

# Review and Evaluation of INAMED Reproductive Toxicity Studies:

## *Fertility/Developmental Toxicity Study of Patched BIOCELL® INTRASHIEL® Shell of Gel-filled Implants and Extended F<sub>1</sub>-Generation Reproductive Toxicity Evaluation of Patched BIOCELL® INTRASHIEL® Shell of Gel-filled Implants*

### 1. Executive Summary

The Food and Drug Administration (FDA) has requested additional data from INAMED Corporation, specifically a 2-generation reproductive toxicity study on the patched BIOCELL® INTRASHIEL® shell of gel-filled implants, to support their Premarket Approval Application, PMA P020056. INAMED has requested that [REDACTED] review and evaluate the currently available reproductive toxicity data for the patched BIOCELL® INTRASHIEL® shell material in order to assess the potential reproductive toxicity of this material as supplemental information to INAMED's PMA submission. This report is a summary of our findings and conclusions regarding the potential reproductive toxicity of the patched BIOCELL® INTRASHIEL® shell material.

INAMED has conducted two developmental and reproductive toxicity studies on the patched BIOCELL® INTRASHIEL® shell material implanted into female Sprague-Dawley rats. The first study examined the fertility and reproduction in female rats implanted with this material and studied developmental effects in the offspring. An extended F<sub>1</sub>-generation reproductive toxicity evaluation has also been conducted to examine the reproductive ability and developmental effects through two generations of directly exposed female rats and male rats that may be exposed indirectly *in utero* and through lactation. Histopathological examinations were conducted in the extended F<sub>1</sub>-generation reproductive evaluation to assess potential cellular changes in the reproductive organs. The findings in these studies include:

- No clinical differences in the behavior or parturition of the animals;
- No signs of toxicity in any of the animals;
- No differences between sham-operated and implanted animals in reproductive functionality as measured by mating and fertility;
- No differences in fetal outcomes between the two groups of animals;
- No differences in fetal or pup development in the gross, visceral or skeletal examinations; and
- No differences in the histopathological examination of reproductive tissues in the F<sub>1</sub> generation of animals from the extended F<sub>1</sub>-generation reproductive toxicity evaluation.

The lack of adverse reproductive and developmental effects is supported by the body of literature on various silicone elastomers, gels and fluids. Few studies have reported effects and essentially all of these effects are either considered to be not treatment related or they could be attributable to maternal toxicity. Additionally, inhalation toxicity data for low-molecular weight siloxanes, although not directly relevant, suggests a threshold for any observed reproductive and developmental effects at high doses of these compounds.

[REDACTED] concludes that INAMED's studies on the patched BIOCELL® INTRASHIEL® shell material do not suggest any adverse reproductive or developmental effects from the implantation of the patched BIOCELL® INTRASHIEL® shell of gel-filled implants in Sprague-Dawley rats. This is based on the lack of any changes in reproductive functionality, lack of developmental effects in two generations of offspring, and the scientific literature on other silicone elastomers, gels, fluids, and low-molecular weight siloxanes. Additional data on the development of the second generation of animals are unlikely to provide any evidence of adverse reproductive effects.

## 7. Bibliography

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