Designation: F1439 – 24

Standard Guide for Performance of Lifetime Bioassay for the Tumorigenic Potential of Implant Materials[1]

This standard is issued under the fixed designation F1439; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

1. Scope

1.1 This guide is intended to assist the testing laboratory in the conduct and evaluation of tumorigenicity tests to evaluate the potential for materials to evoke a neoplastic response.

1.2 Carcinogenicity, which includes tumorigenic potential, is one of several biological effects that should be considered when evaluating the biological response to a material or a final, finished medical device as recommended in Practice F748. It is assumed that the evaluator has already determined that this type of testing is necessary for a particular material or medical device before consulting this guide. The recommendations of Practice F748 should be considered before a study is commenced.

1.3 Whenever possible, it is recommended that a battery of genotoxicity tests be proposed and initiated as an alternative to an *in vivo* tumorigenicity bioassay. Chemical information and data from the literature regarding non-genotoxic carcinogens, if present, may also be considered when evaluating the carcinogenic potential. Genotoxicity assays may also be considered as initial screening procedures due to the sensitivity of the assays, the significant reduction in time to gain valuable data, and the desire to reduce the use of animals for testing. Genotoxicity assays that may be considered are outlined in Guide E1262 and in OECD 471, OECD 487, and OECD 490. The investigator is advised to carefully consider the appropriateness of a particular method for application after a review of the published literature.

1.4 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety, health, and environmental practices and determine the applicability of regulatory limitations prior to use.*

1.5 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

E1262 Guide for Performance of Chinese Hamster Ovary Cell/Hypoxanthine Guanine Phosphoribosyl Transferase Gene Mutation Assay

F748 Practice for Selecting Generic Biological Test Methods for Materials and Devices

2.2 *Other Documents:*

Overview of study designs used by NTP[3]

OECD Guidelines for Testing of Chemicals: Guideline 451 Carcinogenicity Studies[4]

OECD Guidelines for Testing of Chemicals: Guideline 453 Combined Chronic Toxicity/Carcinogenicity Studies[4]

OECD Guidelines for Testing of Chemicals: Guideline 471 Bacterial Reverse Mutation Test[4]

OECD Guidelines for Testing of Chemicals: Guideline 487 In Vitro Mammalian Cell Micronucleus Test[4]

OECD Guidelines for Testing of Chemicals: Guideline 490 In Vitro Mammalian Cell Gene Mutation Tests Using the Thymidine Kinase Gene[4]

21 CFR Part 58 Good Laboratory Practice for Nonclinical Laboratory Studies[5]

ICH S1C Dose Selection for Carcinogenicity Studies of Pharmaceuticals[6]

[1] This guide is under the jurisdiction of ASTM Committee F04 on Medical and Surgical Materials and Devices and is the direct responsibility of Subcommittee F04.16 on Biocompatibility Test Methods.

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[2] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at www.astm.org/contact. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

[3] Available from National Institute of Environmental Health Sciences, 111 T. W. Alexander Drive, Research Triangle Park, NC, August 1988. http://www.niehs.nih.gov/.

[4] Available from Organization for Economic Cooperation and Development, 2001 L Street, N.W., Suite 650, Washington, D.C. 20036-4922. http://www.oecd.org/washington/contact.htm.

[5] Available from U.S. Government Printing Office Superintendent of Documents, 732 N. Capitol St., NW, Mail Stop: SDE, Washington, DC 20401, http://www.access.gpo.gov.

[6] Available from European Medicines Agency, 7 Westferry Circus, Canary Wharf, London, E14 4HB, UK, www.emea.europa.eu.

3. Terminology

3.1 *Definitions of Terms Specific to This Standard:*

3.1.1 *carcinogenic*—a substance is considered to be carcinogenic if it can be shown to be causally related to an increased incidence of malignant neoplastic formation in humans or animals.

3.1.2 *maximum implantable dose*—the maximum weight or volume of the test article which can be reasonably implanted into the test site taking into account the gross distention of tissue which can occur and its possible effects on test results.

3.1.3 *mutagenic*—a substance is considered to be mutagenic if it induces alterations in the genetic code of the cell.

3.1.4 *tumorigenic*—a substance is considered to be tumorigenic if it can be shown to be causally related to an increased incidence of neoplastic formation whether malignant or benign.

4. Significance and Use

4.1 This guide is not intended to specify the exact method of conducting a test for any particular material or final, finished device but only to present some of the criteria that should be considered in method design and possible problems that could lead to misleading results. In the development of the actual test protocol, it is recommended that alternatives to animal testing be considered as appropriate. If tumor bioassays are considered necessary, experimental design should include valid methods[3] and an adequate number of animals should be included for meaningful statistical evaluation of the data.

4.2 The recommendations given in this guide may not be appropriate for all applications, types of implant materials, or all medical devices. These recommendations should be utilized by experienced testing personnel in conjunction with other pertinent information and the requirements of the specific application.

5. Choice of Animal Model

5.1 These types of bioassays for chemical substances have traditionally been performed in mice or rats, or both, because of their small size, relative cost factors, and lifespan. For the testing of materials and medical devices, mice are not recommended because the small animal size is not conducive to the placement of solid implants. The investigator should seriously consider the use of one of the traditional models in order to draw upon the extensive information available about typical tumor formation rates and sites in control animals. The National Toxicology Program (NTP)[3] recommends the use of Fischer 344 (F344/N) rats. However, other readily available species and strains may also be acceptable for the performance of these studies. Other rat species which have been recommended include Sprague-Dawley, Long-Evans, and Wistar. Some investigators have recommended the use of Long-Evans or Wistar rats because of the difficulty of achieving a two-year lifespan for Fischer and Sprague-Dawley rats.

5.2 The currently accepted level of testing in a particular site of implantation or medical specialty should be carefully researched and regulatory requirements determined before a study design is finalized to ensure acceptability of the final results.

5.3 The appropriate choice of male or female animals or a combination should be carefully considered in light of the particular material and application being investigated. If the device will ultimately be used only in the male or female, only one sex may need to be evaluated. Otherwise, both sexes should be used.

5.4 The decision to use other species for study should be carefully documented in terms of a clear need. The use of species which have not previously been used may reduce the amount of comparative data available on control animals. Typical tumor rates for hamsters, rats, and mice have been tabulated and are available in Refs (**1-3**).[7]

6. Selection of Size and Form of Implant

6.1 Tumorigenicity bioassays have traditionally been performed using chemical substances as the challenge. The evaluation of implant materials requires that solid material be implanted in some form.

6.2 It may be important to determine the site of administration of the test material that is most appropriate to the end use before determining implant size. The site of implantation should mimic the anticipated end use, if possible. If the implantation at the target site is not feasible, the site of implantation could be the paravertebral muscle. Where a specific material may be utilized in more than one type of device, multiple sites of relevant administration should be considered for different implants (for instance, materials that may be in contact with bone or implanted into internal organ tissue might be tested in both tissues).

6.3 The physical form of the test material should be representative of that intended for use in human patients and should consider potential material debris, if appropriate. The investigator should be aware that tests have shown (**4**) that powdered polymeric materials may not elicit a tumorigenic response subcutaneously even when prepared from polymers that do induce tumors when implanted in the form of a film. The impact of physical form and surface properties on tumorigenesis must be carefully considered in making decisions about the physical form of the implants (**5-10**).

6.4 Researchers have found that the aspect ratio (length/diameter) of fiber materials may play a role in the tumorigenesis of a particular material (**11, 12**). When new fibrous materials are being tested, the actual fiber length to be anticipated in practice should be studied. If fragmentation can be anticipated or is a worst-case possibility, an attempt should be made to document a clinically relevant fiber length.

6.5 The material to be tested should originate from sample(s) representative of all processing including surface finishing, passivation, and sterilization or other final processing that will occur to a finished medical device.

[7] The boldface numbers in parentheses refer to the list of references at the end of this guide.