Flexcon® Adhesive Omni-Wave™ (Omni-Wave™ 1.0) Safety data sheet review and interpretation of biocompatibility test results for determination of compliance with ISO 10993-1 and CDRH electrocardiograph electrode guidance (1)

I. Purpose

The purpose of the Flexcon (Adhesive Omni-Wave™ (Omni-Wave™ 1.0)) report was to summarize the following for the Flexcon Omni-Wave™ Adhesive (Omni-Wave™ 1.0):

1. A review of Safety Data Sheets (SDS) for the four base compounds regarding skin irritation and sensitization potential.
2. Result interpretations for biocompatibility testing, cytotoxicity per ISO 10993-5 (2009). Biological evaluation of medical devices – Part 5. Tests for in vitro cytotoxicity (2) and irritation and skin sensitization per ISO 10993-10 (2010). Biological evaluation of medical devices – Part 10. Tests for irritation and skin sensitization (3); and
3. Determination of compliance with ISO 10993-1 (2018). Biological evaluation of medical devices -- Part 1: Evaluation and testing within a risk management process (4) guidance for medical devices and the FDA's Guidance for Industry and Food and Drug Administration Staff – Class II Special Controls Guidance Document: Electrocardiograph Electrodes (5).

As described in further detail below, although the Omni-Wave™ Adhesive tested positive for cytotoxic potential, it tested negative for skin irritation and skin sensitization. The SDS for the base components of the Omni-Wave™ Adhesive also support that irritation and sensitization is unlikely.

However, because the irritation study conducted was limited to four hours of exposure, further dermal irritation testing is recommended with duration of at least seven days to provide confidence of negligible skin irritation for intended patient exposure to the Omni-Wave™ Adhesive for this time period.

II. Intended Use and Identification

The Omni-Wave™ Adhesive is intended for use as part of Flexcon's Omni-Wave™ electrocardiograph (ECG) electrode patch components. 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 Omni-Wave™ Adhesive, as used in the Omni-Wave™ ECG patches, is intended to be used in applications that may require continuous patient contact for up to seven days.

III. Safety Data Sheet Review for Base Components

The SDS data sheet review for the base components of the Omni-Wave™ Adhesive suggests that skin irritation and skin sensitization from the base components is unlikely, based on available animal test results. Where no such information/results were available for the base component, the limited residual volume of the base component in the Omni-Wave™ Adhesive suggests that dermal (skin) irritation and sensitization is unlikely to occur from exposure to the Omni-Wave™ Adhesive.

IV. ISO 10993-1 Device Category and Biological Evaluation Tests for the Omni-Wave™ Adhesive

The ISO 10993-1: 2018 guidance 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, the ISO 10993-1: 2018 guidance 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.

Omni-Wave™ ECG patches (which use the Omni-Wave™ Adhesive) are intended for use as components in finished devices that will require surface contact for intact skin for up to seven days. Per ISO 10993-1: 2018 Annex A Table A.1, the medical device category for the Omni-Wave™ ECG patches are surface medical device, intact skin contact, contact duration B-prolonged (> 24 h to 30d). For this category, the applicable ISO 10993-1: 2018 endpoints to be addressed for biological assessment of the Omni-Wave™ Adhesive are cytotoxicity, irritation, and sensitization.

V. Interpretation of Biocompatibility Tests Conducted for the Omni-Wave™ Adhesive

V.a. Cytotoxicity Testing and Results (6)

The purpose of this *in vitro* study was to determine the potential biological reactivity of a mammalian monolayer cell culture (L929) in response to direct contact with the Omni-Wave™ Adhesive.

When the Omni-Wave™ Adhesive was applied directly to a monolayer cell culture of L929 cells, moderate reactivity (Grade 3) 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, such as those that comprise the Omni-Wave™ Adhesive, a positive cytotoxicity result may not be a correct indication of *in vivo* cytotoxic reactivity (4,5).

Although any *in vitro* cytotoxic effect can be of concern, it is primarily an indication of potential for *in vivo* toxicity (i.e., toxicity in the human body) and the adhesive cannot necessarily be determined unsuitable for

the intended clinical application based solely on *in vitro* cytotoxicity data (1). Therefore, evaluation using other tests more specific for the intended clinical application, in accordance with ISO 10993-1: 2018 recommendation, is appropriate, specifically skin irritation and sensitization for the Omni-Wave™ Adhesive categorized as a skin contact (4,5).

V.b. Skin Irritation Testing and Results (7)

The purpose of this study was to evaluate the potential of the Omni-Wave™ Adhesive to produce dermal irritation after a single topical 4-hour exposure (followed by residual test material removed by washing with saline) to the skin of New Zealand White rabbits. Patches of the Omni-Wave™ Adhesive 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, the Adhesive Omni-Wave™ was considered a negligible skin irritant after 4 hours of exposure.

V.c Skin Sensitization Testing and Results (8)

The purpose of this study was to determine the potential of the Omni-Wave™ Adhesive to produce skin sensitization following topical application to albino guinea pigs. Omni-Wave™ Adhesive patches were applied (6-hour exposure, followed by residual test material removed by washing with saline) for three consecutive days per week for three weeks (induction phase). Fourteen days after the last induction application, the Omni-Wave™ Adhesive patch was applied (6-hour exposure, followed by residual test material removed by washing with saline) 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.

Flexcon Company, Inc. | 1 Flexcon Industrial Park. | Spencer, MA 01562-2642. | T: 1 (508) 885-8200 | F: 1 (508) 885-8400