SUBMISSION GUIDELINES
FOR
LONG-ACTING OXYCODONE PRODUCTS

Note: Despite the *Ontario Guidelines for Drug Submission and Evaluation* and the *Streamlining to a Single Monthly Formulary Process*, submissions for long-acting oxycodone products shall not be reviewed through the Ministry's streamlined review process.

Ontario

Submission Requirements

New Regulatory Requirements for Long-Acting Oxycodone Drug Products

Subsections 1(1.2) and 12(9) of Ontario Regulation 201/96 made under the Ontario Drug Benefit Act ("ODBA") and subsection 6(8) of Regulation 935 made under the Drug Interchangeability and Dispensing Fee Act ("DIDFA") set out the following requirements:

O. Reg. 201/96 under ODBA

1(1.2) The executive officer shall not, under section 16 of the Act, make the Act apply in respect of a drug that is a drug product described in subsection 12 (9) of this Regulation, unless the conditions set out in that subsection are met.

12(9) A strength and dosage form of a drug product that contains oxycodone as the only active ingredient and that is a long-acting product that has been formulated in a solid dosage form for oral administration shall not be designated as a listed drug product unless the following conditions are met:

1. There must be evidence satisfactory to the Executive Officer that the drug product exhibits one or more physiochemical properties that, when compared to drugs without the property or properties, make the drug product,
    i. significantly more difficult to alter, break, crush, chew, dissolve or otherwise manipulate in such a way that it could be misused, abused or put to an intended use that is different than the use for which it is prescribed, or
    ii. significantly less effective and less likely to be misused, abused or put to an intended use that is different than the use for which it is prescribed, if the product is altered, broken, crushed, chewed, dissolved or otherwise manipulated.
2. The evidence referred to in paragraph 1 must be demonstrated by,
    i. in vitro testing
    ii. in vivo testing,
    iii. another form of testing of equivalent reliability, or

iv. a combination of any of the forms of testing mentioned in subparagraphs i to iii.

Regulation 935 under DIDFA

6(8) A strength and dosage form of a drug product that contains oxycodone as the only active ingredient and that is a long-acting product that has been formulated in a solid dosage form for oral administration shall not be designated as interchangeable unless the following conditions are met:

1. There must be evidence satisfactory to the Executive Officer that the drug product exhibits one or more physiochemical properties that, when compared to drugs without the property or properties, make the drug product,
    i. significantly more difficult to alter, break, crush, chew, dissolve or otherwise manipulate in such a way that it could be misused, abused or put to an intended use that is different than the use for which it is prescribed, or
    ii. significantly less effective and less likely to be misused, abused or put to an intended use that is different than the use for which it is prescribed, if the product is altered, broken, crushed, chewed, dissolved or otherwise manipulated.
2. The evidence referred to in paragraph 1 must be demonstrated by,
    i. in vitro testing,
    ii. in vivo testing,
    iii. another form of testing of equivalent reliability, or
    iv. a combination of any of the forms of testing mentioned in subparagraphs i to iii.

A manufacturer of a long-acting oral drug product that contains oxycodone as the only active ingredient is required to provide evidence satisfactory to the Executive Officer that the drug product meets the above regulatory requirements before the drug product may be considered for public funding under the ODBA and/or be designated as an interchangeable product under the DIDFA.

In view of the above, the requirements may be satisfied by completing *in vivo* studies, *in vitro* studies, another form of testing of equivalent reliability, or a combination of these forms of testing. In all these cases, the manufacturer must demonstrate that the drug product has physiochemical properties that give the drug product the characteristics described above by submitting the comparative evidence outlined in this document.

Evidence that the long-acting oxycodone product meets the regulatory requirements

In order to satisfy the regulatory requirements, the manufacturer should submit:

I. A full explanation of the formulation properties that exhibit one or more physiochemical properties that would make the drug product more difficult to alter, break, crush, chew, dissolve or otherwise manipulate; or less effective and less likely to be misused or abused, in the event that the product is altered, broken, crushed, chewed, dissolved, or otherwise manipulated.

II. The results of the following *in vitro* tests:
    1. Resistance to particle size reduction.
    2. Dissolution tests, after particle size reduction, in water, household solvents and buffers.
    3. Physical properties of the resulting solution after particle size reduction and dissolution into a small volume of water.
    4. Extraction into advanced solvents after particle size reduction.
    5. Extraction following vaporization techniques.
    6. Extraction and purification of the drug substance from the crushed dosage form using pH adjustment and solvent extraction or filtration.

The assessment of whether the drug product satisfies the regulatory requirements will be based on the results of the *in vitro* tests identified above.

A manufacturer's submission will be deemed incomplete if any of the above components are missing unless the manufacturer proposes alternatives as described below.

The Ministry has not yet developed guidelines on *in vivo* studies because it is believed, at the present time, that *in vitro* studies are simpler for manufacturers to conduct. If a manufacturer would like to perform *in vivo* studies as an alternative to *in vitro* studies,

then it is recommended that the manufacturer consult the Ministry prior to making a submission.

A manufacturer may conduct additional studies, including *in vivo* studies, to support its submissions. Justification, methodology and results for each test must be documented fully.

A manufacturer is encouraged to contact the Ministry to discuss other tests, methodology and specifications, etc., prior to conducting tests not specified in this guideline.

This guideline will be updated periodically as appropriate based on evolving evidence in the field.

Point of Clarification

Formulation Composition

The manufacturer must submit the complete master formulation (CPID) for the drug product and an explanation on how the drug product exhibits one or more physiochemical properties that would make the drug product more difficult to alter, break, crush, chew, dissolve or otherwise manipulate; or less effective and less likely to be misused or abused, in the event that the product is altered, broken, crushed, chewed, dissolved, or otherwise manipulated.

Evidence of Physiochemical Properties

A complete description of the methods and results of the following tests must be submitted by the manufacturer to show how the physiochemical properties of its drug product, when compared to drug products without any such property or properties, make the drug product more difficult to alter, break, crush, chew, dissolve or otherwise manipulate; or less effective and less likely to be misused or abused, if the product is altered, broken, crushed, chewed, dissolved, or otherwise manipulated.

All dosage strengths must be examined or justification provided that testing dosage strengths which bracket the available dosage strengths is representative of all dosage strengths.

The methods must be validated and described fully in the submission. The sample size will be a minimum of six (6) tablets for each test. Precision of the tests should be sufficient to satisfy the requirement that the 90% confidence interval (CI) will be no greater than +/- 20%.

1. **Resistance to particle size reduction:**

   The ability to crush or pulverize the test and reference products by commonly available devices; hammer, pill crusher, knife, mortar and pestle, spoons, food

grinder or other commonly available devices should be determined. The manufacturer must provide all tests listed * (see Appendix). The size of the resulting particles should be determined by sieving or other suitable means.

Particle sizes should be categorized as whole deformed tablet, or as the proportion of tablet weight found as chunks, coarse powder, medium powder, and fine powder, or comparable and appropriate discrimination of particle sizes.

Criteria:

When comparing the manufacturer's drug product to a drug product without the physiochemical properties (the "reference product"), the manufacturer must provide descriptive statistics that demonstrate that its product, when compared to the reference product, is more difficult to alter, break, crush, chew, dissolve or otherwise manipulate; or less effective and less likely to be misused or abused, if the product is altered, broken, crushed, chewed, dissolved, or otherwise manipulated. The test/reference (T/R) ratio of mean particle size must never have a lower 90 % Confidence Interval less than 80% for any test. However, it is expected, that under certain conditions of particle size reduction which demonstrate that the manufacturer's product, when compared to the reference product, is significantly more difficult to alter, break, crush, chew, dissolve or otherwise manipulate, or significantly less effective and less likely to be misused or abused if altered, broken crushed, chewed or dissolved, the mean T/R ratio of particle size should approach 200%. The width of the 90% CI must not exceed ±20%.

2. **Dissolution tests, after particle size reduction, in water, household solvents and buffers.**

The dissolution profiles of the test product following each method of particle size reduction completed above (hammer, pill crusher, coffee grinder etc.) must be compared to the dissolution profiles of a reference product following the same method of particle size reduction in water and common household solvents. Typical solvents will include: water, ethanol, acidic beverage, buffers at several pH values (1, 3, 7, 10) or other suitable solvents. F2 values must be reported.

Criteria:

When comparing the manufacturer's drug product to a drug product without the physiochemical properties (the "reference product"), the f2 value for the dissolution comparison between the manufacturer's drug product and the reference product must be <50 indicating dissimilarity. In addition, the data should demonstrate that the test product has reduced dissolution as compared to the reference product.

3. Physical properties of the resulting solution after particle size reduction and dissolution into a small volume of water.

The drug substance in the crushed tablet should be dissolved in a small volume of water (no more than10 ml) and the viscosity of the resulting solution determined and compared to a reference product.

This test may be conducted on finely powdered fractions of the test and reference products.

Criteria:

When comparing the manufacturer's drug product to a drug product without the physiochemical properties (the "reference product"), the manufacturer must provide descriptive statistics and evidence showing that the T/R viscosity of the manufacturer's product is increased. The test/reference (T/R) ratio of viscosity must never have a lower 90 % Confidence Interval less than 80%. However, it is expected, that under certain conditions of particle size reduction which demonstrate that the manufacturer's product, when compared to the reference product, is significantly more difficult to alter, break, crush, chew, dissolve or otherwise manipulate, or significantly less effective and less likely to be misused or abused if altered, broken crushed, chewed or dissolved, the mean T/R ratio of viscosity should approach 200%. The width of the 90% CI must not exceed ±20%.

4. Extraction into advanced solvents after particle size reduction.

The amount of the drug substance extracted into 30 ml of solvent following each method of particle size reduction of the test product must be compared to amount of drug substance extracted following the same method of particle size reduction of a reference product. The amount of drug substance extracted must be determined after specified periods of time (e.g. 10 and 60 minutes). The test must be conducted at room temperature and at an elevated temperature.

Solvents might include: isopropyl alcohol 70%, paint thinner, other readily available solvents.

Criteria:

When comparing the manufacturer's drug product to a drug product without the same physiochemical properties (the "reference product"), the manufacturer must provide descriptive statistics that demonstrate a significant difference between its product and the reference product. The upper 90% CI of the T/R ratio of the amount of drug substance recovered must not exceed 120% and the width of the 90% CI must not exceed +/- 20%. It is expected that under certain conditions of

particle size reduction and solvents choice, the mean T/R ratio of the amount recovered should approach 50%.

5. **Extraction by vaporization**

It may be sufficient to conduct this test on the finely powdered material obtained from grinding the test and reference tablets. The finely powdered material should be heated in a system that is equipped with a device capable of trapping any volatilized drug substance. The temperature to which the material is subjected should be sufficient to vaporize the drug substance but not cause degradation. The temperature of vaporization should be reported. The amount of drug substance vaporized and the drug substance remaining in the residue after heating should be determined for the test and reference.

Criteria:

When comparing the manufacturer's drug product to a drug product without the physiochemical properties ("the reference product"), the manufacturer must supply descriptive statistics that demonstrate its product's resistance to abuse by vaporization, in comparison to the reference product. The upper 90% CI of the T/R ratio of the amount of drug substance recovered must not exceed 120% and the width of the 90% CI must not exceed +/- 20%. It is expected, that under certain conditions the mean T/R ratio of the amount recovered should approach 50%.

6. **Extraction and Purification of the drug substance from the crushed tablet material using free-basing and filtration or solvent extraction.**

The finely powdered tablet material should be dissolved in a small volume of water or 30 ml 0.1 N HCl. The pH of the extract should be adjusted to precipitate the free base, pH >9. The mixture is then filtered to collect the free base of the drug substance. This test must be conducted at room temperature and after cooling the basic solution.

To determine the ability to recover the drug substance with solvent extraction, the crushed tablet material should be extracted with 0.1 N HCl, the solution filtered and the pH of the filtrate adjusted to >9 with NaOH and commonly available solvents used to extract the free base from the aqueous solution. The resultant residue after solvent evaporation must be assayed for drug substance content.

Criteria:

When comparing the manufacturer's drug product to a drug product without the physiochemical properties, the manufacturer must provide descriptive statistics that demonstrate a significant difference between the amount of drug substance recovered from the test and reference. The upper 90% CI of the T/R ratio of the

amount of drug substance recovered must not exceed 120% and the width of the 90% CI must not exceed +/- 20%. It is expected, that under certain conditions the mean T/R ratio of the amount recovered should approach 50%.

Note: Where applicable, raw data and a quantification of deviations between individual samples should be provided.

Format and Organization of Submissions

Submissions should follow the same format and organization as described in Part II of the Ontario Guidelines for Drug Submission and Evaluation. In order to organize a submission in a manner that will facilitate review, submissions should be clearly tabbed in order, according to the headings of the submission requirements as outlined above. Disorganized or incomplete submissions may be returned at the discretion of the Ministry, at the manufacturer's expense, without prejudice to re-filing.

Despite the *Ontario Guidelines for Drug Submission and Evaluation* and the *Streamlining to a Single Monthly Formulary Process*, submissions for long-acting oxycodone products are not eligible for review through the Ministry's streamlined review process.

*Appendix.

Table 1, Specifications for Each Device in Particle Size Reduction Tests

Device	Duration of Technique	Change with manufacturer's submitted drug product	Change with the reference drug product
2 spoons	30 seconds	No change	Powder
Parmesan cheese grater	30 seconds	No change	Powder
Manual spice or food grinder	30 seconds	No change	Powder
Electric pepper mill	30 seconds	No change	Powder
Electric mini food processor	30 seconds	No change	Powder
Manual pill crusher	30 seconds	Flattened deformed	Powder
Hammer	30 seconds	Flattened	Powder
Ceramic mortar and pestle	60 seconds	Flattened, broken, pieces	Powder
Chopped with 7 inch kitchen knife and sliced with a razor blade	180 seconds	Small pieces	Small pieces
Electric coffee bean grinder (provide description of device)	Specify duration to attain particle size	Small pieces	Small pieces
Electric coffee bean grinder (provide description of device)	Specify duration to attain particle size	Powder	Powder