Column E Explanation

This form is intended as an aid to completing the Column E explanation. It is not an official form and its use is voluntary. Names, addresses, protocols, veterinary care programs, and the like, are not required as part of an explanation. A Column E explanation must be written so as to be understood by lay persons as well as scientists.

1. Registration Number: 41-R-0074

2. Number 12 of animals used in this study.

3. Species (common name) Guinea pig of animals used in the study.

4. Explain the procedure producing pain and/or distress.

Exploratory study evaluating control and test article toxicity following daily subcutaneous dosing for 21 days in Guinea pigs. Purpose is to determine if the Guinea pig is the most appropriate model for testing toxicology of the test article per FDA request. Animals were dosed with either control article, mid-dose test article or High-dose test article.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see Item 6 below)

Study is designed to test the toxicity potential of the test article. The use of anesthetics, analgesics or tranquilizers to alleviate pain is prohibited due to the potential molecular interaction between the drugs and the compounds associated with the test article. This interaction may cause a response (inhibitory or synergistic) and add a confounding variable to the study that could affect the outcome. In order to effectively evaluate the characteristics of the test article the use of medications is prohibited.

6. What, if any, federal regulations require this procedure? Cite the agency, the code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

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1. Registration Number: 41-R-0074

2. Number 74 of animals used in this study.

3. Species (common name) Guinea pig of animals used in the study.

4. Explain the procedure producing pain and/or distress.
Buehler - Three times a week for three weeks the test sample is administered to the left upper back using patches soaked in formaldehyde and the animal is wrapped to keep the patch in contact with the skin for Six hours. 14 days after the last administration all test and control animals are challenged with the formaldehyde on the right upper back using patches soaked in the test sample and the animals is wrapped to keep the patch in contact with the skin for 6 hours. 24 and 48 hours after unwrap the sites are scored for edema and erythema.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see Item 6 below)
This study is designed to test the allergenic potential of medical devices in accordance to ISO 10993-10. The use of anesthetics, analgesics or tranquilizers to alleviate pain is prohibited due to the potential molecular interaction between drugs and compounds associated with the device. This interaction may cause a response (inhibitory or synergistic) that could affect the outcome of the study and create a false positive or false negative.

6. What, if any, federal regulations require this procedure? Cite the agency, the code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

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1. Registration Number: 41-R-0074

2. Number 90 of animals used in this study.

3. Species (common name) Guinea pig of animals used in the study.

4. Explain the procedure producing pain and/or distress.
Guinea Pig Maximization test. Study comprised of 2 induction phases and a challenge phase. Induction I uses 6 intradermal injections (0.1ml each) in combination with Fruends complete adjuvant and the test or control extract to enhance the State of immunological activity of the animal to the material of interest. A pre-treatment of 10% Sodium Lauryl Sulfate is applied to the Skin Prior to the start of induction II. Induction II involves application of a patch containing the test or control sample to the intrascapular region for 48 hours. 14 days after Induction II all animals are challenged with the test and control sample by application of a patch to the left and right flank for 24 hours. 24 and 48 hours after patch removal the test and control application sites are scored for edema and erythema.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see Item 6 below)
Study is designed to test the allergenic potential of medical devices in accordance to ISO 10993-10. The use of anesthetics, analgesics or Tranquilizers to alleviate pain is prohibited due to the potential molecular interaction between drugs and compounds associated with the device. This interaction may cause a response (inhibitory or synergistic) that could affect the outcome of the study and create a false positive or a false negative.

6. What, if any, federal regulations require this procedure? Cite the agency, the code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

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1. Registration Number: 41-R-0074

2. Number 15 of animals used in this study.

3. Species (common name) Rabbit of animals used in the study.

4. Explain the procedure producing pain and/or distress.
Intracutaneous Reactivity test - Each rabbit is dosed with 5 injections (0.2ml) of test and 5 injections (0.2ml) of control intradermally along each dorsolateral side. If polar and non-polar extracts are used this is repeated (for 20 total injections) with the polar solvent injected more dorsal than the non polar solvent. 24, 48 and 72 hours after patch removal dose sites are observed and graded for edema and erythema.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see Item 6 below)
This Study is designed to test the irritation potential of medical devices in accordance to ISO 10993-10. The use of anesthetics, analgesics or tranquilizers to alleviate pain is prohibited due to the potential molecular interaction between drugs and compounds associated with the device. This interaction may cause a response (inhibitory or synergistic) that could affect the outcome of the study and create a false positive or false negative

6. What, if any, federal regulations require this procedure? Cite the agency, the code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

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1. Registration Number: 41-R-0074

2. Number 18 of animals used in this study.

3. Species (common name) Rabbit of animals used in the study.

4. Explain the procedure producing pain and/or distress.
Animal Irritation test - Two control patches and two test patches are applied directly to the skin of each animal. The application sites are wrapped to keep the patches in contact with the skin for 4 hours. 24, 48 and 72 hours after patch removal dose sites are observed and graded for edema and erythema. Positive control used is formaldehyde.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see Item 6 below)
This study is designed to test the irritation potential of medical devices in accordance to ISO 10993-10. The use of anesthetics, analgesics or tranquilizers to alleviate pain is prohibited due to the potential molecular interaction between drugs and compounds associated with the device. This interactions may cause a response (inhibitory or synergistic) that could affect the outcome of the study and create a false positive or a false negative.

6. What, if any, federal regulations require this procedure? Cite the agency, the code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

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Amended Doc included Request 07.23.15

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1. Registration Number: 11-R-0074

2. Number 12 of animals used in this study.

3. Species (common name) Guinea Pig of animals used in the study.

4. Explain the procedure producing pain and/or distress.

Exploratory Study evaluating Control and test article toxicity following daily subcutaneous dosing for 21 days in Guinea Pigs.

Guinea pigs were administered test or control article by subcutaneous injection once daily for 21 days. Animals were observed for signs of toxicity immediately before and after injection daily and observations recorded. Body weight and feed consumption were measured prior to injection. doses were based on the most recent body weight. Animals on study were individually housed to eliminate potentially confounding variables and accurately assess feed consumption. Animal Health, including body weight and feed consumption clinical pathology and histopathology are crucial endpoints to assessing the

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see Item 6 below)

toxicity potential of the test article. The use of anesthetics, analgesics, or tranquilizers to alleviate pain was prohibited due to potential molecular interaction between these drugs and the test article.

6. What, if any, federal regulations require this procedure? Cite the agency, the code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

Agency_____ CFR_____