Japanese Dental Science Review 59 (2023) 23–27

Contents lists available at ScienceDirect

Japanese Dental Science Review

journal homepage: www.elsevier.com/locate/jdsr

A Japanese concept of considerations for evaluation of dental materials for tooth bleaching

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ARTICLE INFO

Article history:
Received 2 June 2022
Received in revised form 29 December 2022
Accepted 22 January 2023

Keywords:
Tooth bleaching
Tooth whitening
Ingredient
Safety
Efficacy

ABSTRACT

Recent advances in bleaching technology, such as bleaching ingredients, have accelerated the development of tooth whitening materials to change the color of natural teeth toward a lighter or whiter shade. Some bleaching materials are used for patients in combination with auxiliary medical devices to activate the bleaching materials by a light or heat source. Bleaching ingredients can be a poisonous and deleterious substance. Some bleaching materials are used in dental offices and the others at home. In clinical development of bleaching materials, appropriate evaluation of safety and efficacy is required according to the intended use. For appropriate and swift approval of the emerging bleaching materials, guideline on evaluation of dental whitening materials was discussed in a commissioned project by the Ministry of Health, Labour and Welfare of Japan for FY2021. Here, we summarize the current principles of the premarketing evaluation of the safety and efficacy.

Contents

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https://doi.org/10.1016/j.jdsr.2023.01.001

1. Introduction

Recent advances in bleaching technology have accelerated the development of dental materials (bleaching materials) used to change the color of natural teeth toward a lighter or whiter shade using chemicals. Bleaching materials are used at home and in dental offices. Bleaching materials may contain poisonous and deleterious substance and sometimes require the application of external energy (e.g. heat and light) to be used. In clinical development, it is imperative to appropriately ensure safety and efficacy according to the product's characteristics.

Bleaching materials are defined to be medical devices with generic names of dental bleaching materials and pharmaceuticals-containing dental tooth surface cleaner auxiliary material, and similar medical devices for dentistry intended for tooth bleaching specified in the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (The Pharmaceutical and Medical Device Act) [1].

The "Project for Development of Guideline on Evaluation of Dental Bleaching Materials" was established as a commissioned project by the Ministry of Health, Labour and Welfare of Japan for FY 2021. For appropriate and swift approval of dental bleaching materials, issues related to the evaluation of efficacy and safety were discussed at the committee of experts from the professional societies, related industry organizations, and government agencies. In this review, the resultant principles were summarized on the premarketing evaluation of bleaching materials in Japan.

2. General matter

To elucidate the evaluation of the bleaching material to be developed (hereinafter "the product"), the following points should be considered as a general matter. Definitions of some terms used in this paper were summarized in Table 1.

Firstly, the uniqueness, improvements, and equivalence when comparing the product with the existing bleaching materials should be clarified. It should be clarified that the product is applied to the patient by a dentist or a dental hygienist under the dentist's supervision (bleaching material for dentist use) or by the patient under the dentist's supervision (bleaching material for patient use). Principle and mechanism of the bleaching efficacy should be clarified, and if the activation of the bleaching ingredient with an auxiliary medical device and/or another ingredient were needed, their principle and mechanism should also be clarified.

Secondly, auxiliary medical devices should be considered for the following points. If a dedicated instrument for the preparation of the bleaching material (e.g. paste and paste mixing) at the time of use, the instrument by its brand name and notification number should be identified and scientific explanation of its validity is required. If no dedicated instrument is to be used, functions, performance, and specifications necessary for the instrument should be identified and the scientific validity be explained. Alternatively, if a medical device intended to activate the bleaching material by a light or heat source is used as a dedicated device, the medical device by its brand name and certification or approval number should be identified. If no dedicated device is to be used, functions, performance, and specifications necessary for the medical device to be used together should be identified. If use any tray for holding the product on the teeth surface or any material for the tray, functions, performance, and specifications of the tray should be identified.

Third point is applicability of the classification as a poisonous and deleterious substance. For instance, products with a hydrogen peroxide concentration exceeding 6.0 % or a carbamide peroxide concentration exceeding 17 % are subject to the Poisonous and Deleterious Substances Control Act [2]. If the ingredients and/or the product are considered poisonous or deleterious substances, the control method at the place of use should be clearly marked.

3. Matters of quality, safety, and performance

The evaluation items considered necessary to ensure the quality, efficacy, and safety are shown below. As a general rule, they should be appropriately evaluated according to the characteristics of the product or the finished product on physical and chemical property [3] and on biological safety [4].

Table 1
Definition of terms in this review.

Terms	Definitions
Bleaching material	A dental material used to change the color of natural teeth (vital and non-vital teeth) toward a lighter or whiter shade using chemicals.
Finished product	A medical device for dentistry or a component of a medical device for dentistry that has undergone all manufacturing processes, including packaging. If applicable, sterilization treatment is also included. However, if a product is processed/prepared before use after shipment, the term denotes the product in the state of actual use (e.g., mixed bleaching material). As many dental materials are used immediately after mixing, the final product includes the product in states both immediately after mixing and after curing.
Product	A product of a medical device for dentistry before processing or preparation (e.g., powder and liquid of a bleaching material, liquid and liquid of a bleaching material) that becomes a finished product after processing or preparation.
Bleaching	Act of removing congenital or acquired staining or discoloration of natural teeth using bleaching materials and, if necessary, in combination with auxiliary medical devices for activation such as a light or heat source.
Bleaching ingredient	Chemical substances that remove congenital or acquired staining or discoloration of natural teeth.
Bleaching material for dentist use	A bleaching material applied to a patient by a dentist or a dental hygienist under the dentist's supervision.
Bleaching material for patient use	A bleaching material used by the patient under the dentist's supervision.

3.1. Quality

When the product is visually inspected, powder, liquid, paste, or gel should be uniform and free from foreign matter. In addition, when the finished product prepared according to the product usage is visually inspected, powder, liquid, paste, or gel should be uniform. The concentration of hydrogen peroxide supplied by the bleaching material before the expiry date must be within a range of + 10 % to −30 % of the concentration indicated by the manufacturer for the unopened product. For products using carbamide peroxide, the value equivalent to the hydrogen peroxide concentration can be obtained by multiplying the carbamide peroxide concentration by 0.36. As the products with a hydrogen peroxide concentration exceeding 6.0 % or a carbamide peroxide concentration exceeding 17 % (hereinafter the "controlled concentration of poisonous and deleterious substances") are subject to the Poisonous and Deleterious Substances Control Act, the postmarketing control should be appropriately implemented [2]. With the bleaching materials for patient use, the controlled concentration of poisonous and deleterious substances shall not be exceeded. The product's stability should be evaluated "Determination of Shelf Life and Stability Studies of Medical Devices" [5].

3.2. Safety

Biological safety test should be performed based on the biological evaluation program in the risk management process of JIS T 14971 after fully considering the characteristics of the bleaching material, such as clinical positioning, users, use environment, and necessity of auxiliary medical devices [6]. In particular, for bleaching materials for patient use, it is necessary to identify hazards assuming the working condition at home and estimate the risks of each hazard. The safety should be demonstrated by evaluating the biological safety [4,7,8]. In the Attached Table 1 of the notification [4], for pharmaceuticals containing dental tooth surface–cleaning aids, the contact site is "Surface (oral)," and the contact duration is "Short to medium term." For dental bleaching materials, the contact site is "Surface (oral)," and the contact duration is "Temporary." In this case, the usage of the product should also be thoroughly considered. Furthermore, the container should be evaluated according to the classification determined on the basis of usage.

3.3. Performance for hardness and erosion

The working conditions of the product and the finished product is different between bleaching materials for dentist use and patient use. In addition, if the product or the finished product contains any ingredient intended for a purpose other than bleaching, the performance for the indication of the ingredient should be evaluated using an appropriate method. For hardness, when tested in accordance with JIS T 6542, the reduction (%) in the Knoop hardness (JIS Z 2251) or the Vickers hardness (JIS Z 2244) after bleaching shall not exceed 10 % [9–11]. The surface erosion of the teeth tested shall not exceed three times the level which is caused by the positive control solution when tested in accordance with JIS T 6542 [9].

3.4. Performance for bleaching efficacy

The bleaching effect should be tested in accordance with JIS T 6542: The color change toward a lighter shade after bleaching treatment shall be at least two shades (in the order of lightness) on the VITA classical shade guide compared with the shade before treatment. When using other shade guides to evaluate the bleaching efficacy, it should be demonstrated that the performance of the shade guide is adequate for the evaluation of the clinical bleaching efficacy. ΔE^*_{ab} before and after bleaching treatment shall be ≥ 2.0. At that time, the L^* value shall be increased and the b^* value shall be decreased after the treatment [12].

3.5. Performance for dentist use

The concentration of the bleaching ingredient should be set based on hardness, erosion, bleaching efficacy, and safety. The range of the concentration of the bleaching ingredients can be set with the lowest concentration and the highest concentration in the bleaching material. In this case, necessary actions should also be clearly indicated so that the dentist can adjust the concentration of the bleaching ingredient appropriately according to the patient's condition.

Application time and number of applications for bleaching material should also be established. The range for the application time can be set with the minimum time to the maximum time, and the range for the number of applications can be set with the maximum number of applications. In this case, necessary actions should also be clearly indicated so that the dentist can adjust the concentration of the bleaching ingredient appropriately according to the patient's condition.

For the concentration of the bleaching ingredient and the application time for the bleaching treatment, the necessary performance assuming the use scenario should be verified in the range of the maximum time at the maximum concentration and the minimum time at the minimum concentration from the bleaching efficacy perspective. When evaluated under the standard concentration and application times, the validity of the set range of the concentrations of the bleaching ingredient and the application times shall be evaluated.

3.6. Performance for patient use

As it is assumed to be used at home, the concentration of the bleaching ingredient should be constant (not adjustable by patients), and a sufficiently safe concentration should be established. If peroxide is used as a bleaching ingredient, the concentration shall not exceed the controlled concentration of poisonous and deleterious substances.

Application time and number of applications for bleaching material should be established. The range for the application time can be set with the minimum time to the maximum time, and the range for the number of applications can be set with the maximum number of applications. As it is assumed to be used at home, the application time and the number of applications should be set considering safety. Regarding the application time and the number

Table 2
Points to be evaluated for the equivalence to the existing approved products.

Points	Items to be considered
Safety	Biological safety [4,7,8]
Quality	– Appearance [9] – Chemical properties [3] – Hydrogen peroxide concentration [9] – Stability [5] – Packaging [9]
Performance	– Hardness [9–11] – Erosion [9] – Bleaching efficacy [9,12] – Evaluation required for differences in products
Others	Evaluation by supplementary tests such as use simulation using animals.

of applications, necessary measures should also be clearly indicated so that a dentist and a dental hygienist under the dentist's supervision can give appropriate guidance according to the patient's condition.

For the application time and the number of applications of the bleaching material at the established concentration of the bleaching ingredient, the necessary performance assuming the use scenario should be verified in the range of the application time and the range of the number of applications from the viewpoint of the bleaching efficacy. When evaluated under the standard application time and number of applications, the justification for the minimum and maximum time and the maximum number of applications should be evaluated.

4. Other matters

For the product and the finished product, if it is difficult to confirm the equivalence to an approved product in accordance with the evaluations explained above. Besides, if the clinical evaluations to demonstrate the clinical efficacy and safety are considered not necessary, the evaluation by supplementary tests, such as animal testing should also be considered depending on the characteristics of the product and the finished product.

4.1. Matters related to nonclinical studies

If the product has been approved in Japan and has no novelty in the usage compared with the existing approved products, the clinical evaluations to demonstrate the clinical efficacy and safety are not required. However, in this case, the product's safety and efficacy should be evaluated appropriately through the evaluations emphasizing the equivalence to the existing approved products (Tables 2 and 3). If there is any concomitant medical device, evaluating auxiliary use is also necessary.

4.2. Matters related to clinical studies

If there is a novelty in the concentration, ingredients, and usage of the bleaching material and if it is difficult to evaluate with nonclinical studies, clinical evaluations may be necessary to demonstrate its clinical safety and efficacy. When performing such evaluations with clinical studies, the safety and efficacy should be properly evaluated through the following items. If there is any auxiliary medical device, evaluating concomitant use would be also necessary. In addition, if the product or the finished product contains any ingredient intended for a purpose other than bleaching, the performance for the indication of the ingredient should be evaluated using an appropriate method.

The safety should be evaluated by history-taking, oral examination, and tests during, immediately after, one week after, and approximately one month after the bleaching procedure.

The efficacy based on the difference in shade determined by shade taking of the teeth before and after bleaching using the VITA classical shade guide with samples arranged in the order of lightness is evaluated. At this time, the color change toward a lighter shade after bleaching treatment shall be at least two shades (in the order of lightness) compared with the shade before treatment. When using other shade guides to evaluate the bleaching efficacy, it should be demonstrated that the performance of the shade guide is adequate for the evaluation of the clinical bleaching efficacy. In addition, as the supplementary evaluation of the appropriateness of the evaluation, the evaluation by tooth color measurement using an electronic color measuring device should also be performed. At that time, ΔE^*_{ab} shall be ≥ 2.0. Moreover, after the test, the L^* value shall be increased, and the b^* value shall be decreased [12].

4.3. Auxiliary medical devices

If any instrument is to be used to prepare the bleaching material, it should be evaluated that appropriate preparation can be obtained by the instrument.

If heating or light irradiation is required to activate the bleaching material, the principle and mechanism of activation should be clarified. It should be also evaluated whether the necessary bleaching efficacy can be attained. In addition, once it is demonstrated, the device should be identified to meet the requirements as a concomitant medical device. If it is not specified as an auxiliary medical device, it is necessary to indicate the irradiation conditions to achieve the necessary bleaching efficacy.

If there is a tray and materials for the tray to hold the bleaching material on the teeth surface, the methods for preparation and use of this tray should be clarified and be evaluated the concomitant use with the bleaching material. In addition, it is necessary to separately evaluate the quality, safety, and performance required for this tray.

Table 3
Some bleaching products approved in Japan.

Product	User	Bleaching ingredient	Safety	Concomitant medical devices
WHITEESSENCE WHITENING PRO	Dentist	35 % hydrogen peroxide	Deleterious substance	Light source
Opalescence BOOST	Dentist	35 % hydrogen peroxide	Deleterious substance	Light source
TION IN OFFICE	Dentist	Approximately 23 % hydrogen peroxide	Deleterious substance	Light source
PYRENEES	Dentist	3.5 % hydrogen peroxide		Light source
HiLite	Dentist	35 % hydrogen peroxide	Deleterious substance	Light source
Opalescence 10 %	Patient	10 % carbamide peroxide		
TION TAKE HOME	Patient	10 % carbamide peroxide		
TION TAKE HOME PLATIUM	Patient	10 % carbamide peroxide		
HiLite Home	Patient	10 % carbamide peroxide		
HiLite SHADE UP	Patient	10 % carbamide peroxide		

5. Conclusions

Here we present a concept for the principles of premarketing evaluation of the safety and efficacy of dental materials used to change the color of natural teeth (vital and non-vital teeth) toward a lighter or whiter shade using chemicals according to the intended use and usage considering that bleaching materials are used in dental offices and at home.

The principles present what is considered crucial at present, given that the principles apply to bleaching materials amid rapid technological innovation. Thus, the concept will be revised in future with further technological innovation and accumulation of knowledge, and it does not have any binding force regarding the contents of the application for regulatory approval. The evaluation of bleaching materials covered by this document should be conducted flexibly in the context of scientific rationale, with a thorough understanding of the individual product characteristics. Furthermore, consideration should be given to consulting this document, as well as other relevant national and international guidelines.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

We thank all members of the committee for their useful comments. The views mentioned here do not necessarily represent the views and findings of the Ministry of Health, Labour and Welfare or the Pharmaceuticals and Medical Devices Agency of Japan. This work was supported by a Grant from the Ministry of Health, Labour and Welfare of Japan.

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[9] JIS T 6542 Materials for external tooth bleaching.
[10] JIS Z 2251 Knoop hardness test – Test method.
[11] JIS Z 2244 Vickers hardness test – Test method.
[12] JIS Z 8781-4 Colorimetry – Part 4: CIE 1976 $L^*a^*b^*$ Color space.