Flexcon® Omni-Wave™ (Omni-Wave™ 2.0): Safety data sheet review and interpretation of biocompatibility test results for determination of compliance with ISO 10993-1 and CDRH electrocardiograph electrode guidance

Purpose

The purpose of this report for Flexcon Adhesive Omni-Wave™ (Omni-Wave™ 2.0) is to provide: 1) A review of Safety Data Sheets for the base compounds regarding skin irritation and sensitization potential, 2) Result interpretations for biocompatibility testing, cytotoxicity per ISO 10993-5 (1) and irritation per ISO 10993-23 (2) and skin sensitization per ISO 10993-10 (3), and 3) Determination of compliance with ISO 10993-1 (4) guidance for medical devices and the CDRH guidance for industry: Electrocardiograph electrodes (5).

Device Intended Use and Identification /Formulation

The Omni-Wave™ ECG patches are intended for use as components for further manufacturing or processing by ECG medical device manufacturers and are not themselves finished devices. The electrocardiograph electrodes are intended to be in continuous patient contact for up to seven days.

Safety Data Sheet Review

Upon review of the SDS for the base components, skin irritation and skin sensitization from the base components are considered unlikely, based on animal test results or limited residual volume for component with no information available. Per ISO 10993-1: 2018, biological evaluation tests for consideration are cytotoxicity, irritation, and sensitization.

ISO 10993-1 Device Category and Biological Evaluation Tests for Flexcon Adhesive Omni-Wave™

ISO 10993-1: 2018 guidance (4) addresses the determination of the effects of medical devices on tissues, mostly in a general way, rather than in a specific device-type situation. Thus, for a complete biological safety evaluation, it classifies medical devices according to the nature and duration of their anticipated contact with human tissues when in use and indicates, in matrices, the biological data sets that are thought to be relevant in the consideration of each device category. Per ISO 10993-1: 2018 Annex A Table A.1, the Flexcon Adhesive Omni-Wave™ may be categorized as surface device, intact skin contact, and contact duration B-prolonged (> 24 h to 30d), based on continuous patient contact for up to seven days. The ISO 10993-1: 2018 biological evaluation tests for consideration are cytotoxicity, irritation, and sensitization. Biocompatibility testing performed per Electrocardiograph Electrodes Guidance for Industry and ISO 10993-1 guidelines is summarized in Table 1.

Table 1. Biological Effects Considered for Adhesive Omni-Wave™ Formulation

ISO 10993-1 **Evaluation endpoint considered**	**Report**	**Report Date**	**Results**
Cytotoxicity - L929 Direct Contact ISO 10993-5:2009	LabCorp 23-01728-G1	12/8/2023	Cytotoxic
Sensitization - Direct Buehler ISO 10993-10:2021	LabCorp 23-01728-G3	2/9/2024	Non-sensitizer
Irritation - Direct Primary Skin ISO 10993-23:2021	LabCorp 23-01728-G2	12/19/2023	Non-irritant

Interpretation of Biocompatibility Tests Conducted for Adhesive Omni-Wave™

Cytotoxicity test results (6): The purpose of the study was to determine the potential biological reactivity of a mammalian monolayer cell culture (L929) in response to direct contact with Adhesive Omni-Wave™ (Omni-Wave™ 2.0). When Adhesive Omni-Wave™ (Omni-Wave™ 2.0) was applied directly to a monolayer cell culture of L929 cells, severe reactivity (Grade 4) occurred similar to that of the positive control, indicating a cytotoxic potential. However, it is well known that due to the composition of some gels and soft rubbers, a positive cytotoxicity result may not be a correct indication of *in vivo* cytotoxic reactivity (5). Although any *in vitro* cytotoxic effect can be of concern, it is primarily an indication of potential for *in vivo* toxicity and the device cannot necessarily be determined unsuitable for the intended clinical application based solely on cytotoxicity data (1). Therefore, evaluation using other tests more specific for the intended clinical application in accordance with ISO 10993-1: 2018 recommendation are appropriate, specifically skin irritation and sensitization for Adhesive Omni-Wave™ (Omni-Wave™ 2.0) categorized as a skin contact device (5).

Skin Irritation test results (7): The purpose of this study was to evaluate the potential of Adhesive Omni-Wave™ (Omni-Wave™ 2.0) to produce dermal irritation after a single topical 4 hour exposure (followed by residual test material removed by rinsing with sterile water for injection) to the skin of New Zealand White rabbits. Patches of Adhesive Omni-Wave™ (Omni-Wave™ 2.0) were applied directly to the skin and kept in contact with the skin for 4 hours. Following 4 hours, the patches were removed and the animals were observed for signs of erythema and edema at 1, 24, 48 and 72 hour post patch removal. No signs of erythema or edema were observed at any observation point. Therefore, Adhesive Omni-Wave™ (Omni-Wave™ 2.0) was considered a negligible skin irritant after 4 hours of exposure.

Skin Sensitization test results (8): The purpose of this study was to determine the potential of Adhesive Omni-Wave™ (Omni-Wave™ 2.0) to produce skin sensitization following topical application to albino guinea pigs. Adhesive Omni-Wave™ (Omni-Wave™ 2.0) patches were applied (6 hour exposure, followed by residual test material removed by rinsing with sterile water for injection) for three consecutive days per week for three weeks (induction phase). Fourteen days after the last induction application, Adhesive Omni-Wave™ (Omni-Wave™ 2.0) patch was applied (6 hour exposure, (followed by residual test material removed by rinsing with sterile water for injection) to a naïve skin site (challenge application). At 24 and 48 hours after removal of the challenge patch, skin reaction was scored. No skin reaction at the challenge sites were observed, indicating negligible skin sensitization. Based on the results of this study, there appears to be no potential for sensitization in humans for intended continuous patient contact for up to seven days.

Data Review Summary

Taking into consideration the intended use of the Flexcon Adhesive Omni-Wave™ as a dermal contact device, the review of the Safety Data Sheets for the base components with regards to skin irritation and skin sensitization indicated that skin irritation and skin sensitization from the base components is considered unlikely from limited, direct exposure to some of the base compounds. For confirmation, the biological tests recommended in CDRH guidance (5), cytotoxicity, skin irritation, and skin sensitization, were conducted.

The cytotoxicity test indicated a cytotoxic potential. Although any *in vitro* cytotoxic effect can be of concern, it is primarily an indication of potential for *in vivo* toxicity and the device cannot necessarily be determined unsuitable for the intended clinical application based solely on cytotoxicity data. Therefore, evaluations using other tests more specific for the intended clinical application in accordance with ISO 10993-1: 2018 recommendation are appropriate, specifically skin irritation and skin sensitization for Adhesive Omni-Wave™ categorized as a skin contact device. The skin irritation test resulted in no signs of skin irritation observed and, therefore, Adhesive Omni-Wave™ was considered a negligible skin irritant, when applied for no more than 4 hours. The skin sensitization test resulted in no skin reaction observed at the induction and challenge sites, indicating negligible potential for skin sensitization.

Conclusion

The Food and Drug Administration Center for Devices and Radiological Health (5) recommends that, to ensure the device (i.e., electrocardiograph electrodes) performs as intended, the following electrode characteristics are to be evaluated: biocompatibility, electrical performance, adhesive performance, and shelf life. With regards to electrical performance, adhesive performance, and shelf life, no data were reviewed to allow for an opinion as to safety for clinical testing. The biocompatibility testing performed for Adhesive Omni-Wave™, specifically cytotoxicity, skin irritation, and skin sensitization, resulted in determinations of negligible skin sensitization potential and negligible skin irritation potential for applications of 4-6 hours, followed by residual test material removed by rinsing with sterile water for injection after each exposure. In that continuous patient contact of about 3-7 days is anticipated, it is recommended that a dermal irritation (i.e., continuous exposure) study be conducted with duration of at least 7 days to provide confidence of negligible skin irritation for intended patient exposure to Adhesive Omni-Wave™.

References

1. ISO 10993-5 (2009). Biological evaluation of medical devices – Part 5. Tests for in vitro cytotoxicity.
2. ISO 10993-23 (2021). Biological evaluation of medical devices – Part 23. Tests for irritation.
3. ISO 10993-10 (2010). Biological evaluation of medical devices – Part 10. Tests for skin sensitization.
4. ISO 10993-1. (2018). Biological evaluation of medical devices -- Part 1: Evaluation and testing within a risk management process.
5. Electrocardiograph Electrodes – Class II Special Controls Guidance for Industry and Food and Drug Admiistration Staff. July 21, 2011(content current as of June 28, 2018).
6. L929 Direct Contact Cytotoxicity Test – ISO. Final GLP Report: 23-01728-G1. LabCorp Corporation. December 28, 2023.
7. Direct Primary Skin Irritation Test – ISO. Final GLP Report: 23-01728-G2. LabCorp Corporation. December 19, 2023.
8. Direct Buehler Sensitization Test – ISO. Final GLP Report: 23-01728-G3. LabCorp Corporation. February 9, 2024.

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