products whereby an aversive agent has been added to the product formulation.

For all types of drug submissions, depending on the approach chosen by manufacturers in developing the tamper-resistance formulation features of their product, additional clinical efficacy and/or safety studies may be needed for novel or unique technologies. Furthermore, additional safety studies and/or monitoring may be required for product features that could potentially lead to changes to the conditions of use or patient safety issues, to ensure that the inclusion of these features does not adversely impact patient safety.

Sponsors of products may choose to establish the tamper-resistance features of their product with or without making comparisons to a marketed drug product. Since technology is evolving in this field, data submitted for demonstrating tamper-resistance features will be evaluated on a case-by-case basis.

Tamper-resistance properties may be established by comparison to appropriate controls and other products. Market authorization of a drug product however, is subject to the *Patented Medicines (Notice of Compliance) Regulations* and C.08.004.1 of the *Food and Drug Regulations*. Sponsors should refer to related guidance documents entitled, "Guidance Document: Data Protection under C.08.004.1 of the *Food and Drug Regulations*" and "Guidance Document: *Patented Medicines (Notice of Compliance) Regulations*".

Sponsors seeking to obtain an approval for the inclusion of scientific statements and claims of tamper resistance in PMs, should be supported by appropriate studies such as *in vitro* manipulation and extraction studies, pharmacokinetic studies and clinical trial data

demonstrating a reduction in "drug liking" as per Section 2.2 (below), Pre-market studies: Criteria and Data Requirements.

New Drug Submissions (NDS)

As with all NDS, evidence is required to support all aspects of an application for authorization, that is (i.e.), data on safety, efficacy and quality of the product for its intended use. In addition, sponsors wishing to include statements, or label claims of tamper-resistance, should provide evidence from *in vitro* laboratory, pharmacokinetic and clinical abuse liability studies. Excluding some non-clinical and clinical data may be considered for products with new claims of tamper resistance which are otherwise equivalent to a suitable reference product with respect to safety, efficacy, and quality. However this should be discussed in pre-submission meetings with Health Canada officials.

Abbreviated New Drug Submissions (ANDS)

An ANDS may be filed for a generic tamper-resistant opioid drug product that establishes equivalent tamper-resistance properties and performance of the product in comparison to those of a Canadian Reference Product[2] (CRP). As required of all ANDS, the criteria to be met include a demonstration of pharmaceutical equivalence and bioequivalence to the CRP, the route of administration must be the same as the CRP, and the conditions of use must fall within the conditions of use for the CRP. Additional data should be provided to demonstrate equivalence with respect to tamper-resistance properties and performance in comparison to the CRP. A demonstration of equivalence to the CRP implies that the proposed product can be expected to have the same therapeutic effects and safety profile as the CRP when administered under the conditions specified in the labelling and would permit similar labelling regarding tamper-resistance properties and claims as those for the CRP.

The comparative studies provided in support of the tamper-resistance features should provide sufficient evidence to support equivalent performance of the proposed product to the CRP with respect to the tamper-resistance properties. Depending on the design of the product, *in vitro* laboratory manipulation and extraction studies, and/or pharmacokinetic studies may be required.

[2] Canadian Reference Product (CRP): As per the *Food and Drug Regulations*: (a) a drug in respect of which a notice of compliance is issued under section C.08.004 or C.08.004.01 and which is marketed in Canada by the innovator of the drug; (b) a drug, acceptable to the Minister, that can be used for the purpose of demonstrating bioequivalence on the basis of pharmaceutical and, where applicable, bioavailability characteristics, where a drug in respect of which a notice of compliance has been issued under section C.08.004 or C.08.004.01 cannot be used for that purpose because it is no longer marketed in Canada; or (c) a drug, acceptable to the Minister, that can be used for the purpose of demonstrating bioequivalence on the basis of pharmaceutical and, where applicable, bioavailability characteristics, in comparison to a drug referred to in paragraph a)." Refer to the Health Canada Policy: Canadian Reference Product, for information regarding acceptance criteria for the use of a non-Canadian reference product, pursuant to paragraph (c) of this regulation.

In addition, a comparative clinical abuse-liability study would be required for a generic product that employs a different aversive agent from that of the CRP.

Existing Marketed New Drugs

Supplemental New Drug Submissions (SNDS)

The addition of tamper-resistance features to an existing drug product may have an impact on the safety and effectiveness of the drug. A change in formulation or manufacturing process may adversely affect the identity, strength, quality, purity, potency or performance of the product. Therefore, sponsors may need to submit additional clinical or quality information to support proposed changes to the formulation in a SNDS.

Submissions filed with data to support revisions under Actions and Clinical Pharmacology to an existing PM, require both a clinical and chemistry and manufacturing review.

Supplemental Abbreviated New Drug Submissions (SANDS)

Sponsors whose marketed products were authorized through an ANDS and for which the CRP adds tamper-resistance features, may file an SANDS to add equivalent tamper-resistance features to their product. Evidence should be provided to clearly demonstrate the equivalence of the performance of the tamper-resistance features to those of the CRP.

2.2 Pre-Market Studies: Criteria and Data Requirements

Criteria and data requirements for demonstrating tamper-resistance properties are evolving as experience is gained with the pharmaceutical development and testing of new formulations, and as experience emerges with marketed products.

Opioid abuse can occur via different routes of administration, including but not limited to oral, intravenous, intranasal and inhalational. The design of *in vitro,* pharmacokinetic and abuse liability studies should be based on the types of abuse that are expected. Studies should address the route of administration by which the product is predominantly abused to demonstrate a clinically meaningful reduction in its abuse. For example, if a drug is expected to be significantly abused via the intravenous route, studies should address this route of abuse. All routes of administration that are expected to be seen in situations of abuse should be studied to evaluate the overall tamper-resistance potential of the product. The magnitude of the decrease in likelihood to tamper with the product and in abuse liability that will be considered clinically significant will be determined on a case-by-case basis. A summary of the results of studies performed are to be included in the product monograph's Part I ACTIONS AND CLINICAL PHARMACOLOGY section.

Use of Comparators

The ability of a comparative trial to detect a difference between treatments when one exists needs to be established because a trial incapable of distinguishing between treatments that are in fact different, cannot provide useful comparative information. Formulations that are intended to mitigate abuse liability (for example [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 a conventional formulation of the same compound.

For the purposes of demonstrating tamper-resistance, the appropriate comparator should be an approved, marketed tamper-resistant product using the same active ingredient when available. If the same active ingredient is not available, an appropriate comparator should be used which may, or may not be, tamper-resistant. For generic products, they should be compared to the CRP with tamper-resistance properties to compare its degree of resistance to tampering. A positive control should be used to employ discriminatory conditions for the comparisons.

The following provides information on what is expected from studies designed to demonstrate the tamper-resistance characteristics of the formulation. Studies include: *in vitro* laboratory studies; pharmacokinetic studies; and clinical abuse liability studies. Results from one type of study may influence the design, or the need, for subsequent studies. Health Canada may adapt its current approach as new evidence/information evolves.

2.2.1 In Vitro Laboratory Studies

In vitro studies are the first step in evaluating the tamper-resistance properties of a product designed as such.

The objective of laboratory studies is to fully characterize a product's resistance to methods of tampering representative of those likely to be encountered in "real-world" scenarios. The goal of the *in vitro* studies is to demonstrate that a product's tamper-resistance properties are effective in thwarting the most likely methods of tampering. The rationale for the study design should be clearly stated. *In vitro* studies should address the tampering methods most likely to yield significant or rapid release of the opioid and may provide information relevant to the design of pharmacokinetic and clinical abuse liability studies.

To perform a meaningful assessment of a product's resistance to tampering, a complete description should be provided of the product's tamper-resistance design properties and mechanism(s), the scientific rationale for the mechanism(s) and their relevance to "real-world" tampering scenarios and abuse potential.

While a completely tamper-proof product may not be achievable, *in vitro* studies should assess the limitations of products designed to be tamper-resistant when subject to a range of tampering methods. The goal of these studies is to manipulate the product to the point of defeating its tamper-resistance properties.

The stability of the tamper-resistance mechanism should be evaluated over the entire proposed shelf-life of the product.

The *in vitro* tests to evaluate tamper-resistance should be conducted along a continuum ranging from: (1) accidental misuse of a product, for example (e.g.), crushing or dividing a tablet for easier administration; to (2) deliberate abuse where the intent is to defeat tamper-resistance either at a relatively low level of sophistication of tampering is relatively low (e.g., use of common household appliances, solvents etc.), or to tampering by more determined individuals using more sophisticated means and methods including potentially specialized equipment, multiple manipulation steps, sequential extractions , the use of less common solvents, extended time frames, etc.

While the science of designing tamper-resistance products, as well as methodologies to defeat them are rapidly and constantly evolving, in general, the following points should be addressed as relevant to both the product and potential methods of tampering:

Particle size distribution - Reduction of an intact product into smaller particles may significantly alter the rate and extent of release of the active ingredient under various conditions or render the product suitable for alternate routes of administration e.g., insufflation. Where a product's tamper-resistance mechanism relies on decreasing the ease of rendering the product into smaller particles (for example, crush-resistance) the time and effort required to reduce product particle size by a variety of techniques (e.g., crushing, grinding, cutting etc.) including the use of mechanical means (e.g., pill crushers, grinders, scrapers etc.) and at reduced and elevated temperatures, should be evaluated. Where relevant, a range of particle sizes, including coarse, medium and fine particles, should be evaluated to determine the effect of particle size reduction on the products tamper-resistance properties. The particle size range which shows the greatest increase in rate and extent of opioid release relative to the intact product should be evaluated in subsequent studies (i.e. dissolution, injectability, abuse-liability etc.)

In vitro release of the resultant particles across the range of particle sizes should be evaluated with respect to: maintenance of the controlled release mechanism (if present), extractability of the active from the resultant particles, extractability of any aversive/agonist/antagonist agents or other agents intended to deter tampering, and suitability of the particles for insufflation.

Dissolution – Anti-tampering designs should be assessed with respect to their potential impact on the rate and extent of release of the opioid under a variety of *in-vitro* conditions. The methods employed to determine the rate and extent of release of an ingredient (opioid or a counter-tampering agent) from a drug product should be capable of discriminating *in-vitro* performance differences in dissimilar products (both intact versus manipulated product and different levels/methods of tampering or degrees of tampering for the same product). Analytical methods should be suitably validated.

Tampered products (e.g., across a range of particle sizes, tampering methods) should be assessed with respect to the rate and extent of *in vitro* release of the active ingredient as well as the rate and extent of release of any additional agents intended to deter tampering. The extent of release of aversive, agonist/antagonist or other anti-tampering agents should be assessed and justified with respect to clinical effect.

Extractability - Products designed to be tamper resistant should be evaluated against potential tampering methods designed to extract and isolate the opioid from the formulation. Assessment should be performed with respect to the time, effort, equipment and knowledge required to extract the active ingredient and/or to isolate the active ingredient from ingredients in the formulation which may deter tampering.

Extractability should be evaluated in multiple solvents representing a range of physicochemical conditions (i.e., pH, polarity) and include commonly available household solvents (e.g., water, alcohols, acids such as vinegar, lipid-soluble media such as cooking oils, etc.) as well as generally commercially available solvents not as commonly used for household purposes. The effects of time, temperature, pH and agitation on extractability should be assessed. Liquid/liquid extractions should be evaluated using suitable organic solvents. Assessment of methods designed to alter the solubility of the active ingredient, to render it more amenable to extraction and isolation, should be included (e.g., “freebasing”, substances designed to alter pH of solutions during extraction, etc.). Due to the use of food to aid in swallowing a drug, extractability should further be studied with foods under certain conditions, such as apple sauce, which may alter the solubility of the product.

For combination products with multiple substances, extractability and solubility studies should be designed to determine whether any of the ingredients might be differentially solubilized and extracted.

Where an excipient is added to the formulation to change the active pharmaceutical ingredient (API) solubility or availability when the product is tampered with (e.g., adding base to tablets to cause precipitation of the opioid when the drug product is dissolved in

water) data should be provided to demonstrate that the added excipient functions as intended and that the amount and effect of the excipient is sufficient for its stated purpose.

Injectability - Products which are not designed for injection may nevertheless be tampered with to render them more suitable for this method of administration. Products designed to reduce the ease or desirability of modifying them to be injected should be assessed with respect to the ease (time, effort, level of sophistication) of preparing an extract suitable for injection. Extracts prepared for injection via relevant tampering methods should be assessed with respect to the concentration of the opioid in the extract as well as for suitability of the extract for injection, addressing for example: presence of particulates, viscosity, appearance, as well as any other properties which may render the product less suitable or desirable for injection. The ease of uptake and expulsion of the extract from needles of various gauges should also be assessed.

Vaporization - Products designed to be resistant to vaporization or smoking and any relevant extracts (for example, the "free base") should be evaluated with respect to the concentration of opioid in vapour produced at the range of temperatures between the opioid melting point and degradation point.

Insufflation - Tamper-resistance should be evaluated with respect to barriers to manipulation designed to render the product suitable for insufflation. For a product with potential for abuse by the nasal route, the smallest particle size obtained in manipulation tests should be used in subsequent pharmacokinetic and/or clinical studies.

2.2.2 Pharmacokinetic Studies

Pharmacokinetic studies should demonstrate that the tamper-resistance feature of the product does not affect the dosage, absorption, distribution and elimination of the administered drug when the product is taken as directed. Such studies should provide comparisons of the manipulated and intact formulations of the tamper-resistant and comparator drugs following administration through one or more routes. Methods employed for *in vitro* testing that are expected to result in the greatest drug release should inform the method of manipulation to be used for pharmacokinetic studies. What is known about the abuse of a similar product will likely inform the routes of administration chosen to be relevant to the studies of the proposed product.

Pharmacokinetic studies may be carried out in healthy volunteers or non-dependent, recreational users, with the use of an opiate antagonist to block the pharmacodynamic effects of the opioids. When evaluating the pharmacokinetic profile for the nasal and/or intravenous routes of administration, it is important to consider the safety of the formulation, for example, the excipients used, particle size, etc. For these studies, only

subjects with a history of nasal or intravenous abuse of opioids should be recruited. It may be possible to combine pharmacokinetic and pharmacodynamics assessments within the clinical abuse liability studies.

Studies should assess the pharmacokinetic profiles of the parent drug as well as any relevant psychoactive metabolites. For products with different abuse potential among formulations or routes of administration, the rate of increase in drug concentration should be assessed. For further information on the design and conduct of studies, refer to Health Canada's guidance entitled: *Conduct and Analysis of Comparative Bioavailability Studies*.

Examples of studies include, but are not limited to, the following:

- Pharmacokinetic studies should demonstrate the controlled-release properties of the therapeutic product after tampering actions such as vigorous chewing, cutting, grinding, crushing (finely versus coarsely crushed tablets), and scraping, followed by oral ingestion, and/or intranasal administration. Ideally, the controlled-release properties should be retained.

- For products with an aversive agent or an antagonist intended to deter abuse, pharmacokinetic studies should demonstrate that the antagonist or aversive agent is released at an effective concentration from the tampered product when administered by the potential route(s) of abuse. Pharmacokinetic profiles for the intact product and a suitable positive control should be included for comparison. For products that include a sequestered antagonist or aversive agent, studies should further demonstrate that the antagonist or the aversive agent is not released from the intact product.

- The effect of food and alcohol on the formulation should be studied under discriminatory conditions with respect to systemic exposure. These studies should provide a comparison of these effects on both the tampered and intact product. The underlying mechanism for the food effect should be established by assessing whether the effect is based on the drug substance or the formulation and whether the effect is present with the intact product as well as with manipulated product.

2.2.3 Clinical Abuse-Liability Studies for Tamper-resistance Property

Clinical abuse liability studies[3] are used to evaluate relative abuse potential and provide data in assessing a product demonstrating a significant decrease in measures of abuse liability, such as likability, compared to a positive control. The positive control should be

[3] Information on the clinical assessment of abuse liability is found in Health Canada's *Guidance Document: Clinical Assessment of Abuse Liability for Drugs with Central Nervous System Activity*.

a product that has the same active ingredient as the test product, but without tamper-resistance properties.

When food is expected to impact exposure, subsequent abuse liability studies of the oral route should be conducted in the state (fed or fasted) leading to the maximum systemic exposure. Studies should be designed around pre-determined, validated, measures to test the ability to tamper with the formulation or test the abuse potential of the formulation. Also, the clinical abuse-potential should be assessed with instruments that have been validated and established to measure subjective responses predictive of the likelihood of abuse.

Abuse liability studies are usually carried out in non-dependent, recreational drug users and should be designed based on the routes of administration by which the product is expected to be abused. The studies should, where possible, use various randomized, double-blind, placebo controlled and active controlled crossover design studies with the intact product, the tampered product, the tampered positive control (non-tamper-resistant), the non-tampered positive control and a placebo. A placebo is used to ensure internal validity to the study.

A cross-over design may not be feasible when testing the abuse-liability via the nasal route as subjects may be able to see differences in the appearance of the ground/crushed product among the positive control, placebo, and test drug. Various blinding methods may be examined including darkened dosing containers, altered lighting conditions, matching placebos in double/triple dummy designs and multiple bottles to account for differences maintaining both the double blind and the ideal crossover design. A parallel group design may be used to avoid this type of potential bias. Studies demonstrating the impact of the tamper-resistance formulation on the likelihood of abuse via different routes of administration should compare, if applicable, the tampered product to the intact product, as well as compare to a suitable positive control. If there are no approved products with the same drug substance, the positive control should be a drug with a similar pharmacological profile (pharmacokinetic and pharmacodynamic effects).

Care should be taken in designing studies testing parenteral routes of abuse for oral formulations. For example, the oral formulation may not be safe for intravenous use. In these cases, a solution for injection should be prepared using marketed products that are safe for intravenous use in humans.

Controls and Comparators

A positive control should be used in all laboratory and clinical studies, where possible. Comparators may differ based on routes of administration being evaluated for abuse.

For tamper-resistant products with the same active ingredient as the reference product, abuse liability studies are required to demonstrate that the tamper-resistant product is less liable to abuse than a non-tamper-resistant product. If a marketed non-tamper-resistant version of the same active ingredient is not available, other suitable comparators may be used. To address new tamper-resistant products, a relevant marketed comparator drug at an equianalgesic dose to the new tamper-resistant test product should be used. Comparators should also be chosen based on their established abuse liability, and should produce similar or equal euphoric effects as compared to the active ingredient of the new tamper-resistant product, at the doses chosen for the study. A rationale should be submitted to support the choice of comparator.

Studies demonstrating the impact of the tamper-resistance formulation on the likelihood of abuse via different routes of administration should compare the tampered product to the intact product, as well as compare to a suitable positive control. For studies using the intranasal route, the tamper-resistant product and comparator study drug should be designed with similar particle size distribution based on a detailed protocol for the preparation of the samples. Some formulations may contain a high volume of the crushed tablet/capsule or larger particle size which may inhibit complete intranasal administration and, therefore, contribute to deterrence effects. In order to evaluate these effects, it may be necessary to maintain differences in tablet/capsule volume between the potentially tamper-resistant product and the comparator.

Methodological Considerations

Subjective measures ("Drug Liking") and objective (e.g., pupillometry) measures should be used as well as other outcomes specific to the type of administration. For example, outcome measures such as nasal irritation should be used for intranasal administration. The subjective rating of liking is one of the most sensitive predictors of abuse liability. The most common practice is to use a visual analog liking scale (VAS liking scale) using either a unipolar or bipolar (disliking-liking) scale. In 2012, the IMMPACT group (Initiatives on Methods, Measurement, and Pain Assessment in Clinical trials) convened a consensus meeting to provide recommendations for key primary outcomes for abuse liability studies. They recommended four subjective measures to be used in abuse liability studies of opioids: drug liking, likelihood to take again, drug identification and drug high (primary outcome measures) and physiological responses (pupillary constriction, oxygen saturation and respiratory rate) as core secondary measures.[4]

[4] Comer, SD, Zacny, JP, Dworkin, RH et al. Core outcome measures for opioid abuse liability laboratory assessment studies in humans: IMMPACT recommendations. Pain (2012):2315-2324.

Drug Discrimination Phase[5]

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. The primary goal of the qualification procedure is to identify subjects who report 'liking' the positive control and experience pharmacological effects that are consistent with the known pharmacology of the prototypical drug. Furthermore, the qualification phase is essential to ensure that subjects are able to tolerate the study treatments at the given doses. Only those 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.

2.2.4 Safety and Efficacy of Tamper-resistance Formulations

Sufficient data should be submitted to support the safety and efficacy of the tamper-resistance formulation when used by a patient under the specified clinical conditions of use.

Clinical safety and efficacy trials are required in the intended patient population for those formulations introducing tamper-resistance properties. Examples of formulation changes may include, but are not limited to, addition of aversive agents or opioid antagonists, new excipients, or new combination of known excipients to the formulation. The tamper-resistance properties must be effective against manipulation while maintaining the product's safety and efficacy profile in the patient population.

Sponsors may also be asked to submit a Risk Management Plan (RMP)[6] to describe the different pharmacovigilance activities to characterise the safety profile and assist in minimisation of risks associated with the product.

[5] As per Section 4.2.3, Pre-Testing Qualification Phase, of Health Canada's *Guidance Document: Clinical Assessment of Abuse Liability for Drugs with Central Nervous System Activity*.

[6] Refer to Health Canada's *Guidance Document - Submission of Risk Management Plans and Follow-up Commitments*.

2.3 Product Monographs

The product monograph is a factual, scientific document on the drug product that, devoid of promotional material, describes the properties, claims, indications, and other conditions of use for the drug, and that contains any other information that may be required for optimal, safe, and effective use of the drug. The science of abuse deterrence is relatively new and there are currently no existing standards for tamper-resistance formulations.

The development of tamper-resistance formulations is intended to address the risk of abuse outside the therapeutic context for which the product was developed. Health Canada will allow the inclusion of explicit statements stating the product is formulated with tamper-resistance properties. Studies supporting the tamper-resistance claim will be described in the PM only if a claim is sought by a sponsor and authorized by Health Canada. Similar to all drug products authorized in Canada, Phase IV[7], epidemiological studies are not to be used to support a claim of tamper-resistance. Such studies are meant to support post-market safety of the product. Furthermore, studies that imply comparative efficacy or parity should not be included, unless deemed pivotal by Health Canada upon issuance of a NOC[8]. It is to be noted, that the status of a product claiming to deter abuse can change with various factors such as demographics, availability of tools to overcome the tamper-resistance properties, availability of non-tamper-resistant prescription opioids, ease of accessibility to illicit drugs, etc. Therefore, no claims of real world abuse-deterrence will be included in the PM.

In addition to the information that is to be included for the class labelling of controlled-release opioids, information about the tamper-resistance properties of the formulation may be included in the PM as per the following:

PART I:

WARNINGS AND PRECAUTIONS

Addiction, Abuse and Misuse

Like all opioids, **BRAND NAME** is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, **BRAND NAME** should be prescribed and handled with caution.

Tamper-resistance properties do not render this product less addictive.

[7] Health Canada's *Guidance Document for Industry*: *Reporting Adverse Reactions to Marketed Health Products*, see Phase IV studies http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2011-guidance-directrice_reporting-notification/index-eng.php

[8] Health Canada's Guidance Document entitled: *Product Monograph* (section 4.2.1) (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/monograph/pm_mp_2013-eng.php)

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of **BRANDNAME** and there is a potential for development of psychological dependence.

Tamper-resistance properties do not affect the development of tolerance and/or dependence.

ACTIONS AND CLINICAL PHARMACOLOGY
Tamper-resistance Properties

Abuse of [**BRAND NAME**] can lead to overdose and death (see **SERIOUS WARNINGS AND PRECAUTIONS**).

[**BRAND NAME**] is formulated with ingredients and/or manufacturing processes intended to reduce misuse and abuse. The following studies show that **BRAND NAME** has [physicochemical] properties that may make the product difficult to misuse or abuse by [specific] routes of administration. Abuse potential for other routes is not addressed. Abuse by any route remains possible. These studies have not been shown to predict the actual real-world abuse of [**BRAND NAME**].

In vitro testing:

Brief high level summary of the study results.

In vivo testing:

Brief high level summary of the study results.

As well a reference to the tamper-resistance formulation could be allowed under **DOSAGE FORMS, COMPOSITION AND PACKAGING** as follows:

Dosage Forms

BRAND NAME has been formulated with features intended to be tamper-resistant (see **ACTION AND CLINICAL PHARMACOLOGY**, **Tamper-resistance Properties).**

3 CONTACT INFORMATION

Bureau of Cardiology, Allergy and Neurological Sciences (BCANS)
Therapeutic Products Directorate
Health Products and Food Branch
Health Canada
1600 Scott Street
Holland Cross, Tower B, 2nd Floor
Ottawa, Ontario
K1A 0K9
E-mail: bcans_enquiries@hc-sc.gc.ca

4 REFERENCES

i. *Guidance Document: Clinical Assessment of Abuse Liability Drugs* (May 16, 2007). (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/abus/abuse_liability_abusif_usage_clin-eng.php)

ii. *Guidance Document: Data Protection under C.08.004.1 of the Food and Drug Regulations* (October 11, 2011) (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/data_donnees_protection-eng.php)

iii. *Patented Medicines (Notice of Compliance) Regulations*, S.O.R./93-133 (as amended) and data protection provisions of section C.08.004.1 of the *Food and Drug Regulations*

iv. *Guidance Document: Patented Medicines (Notice of Compliance) Regulations* (Revised 2012) (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/patmedbrev/pmreg3_mbreg3-eng.php)

v. *Guidance for Industry: Management of Drug Submissions* (December 20, 2013) (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/mgmt-gest/mands_gespd-eng.php)

vi. *Guidance Document: Conduct and Analysis of Comparative Bioavailability Studies* (2012) (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/bio/gd_cbs_ebc_ld-eng.php)

vii. *Guidance Document: Product Monograph* (2014) (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/monograph/pm_mp_2013-eng.php)

viii. *Guidance Document for Industry: Reporting Adverse Reactions to Marketed Health Products* (http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2011-guidance-directrice_reporting-notification/index-eng.php)

ix. Comer, SD, Zacny, JP, Dworkin, RH et al. Core outcome measures for opioid abuse liability laboratory assessment studies in humans: IMMPACT recommendations. Pain (2012):2315-2324

x. *Draft Guidance for Industry: Submission of Risk Management Plans and Follow-up Commitments* (http://www.hc-sc.gc.ca/dhp-mps/consultation/medeff/_2014/rmp-pgr/index-eng.php)

xi. Health Canada Policy: Canadian Reference Product (December 5, 1995) (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/pol/crp_prc_pol-eng.php)