# Evidence of safety requirements for tooth whitening products containing peroxide and peroxide-generating compounds

CONSUMER AND HAZARDOUS PRODUCTS SAFETY DIRECTORATE

Health Canada Santé Canada

Canada

**Disclaimer**

This document guides cosmetic notifiers to meet the Evidence of Safety requirements for cosmetic tooth whitening products. This document is not a part of the *Food and Drugs Act* (the Act) or the *Cosmetic Regulations.* The Act or the regulations take precedence if there is any inconsistency or conflict between them and this document.

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Également disponible en français sous le titre :
Exigences relatives aux preuves d'innocuité pour les produits de blanchiment des dents contenant des peroxydes et des substances générant des peroxydes

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Publication date: September 2024



Cat.: H129-163/2024E-PDF
ISBN: 978-0-660-73274-9
Pub.: 240497

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# 1 Glossary

| | |
|---|---|
| ASTM: | American Society for Testing and Materials |
| CNF: | Cosmetic Notification Form |
| GCP: | Good Clinical Practices (https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-clinical-practices.html) |
| GLP: | Good Laboratory Practices (PMRA Guidance Document, Good Laboratory Practice Requirements for Scientific Studies Supporting Pest Control Products - Canada.ca) |
| ICH: | International Council for Harmonization |
| ISO: | International Organization for Standardization |
| OECD: | Organization for Economic Co-operation and Development |
| QA/QC: | Quality Assurance / Quality Control |
| SCC: | Standards Council of Canada (www.scc.ca) |
| SDS: | Safety Data Sheet |
| SOP: | Standard Operating Procedure |

## 2 Scope

The *Cosmetic Regulations* (Sections 30 and 31) require manufacturers and importers of a cosmetic product to notify certain information about the product to Health Canada. They must send the information by filling out a cosmetic notification form (CNF) within 10 days after they first sell the product in Canada. Health Canada does not approve cosmetic products for sale. For some cosmetic products, Health Canada asks for specific evidence to show the product is safe to use. The *Cosmetic Regulations* (Section 13) prohibit selling very acidic stain-removing products for teeth. Other requirements may also apply, such as ensuring the product label includes directions specific to tooth whitening products (Section 24).

Tooth whitening products sold as cosmetics cannot include therapeutic claims (e.g., anti-cavity or sensitivity protection) on the product labels/inserts or websites. For information on representation and acceptable claims on cosmetics, please consult "Guidelines for the non-prescription and cosmetic industry regarding non-therapeutic advertising and labelling claims" (ASC, 2016).

In this document, the term "notifier" refers to the manufacturer or importer of a cosmetic product. Notifiers are responsible to make sure a cosmetic product sold in Canada meets all legislative requirements. This document will help them to comply with relevant sections of:

- *Food and Drugs Act*;
- *Cosmetic Regulations;* and,
- Health Canada's Cosmetic Ingredient Hotlist.

This document outlines which safety data Health Canada evaluates for tooth whitening products containing peroxide and peroxide-generating compounds. It includes three checklists that serve as a quick reference to information needed for review. Notifiers should fill out and send in all three checklists. This may avoid unnecessary follow-ups and delays during the review.

## 3 Cosmetic Ingredient Hotlist

The *Food and Drugs Act* (Section 16) prohibits selling cosmetics that may injure the health or safety of the user when used according to the directions on the label. To help notifiers comply with this rule, Health Canada developed the Cosmetic Ingredient Hotlist ('Hotlist'). The Hotlist describes certain cosmetic ingredients as restricted or prohibited because they may cause harm to the health and safety of the user. The Hotlist is an administrative tool that informs notifiers that certain ingredients, when present in cosmetics, may violate the general prohibition clause (Section 16) of the *Food and Drugs Act* or various provisions of the *Cosmetic Regulations*. The Hotlist also advises notifiers that the presence of certain ingredients[1] in a product could breach the definition of a cosmetic under the *Food and Drugs Act*.

Appendix I[2] lists the current Hotlist entry for peroxide and peroxide-generating compounds.

[1] Often, these are ingredients with no known cosmetic or functional purpose in a cosmetic formulation.

[2] Health Canada reviews and updates information on the Hotlist periodically. Please consult the latest version of the Hotlist to obtain information on specific cosmetic ingredients.

## 4 Evidence of Safety information

The following section outlines information Health Canada reviews to determine the safety of tooth whitening products containing peroxides or peroxide-generating compounds.

### 4.1 Label information

Send all label information to Health Canada. This includes all product labels, inserts, and packaging. Show clearly where on the labels and packaging the directions for use, safety information, and product claims will be presented. The Hotlist describes some label conditions for tooth whitening products containing peroxide and peroxide-generating compounds (see Appendix I). Product labels must meet those conditions. Cosmetic products cannot claim to have any therapeutic effects (ASC, 2016). All label information must be in both English and in French.

### 4.2 Concentration of peroxide and peroxide-generating compounds

The *Cosmetic Regulations* (Section 30(2) (d)) requires that notifiers give Health Canada the names and concentration or concentration ranges of the product ingredients. For peroxide or peroxide-generating compounds, Health Canada needs the **exact concentration**, rounding to two decimal places (for example, 5.04921% would be reported as 5.05%). The second decimal mitigates the impact of rounding errors. Conversion factors for peroxide and peroxide-generating compounds are available in Appendix II.

### 4.3 Directions of use

Make sure that the product label tells users how to prepare, apply and remove the product. The directions on the label should include the following information:

- how much product to apply;
- any mixing steps before applying the product;
- directions on diluting the product before use (if applicable);
- how long to keep the product on before removing;
- how to remove the product; and,
- how often the product can be applied.

## 5 pH data

The *Cosmetic Regulations* (Section 13) requires that the acidity of all tooth whitening products[3] must have a pH greater than 4.00. Test the product pH "*as applied to the teeth"*[4]. Report the pH value rounded to two decimal places. Measure the product pH in triplicate (that is, three times).

[3] Tooth whitening products include toothpastes intended to whiten teeth.
[4] The term "*as applied to teeth*" refers to the final form of the product the users will apply on their teeth.

## 5.1 pH method

The laboratory should always use calibrated instruments and a validated method for pH testing. The laboratory should measure the pH of the cosmetic products using a benchtop pH meter and electrode system. Portable pH meters are less precise and less accurate when compared to benchtop pH meters. They also don't offer a wide choice of pH electrodes. Hence, Health Canada does not recommend portable pH meters for measuring pH of tooth whitening products. Testing the pH of products with litmus paper won't be acceptable.

Calibrate the pH meter immediately before measuring the pH of the test sample. Use at least two standard buffer solutions (also known as certified buffer solutions)[5] for calibration. One of the buffers used should have a pH value of 7. The expected pH of the sample should be within the calibration range. **Measure and report the product pH in triplicate.**

The pH electrode used should be suitable for measuring the pH of the product form (such as a gel, semi-solid, etc.). Electrodes equipped with automatic temperature compensation are highly recommended. The pH measurement of certain tooth whitening products, such as tooth whitening strips, may require specialty pH electrodes or may require additional sample preparation steps. The notifier should verify that the pH electrode used by the testing laboratory is suitable for their product form.

The interpretation of pH data for non-aqueous samples is not well-defined. If the product sample contains less than 5% water (w/w), testing its pH using traditional procedures[6] may produce invalid results. In such situations, notifiers should contact Health Canada for further guidance.

To verify the accuracy, measure the pH of a standard buffer solution after measuring the pH of the samples. The pH of the verification buffer should not be the same as those used for calibration. The measured pH of the verification buffer should be within the tolerance limits of the certified pH value. If this is not the case, recalibrate the pH meter and repeat the pH measurements.

Submit a study report with details on the pH method that include the following information:

i. brand and model of the pH meter;
ii. brand and model of the pH electrode;
iii. pH of the calibration buffers used to calibrate the pH meter;
iv. pH of the verification buffer used; and,
v. the pH electrode's manual, technical specifications, or brochure.

## 5.2 Laboratory accreditation

Health Canada asks that the testing laboratory follow Good Laboratory Practices (GLP) during

[5] The standard buffer solutions are off-the-shelf products easily obtainable from laboratory chemical suppliers. They are either buffer solutions issued by the National Institute of Standards and Technology (NIST) or buffer solutions with certified pH values traceable to buffer standards from the NIST

[6] Procedures that are applicable to aqueous samples

pH measurements. Standardization agencies such as the Standards Council of Canada (SCC) offer GLP accreditation for laboratories. Send the laboratory's accreditation certificate to Health Canada, if available.

If the laboratory does not have a valid accreditation certificate, the notifier should send completed Checklist 1[7] and Checklist 3. These checklists ask for the following information:

- product name;
- name of the testing laboratory;
- laboratory accreditation;
- pH test method;
- QA/QC steps taken; and,
- pH study report (including test method).

**The laboratory manager (or other authorized personnel) should fill in and sign these checklists verifying that the information is accurate.** Please send details of all QA/QC steps and the test method along with the checklists.

### 5.3 pH study report

The laboratory study report should include:

- the sample preparation procedure (if applicable);
- the procedure used to calibrate and measure the pH (see section 4.1); and,
- the pH value of each trial and the average pH value (to two decimal places);

Health Canada cannot accept pH values of the products sent over phone or sent in an email.

Health Canada does not need a Safety Data Sheet (SDS) or product specification sheet. These documents are not equivalent to a pH study report.

## 6 Salivary peroxide study

Peroxides and peroxide-generating compounds are highly reactive chemicals. Chromogens are high molecular weight, complex organic molecules that cause tooth stains and discoloration. Peroxides react and degrade chromogens thereby reducing or eliminating tooth stain (SCCP, 2007). However, exposure of oral cavity to high concentrations of peroxide-containing products may cause adverse effects such as tooth sensitivity and gingival irritation (Pontes et al., 2020). Concentration of peroxides in the product, frequency, and duration of use are some of the factors that could contribute to the adverse effects. Generally, such adverse effects were observed with products containing greater than 3% w/w total peroxide concentration (Goldberg et al., 2010; Walsh, 2000).

[7] Health Canada recommends that you submit this information at the time of notification, prior to selling the product in Canada. If you are unable to demonstrate the safety of the product, Health Canada may remove the product from sale, refuse shipments at the border, or take other enforcement measures.

## 6.1 Clinical study

Health Canada requires salivary peroxide levels if the tooth whitening products contain more than 3% w/w hydrogen peroxide equivalents[8]. The salivary peroxide levels should be measured in a clinical study.

Before starting the clinical study:

- Prepare a detailed study design that includes:
  - the criteria for including or excluding participants,
  - written consent forms for the participants,
  - a detailed study plan,
  - study protocols and Standard Operating Procedures (SOPs) for applying the product, collecting the saliva samples, and analyzing the peroxide concentration, and,
  - a summary and interpretation of the salivary peroxide data;
- An independent ethics committee should review and approve the study design;
- Trained staff, such as a dentist, must screen all participants;
- All participants should fill in and sign the consent form; and,
- Recruit enough participants so that at least ten (10) will finish the study.

During the clinical study:

- Apply the product to the participants' teeth as per the directions of use on the label. This is to make sure that it matches real life conditions.
- The test product must be the same as described in the CNF (same ingredients, concentrations, physical form, and application method).
- Collect saliva samples at the recommended timepoints. Align collection times to match with how long the product is to stay on the teeth. See Appendix III for recommended timepoints.
- Measure peroxide concentration in the saliva samples using a validated analytical method. Stabilize the samples if peroxide concentration is not measured immediately. After the study, collect and organize salivary peroxide data for each participant and for each time point.
- Calculate the mean (and associated standard deviation) for each timepoint.
- Report the maximum peroxide level observed (including participant ID and time point), the range, and the mean.

Please refer to the International Council for Harmonization (ICH) guidelines for more guidance for conducting clinical trials (EMA, 2021).

[8] See Appendix II for conversion factors and illustration

## 6.2 Measure salivary peroxide concentration

Peroxides degrade rapidly in saliva (SCCP, 2007). Previous studies have indicated that pH, temperature, and the presence of certain metal ion impurities could significantly decompose peroxides in aqueous samples (Schumb, 1949). Therefore, analyze the samples as they are collected. If there is a delay, the laboratory should ensure the stability of peroxides in the samples until the time of analysis. Adjusting the pH and addition of stabilizing agents may be considered. In case of delayed analysis, the laboratory should provide additional data to demonstrate stability of peroxides.

Both enzymatic and non-enzymatic methods are available for measuring peroxides in aqueous and saliva samples (Hannig et al., 2003; Reichert et al., 1939). Enzymatic methods are more favorable as they are less prone for interferences from other organic matters present in saliva (Mailart et al., 2020). The laboratory should use a validated analytical method to measure the salivary peroxide concentrations. It should follow a pre-established laboratory SOP. Record all deviations from the SOP, rationale for the deviation, and any corrective measures taken and include them in the study report. Include the calibration curves for the salivary peroxide concentrations and QA/QC steps in the study report.

## 6.3 Laboratory accreditation

The laboratory should conduct the clinical study following Good Clinical Practices (GCP). If a valid GCP accreditation certificate is unavailable, the notifier should send to Health Canada the information outlined in Checklist 2 and Checklist 3. The laboratory manager (or other authorized person) should fill in and sign these checklists. Please send details of study protocol and all QA/QC steps. Health Canada uses these to determine whether the salivary peroxide measurements are reliable.

## 6.4 Clinical study report

Send to Health Canada a detailed study report prepared by the laboratory. The report should include:

- study design;
- criteria for including and excluding participants;
- number of participants (at least ten (10) must finish the study);
- age and sex of each participant;
- brand and name of the tested product;
- hydrogen peroxide content of the product (see Appendix II for hydrogen peroxide equivalents);detailed method description for measuring peroxide in saliva;
- QA/QC procedures;
- all salivary peroxide data, collected at various timepoints, for each participant; and,
- conclusions that are consistent with the results.

The laboratory manager (or other authorized personnel) should sign the study report. Health Canada will not accept a summary of the salivary peroxide data without the full report.

## 7 Document submission

Health Canada will review the following documents:

- label information;
- directions of use;
- pH study report; and,
- GLP accreditation for the pH testing laboratory. If a valid accreditation certificate is unavailable, complete Checklist 1 and Checklist 3 and send all the supporting documents.

For products that contain more than 3% peroxide or peroxide-generating compounds, Health Canada will also review the following documents:

- clinical study report; and,
- GCP accreditation for the testing laboratory. If a valid accreditation certificate is unavailable, complete Checklist 2 and Checklist 3 and send all the supporting documents.

Send all evidence of safety data when you notify your product. If Health Canada does not receive the requested data, it may:

- request a stop distribution of the product;
- refuse shipments at the border; or
- use other enforcement measures.

There are two ways to send the pH and clinical study data to Health Canada:

a) When notifying a product, include these reports in Section 6 of the CNF; or,
b) If the CNF has been already submitted, notifiers can use the "Transport Form"[9] to send these reports.

[9] The form "*Submitting Additional Documents to Health Canada*" is available at https://healthycanadians.gc.ca/apps/radar/HCT-TSC-0001.08.html

# 8 References


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## 9 Appendix I: Hotlist conditions for tooth whitening products containing peroxide and peroxide-generating compounds[1]

| Ingredient Information | | | Restrictions | | |
|---|---|---|---|---|---|
| Chemical | CAS (including but not limited to)[2] | Synonyms and Related Compounds (Including but not limited to)[3] | Conditions of Use by product type[4] | Maximum Concentration Permitted[5] | Warnings and Cautionary Statements: (to the effect of)[6] |
| Peroxide and peroxide-generating compounds | 124-43-6; 1305-79-9; 7722-84-1; 1335-26-8; 7632-04-4; 1314-22-3 | Urea peroxide; calcium peroxide; calcium dioxide; hydrogen peroxide; magnesium peroxide; sodium perborate; zinc peroxide | Oral products containing peroxides or peroxide-generating compounds:<br><br>Manufacturers should have the following information on hand as it may be requested by Health Canada:<br><br>1. A laboratory report providing pH of the product as applied to tooth or teeth. Section 13 of the Cosmetic Regulations requires that the pH is greater than or equal to 4.0<br>2. Product labelling indicating the directions of use and cautionary statements.<br>3. If an oral cosmetic contains more than 3% hydrogen peroxide (or | | "If irritation (such as redness, swelling, soreness) of the gums or the mouth occurs, discontinue use and consult an oral health professional."<br><br>"Products containing peroxides are not recommended for use by children under 12 years of age."<br><br>"Consult your oral health professional before prolonged use of this product."<br><br>"Avoid swallowing the cosmetic or part thereof."<br><br>"Avoid contact of the product with the eye." |

[1] Health Canada reviews and update information on the Hotlist periodically. Please consult the latest version of the Hotlist to obtain information on specific cosmetic ingredients.
[2] Cells in this column are left blank when the substance does not have a known CAS
[3] Cells in this column are left blank when no synonyms or related compounds are provided for the entry
[4] Cells in this column are left blank when no condition of use is specified, and the restriction applies to all cosmetic products
[5] Cells in this column are left blank when no maximum concentration is specified
[6] Cells in this column are left blank when no warning or cautionary statements are specified

| | | | | | |
|---|---|---|---|---|---|
| | | | equivalent), notifiers must submit a clinical study to demonstrate the salivary peroxide levels do not exceed 3% during the use of the product as per the directions of use.<br><br>NB: Be aware of the conversion factor between hydrogen peroxide and other peroxide-generating compounds. For example, 10% carbamide (urea) peroxide is approximately equivalent to 3% hydrogen peroxide. | | "Avoid direct contact of the active surface of the tooth whitening product with the gums and/or salivary flow." |

## 10 Appendix II : Conversion factors for peroxide and peroxide-generating compounds

| 1% of peroxide ingredient | Hydrogen Peroxide Equivalents* (%) |
|---|---|
| hydrogen peroxide | 1.00 |
| calcium peroxide | 0.472 |
| urea peroxide | 0.361 |
| magnesium peroxide | 0.602 |
| zinc peroxide | 0.349 |
| sodium perborate** | 1.00 |

** NOTE: Perborate salts are included in the "Boric acid and its salts" Hotlist entry. As such, products containing perborates should comply with Hotlist conditions for "peroxides and peroxide generating compounds" and "Boric acid and its salts".

**Example**: Hydrogen peroxide equivalents for a tooth whitening product containing 27.70% w/w urea peroxide is calculated as follows

Concentration of urea peroxide in the product = 27.70%

Conversion factor (from the above table) = 0.361

Hydrogen peroxide equivalents = 27.70 × 0.361

= 10.00% w/w

When a product contains more than one peroxide generating ingredient, convert the concentration of each ingredient into hydrogen peroxide equivalents as illustrated above and sum them to derive the total hydrogen peroxide equivalents.

## 11 Appendix III: Recommended timepoints for saliva collection

| Duration of product use, according to label instructions | Timepoints for saliva collection* | | | |
|---|---|---|---|---|
| | First | Second | Third | Fourth |
| 30 seconds | 0 seconds | 5 seconds | 15 seconds | 30 seconds |
| 5 minutes | 0 minutes | 1 minute | 3 minutes | 5 minutes |
| 15 minutes | 0 minutes | 1 minute | 5 minutes | 15 minutes |
| 20 minutes | 0 minutes | 1 minute | 5 minutes | 20 minutes |
| 30 minutes | 0 minutes | 1 minute | 5 minutes | 30 minutes |
| 8 hours | 0 minutes | 1 minute | 5 minutes | 30 minutes |

*Normally, salivary peroxide concentration peeks within the first 30 minutes of use.

# 12 CHECKLIST 1: pH data for tooth whitening products

## 12.1 Product information

a. Product name: _____

b. Regulatory ID *(if available)*: _____

c. Product form

☐ Liquid _____

☐ Semi-solid (such as gel) _____

☐ Other (e.g., tooth whitening strips)*; please specify*

_____

d. Does the product contain less than 5% (w/w) water?

☐ Yes

☐ No

e. Lot/Batch #: _____

f. Product pH (as applied to the teeth; **to two decimal places**): _____

## 12.2 Laboratory information

a. Name of the testing laboratory: _____

b. Laboratory address: _____

_____

c. Laboratory accreditation

i. Is the laboratory accredited to perform the study following Good Laboratory Practices or other quality management system?

☐ Yes *(please specify the name of the accreditation body)*:

_____

☐ No (fill in Checklist 3: Laboratory Qualifications)

ii. Did the laboratory send proof of accreditation (such as certificate or a statement on the letterhead of the accreditation body)?

☐ Yes

☐ No (fill in Checklist 3: Laboratory Qualifications)

## 12.3 Study method

a. Brand name and model of the pH meter: _____

b. Brand name and model of the pH electrode: _____

c. Calibration

i. Was the pH meter calibrated before the study?

☐ Yes. Date of calibration: _____

☐ No (*Give rationale*)

_____

_____

_____

_____

ii. State the pH of the calibration buffers used (to two decimal places):

Standard Buffer[1] 1 pH = _____

Standard Buffer 2 pH = _____

Standard Buffer 3 pH (Optional) = _____

iii. Were calibration standards used prior to their expiry date?

☐ Yes

☐ No

iv. Were the pH measurements within the calibration range?

☐ Yes

☐ No

v. Was the pH study performed according to a standard method (such as OECD, ASTM, ISO)?

☐ Yes (*Give the method name and state any deviations from the protocol*)
Methodology name: _____
(*Send a copy of the method, if not publicly available*)

☐ No (*give the detailed study protocol*)

[1] The standard buffer solutions are off-the-shelf products easily obtainable from laboratory chemical suppliers. They are either buffer solutions issued by the National Institute of Standards and Technology (NIST) or buffer solutions with certified pH values traceable to buffer standards from the NIST.

d. Performance verification

i. pH of the standard buffer (verification buffer):

_____

ii. Was the pH of the buffer tested immediately after the pH measurements of the sample(s)?

☐ Yes

☐ No (*Give rationale*):

_____

_____

_____

_____

iii. Was the pH of the verification buffer within the tolerance limits of its certified pH value?

☐ Yes

☐ No

If no, was the pH meter re-calibrated and were the pH measurements of the samples repeated?

☐ Yes

☐ No: The reported pH values of the products are not acceptable.

## 12.4 Study report

Please note that the study report should be on the official letterhead of the testing laboratory. The laboratory manager (or other authorized personnel) should sign the report.

a. Is a laboratory report provided with the submission of this checklist?

☐ Yes

☐ No (*Give rationale*)

_____

_____

_____

_____

## 12.5 Declaration

☐ The laboratory tested the notified product "as applied to teeth"[2]

☐ The pH electrode was suitable for testing the pH of the product form *(Send documents such as pH electrode manual to support your claim).*

☐ I confirm that all the information supplied in this checklist is true and exact.

Name[3]: _____

Position title: _____

Signature: _____

Date: _____

[2] The term "as applied to teeth" refers to the final form of the product the users will apply on their teeth.
[3] The laboratory manager or an authorized personnel of the testing laboratory should fill out and sign this checklist

# 13 CHECKLIST 2: Salivary peroxide study

## 13.1 Product information

a. Product name:
_____

b. Regulatory ID *(if available)*: _____

c. Product form

☐ Liquid _____

☐ Semi-solid (such as gel) _____

☐ Other (e.g., tooth whitening strips)*; please specify*

_____

d. Lot/Batch #: _____

## 13.2 Laboratory information

a. Name of the testing laboratory: _____

b. Laboratory address: _____
_____

c. Laboratory accreditation

i) Is the laboratory accredited to perform the study as per Good Clinical Practices (GCP) or other quality management system?

☐ Yes *(please specify the name of the accreditation body)*:
_____
_____

☐ No (fill in Checklist 3: Laboratory Qualifications)

ii) Did the laboratory send proof of laboratory accreditation (for example, an accreditation certificate or a statement on the letterhead of the accreditation body)?

☐ Yes

☐ No (fill in Checklist 3: Laboratory Qualifications)

## 13.3 Study Method

a. Study design

i) Did the study use human participants that are representative of the intended users (such as age, sex or gender) as per the label instructions?

☐ Yes
☐ No (*Give rationale*)

_____
_____
_____
_____

ii) How many participants completed the study? _____

iii) List the inclusion and exclusion criteria for the participants: (*if you need more space, attach a separate sheet*)

Inclusion criteria:

- 
- 
- 
- 

Exclusion criteria:

- 
- 
- 
- 

iv) Did study participants sign a written consent to take part in the study?

☐ Yes
☐ No. The clinical study is not acceptable.

v) Did an independent ethics board approve the study design?

☐ Yes
☐ No. The clinical study is not acceptable.

vi) Did the laboratory submit a detailed study protocol?

☐ Yes
☐ No. Notifiers should submit a detailed clinical study protocol with this checklist.

vii) Did the study deviate from the approved study protocol?

☐ Yes (give rationale)

_____
_____
_____
_____

☐ No

b. Product application

i) Do the chemical composition and physical form of the product used in the clinical study match exactly the notified product?

☐ Yes
☐ No (give rationale)

_____
_____
_____
_____

ii) Did the laboratory test the product "as applied to teeth"[1]?

☐ Yes
☐ No (give rationale)

_____
_____
_____
_____

[1] The term "as applied to teeth" refers to the final form of the product the users will apply on their teeth.

iii) Did the laboratory apply the product following all the directions of use?

☐ Yes
☐ No (give rationale)

_____
_____
_____
_____

iv) Did a dentist or trained personnel (such as dental technicians supervised by a dentist) apply the product to the participants?

☐ Yes
☐ No (give rationale)

_____
_____
_____
_____

c. Saliva sample collection

i) Were the sample collection timepoints consistent with the duration of application?

☐ Yes
☐ No (give rationale)

_____
_____
_____
_____

ii) Was a baseline saliva sample (that is, before applying the product) collected?

☐ Yes
☐ No (give rationale)

_____
_____
_____
_____

iii) Was there a time delay between saliva sample collection and analysis?

☐ Yes . If there was a time delay, how were the samples stabilized?

_____
_____
_____
_____

☐ No

iv) Are the data to support the stability of peroxides in saliva until the analysis included in the study report?

☐ Yes
☐ No (give rationale)

_____
_____
_____
_____

d. Salivary peroxide analysis

i) Did the laboratory use a standardized method for the analysis of peroxide content?

☐ Yes. (Name of the method and attach a copy of the standard or literature)

_____
_____
_____
_____

☐ No. (Send a detailed method description)

## 13.4 Study report

a. Did the laboratory send a detailed laboratory report?

☐ Yes
☐ No. Notifiers should submit a detailed laboratory report. Summary reports are not acceptable.

b. Does the study report include a detailed study method?
   ☐ Yes
   ☐ No

c. Does the report include salivary peroxide concentration data for all participants at all timepoints?
   ☐ Yes
   ☐ No. Notifier should submit all experimental data. Summary data (for example, average, median) are not sufficient.

d. Did the laboratory manager (or other authorized personnel) sign the study report?
   ☐ Yes
   ☐ No

## 13.5 Declaration

☐ I confirm that the information supplied in this checklist is true and exact.

Name[2]: _____

Position: _____

Signature: _____

Date: _____

[2] The laboratory manager (or other authorized personnel) of the clinical laboratory should fill out and sign this checklist.

# 14 CHECKLIST 3: Laboratory qualifications[1]

Note: Health Canada uses a variety of criteria, including the information on this page, to assess the safety of the product. Laboratories should complete this form for EACH submitted study.

## 14.1 Product information

a. Product name:
_____

b. Regulatory ID *(if available)*: _____

c. Product form

☐ Liquid _____
☐ Semi-solid (such as gel) _____
☐ Other(e.g., tooth whitening strips)*; please specify*
_____

d. Lot/Batch #: _____

## 14.2 Laboratory information

a. Name of the testing laboratory: _____

b. Laboratory address: _____
_____

## 14.3 Laboratory accreditation

a. What was the type of study performed by the laboratory?

☐ pH (go to question (3)b)
☐ Salivary peroxide (go to question (3) c)

b. Is the laboratory accredited to perform the study in accordance with Good Laboratory Practices (GLP) or other quality management system?

☐ Yes (please specify the name of the accreditation body):
_____
_____
_____
_____

[1] If the laboratory that tested pH of the tooth whitening product or conducted salivary peroxide study is not accredited, it can complete and submit this checklist with all the supporting documents in lieu of laboratory accreditation certificate. The laboratory should submit a separate form for both the pH study and the salivary peroxide study.

☐ No (go to question (3)e)

c. Is the laboratory accredited to perform the study in accordance with Good Clinical Practices (GCP)?

☐ Yes (please specify the name of the accreditation body):
_____
_____
_____
_____

☐ No (go to question (3)d)

d. Was a proof of accreditation (for example, an accreditation certificate or a statement on the letterhead of the accreditation body) submitted?

☐ Yes (go to Section 4)
☐ No

e. Did the laboratory use a standard study protocol (such as ASTM method)?

☐ Yes
☐ No (send a copy of the detailed study protocol)

f. Does the study protocol give details on GLP-compliant practices, **including** QA/QC protocols followed?

☐ Yes

☐ No (describe the QA/QC steps followed)

_____
_____
_____
_____

g. Did trained staff perform all laboratory testing?

☐ Yes
☐ No

h. Did the Study Director approve the study plan and all relevant SOPs before the study?

☐ Yes
☐ No

i. Did the laboratory record deviations from the study protocol?

☐ Yes (describe the deviations)

_____

_____

_____

_____

☐ No (i.e., no deviations from the study protocol)

j. Did the study staff clean, maintain, calibrate, and inspect all equipment on a regular schedule?

☐ Yes
☐ No

k. Did the study staff label all reagent bottles clearly and use them before the expiration date?

☐ Yes
☐ No

l. Did the study staff record all raw data promptly and accurately?

☐ Yes
☐ No

## 14.4 Declaration

☐ The final report accurately and completely describes the methods, procedures and observations, and the raw data.

☐ The laboratory has an active Quality Assurance Program.

☐ I confirm that the information supplied in this checklist is true and exact.

Name[2]: _____
Position: _____
Signature: _____
Date: _____

[2] The laboratory manager or an authorized individual of the laboratory should fill out and sign this checklist.