Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices
May 1, 1995 (G95-1)

This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP's.

NOTE: This memo was distributed with Blue Book Memorandum #G95-1, entitled Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" and relates to implementation of #G95-1.

May 1, 1995

Director, Office of Device Evaluation (ODE)

Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices

Division Directors, ODE

The new blue book memorandum #G95-1 entitled "Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part-1: Evaluation and Testing," includes an FDA-modified matrix that designates the type of testing needed for various medical devices (copy attached). It also includes a flow chart entitled "Biocompatibility Flow Chart for the Selection of Toxicity Tests for 510(k)s." The guidance will be effective for all submissions that will be received on or after July 1, 1995. The former guidance, #G87-1 entitled "Tripartite Biocompatibility Guidance," may continue to be applied until a final decision is reached on each submission received prior to July 1, 1995. Sponsors may, however, choose to follow this new memorandum immediately. In addition, questions presented to staff by submitters regarding this change in biocompatibility testing should be discussed with you to determine the most appropriate resolution of the issues.

To implement the new blue book policy, it is essential that we train all our reviewers in the proper use of the ISO-10993 with modified matrix. I have asked Dr. Raju Kammula to arrange training sessions to train all reviewers in ODE.

Through CDRH Staff College he will be scheduling several training sessions to discuss the differences between the Tripartite and ISO

guidances and how to use the new bluebook guidance with modified ISO matrix. These training sessions will be conducted in May and June. Please advise all reviewers in your division to attend a training session so that they will be fully informed and knowledgeable on how to use the ISO standard before July 1, 1995.

I have also asked Raju Kammula to coordinate the development of toxicology profiles for devices in prolonged and permanent contact categories and devices with a significantly large volume of submissions. Each division must identify the appropriate devices and develop these profiles. Please provide the name of at least one individual to work with Raju Kammula to develop these profiles.

Attachment

cc: D. Bruce Burlington M.D.

General Program Memorandum - #G95-1

May 1, 1995

Director, Office of Device Evaluation (ODE)

Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing"

ODE Reviewing Staff

Purpose

The purpose of this memo is to replace, after July 1, 1995, the use of ODE General Program Memorandum G87-1, entitled "Tripartite Biocompatibility Guidance", dated April 24, 1987 with Part-1 of the ISO standard "Biological Evaluation of Medical Devices", which includes an FDA-modified matrix.

Background

Biological evaluation of medical devices is performed to determine the potential toxicity resulting from contact of the component materials of the device with the body. The device materials should not, either directly or through the release of their material constituents: (i) produce adverse local or systemic effects; (ii) be carcinogenic; or, (iii) produce adverse reproductive and developmental effects. Therefore, evaluation of any new device intended for human use requires data from systematic testing to ensure that the benefits provided by the final product will exceed any potential risks produced by device materials.

When selecting the appropriate tests for biological evaluation of a

medical device, one must consider the chemical characteristics of device materials and the nature, degree, frequency and duration of its exposure to the body. In general, the tests include: acute, sub-chronic and chronic toxicity; irritation to skin, eyes and mucosal surfaces; sensitization; hemocompatibility; genotoxicity; carcinogenicity; and, effects on reproduction including developmental effects. However, depending on varying characteristics and intended uses of devices as well as the nature of contact, these general tests may not be sufficient to demonstrate the safety of some specialized devices. Additional tests for specific target organ toxicity, such as neurotoxicity and immunotoxicity may be necessary for some devices. For example, a neurological device with direct contact with brain parenchyma and cerebrospinal fluid (CSF) may require an animal implant test to evaluate its effects on the brain parenchyma, susceptibility to seizure, and effects on the functional mechanism of choroid plexus and arachnoid villi to secrete and absorb (CSF). The specific clinical application and the materials used in the manufacture of the new device determines which tests are appropriate.

Some devices are made of materials that have been well characterized chemically and physically in the published literature and have a long history of safe use. For the purposes of demonstrating the substantial equivalence of such devices to other marketed products, it may not be necessary to conduct all the tests suggested in the FDA matrix of this guidance. FDA reviewers are advised to use their scientific judgement in determining which tests are required for the demonstration of substantial equivalence under section 510(k). In such situations, the manufacturer must document the use of a particular material in a legally marketed predicate device or a legally marketed device with comparable patient exposure.

International Guidance and Standards

In 1986, FDA, Health and Welfare Canada, and Health and Social Services UK issued the Tripartite Biocompatibility Guidance for Medical Devices. This Guidance has been used by FDA reviewers, as well as by manufacturers of medical devices, in selecting appropriate tests to evaluate the adverse biological responses to medical devices. Since that time, the International Standards Organization (ISO), in an effort to harmonize biocompatibility testing, developed a standard for biological evaluation of medical devices (ISO 10993). The scope of this 12-part standard is to evaluate the effects of medical device materials on the body. The first part of this standard "Biological Evaluation of Medical Devices: Part 1: Evaluation and Testing", provides guidance for selecting the tests to evaluate the biological response to medical devices. Most of the other parts of the ISO standard deal with appropriate methods to conduct the biological tests suggested in Part 1 of the standard.

ISO 10993, Part 1, and the FDA-modified Matrix

The ISO Standard, Part 1, uses an approach to test selection that is very similar to the currently-used Tripartite Guidance, including the same seven principles. It also uses a tabular format (matrix) for laying out the test requirements based on the various factors discussed above. The matrix consist of two tables. See Attachment A, Table 1 - Initial Evaluation Tests for Consideration, and Attachment B, Table 2 -

Supplementary Evaluation Tests for Consideration. Attachment C is a biocompatibility flow chart for the selection of toxicity tests for 510(k)s. It may be applicable to some PMAs also but not all PMAs. In addition, FDA is in the process of preparing toxicology profiles for specific devices. These profiles will assist in determining appropriate toxicology tests for these devices.

To harmonize biological response testing with the requirements of other countries, FDA will apply the ISO standard, Part 1, in the review process in lieu of the Tripartite Biocompatibility Guidance.

FDA notes that the ISO standard acknowledges certain kinds of discrepancies. It states "due to diversity of medical devices, it is recognized that not all tests identified in a category will be necessary and practical for any given device. It is indispensable for testing that each device shall be considered on its own mertis: additional tests not indicated in the table may be necessary." In keeping with this inherent flexibility of the ISO standard, FDA has made several modifications to the testing required by ISO 10993-Part 1. These modifications are required for the category of surface devices permanently contacting mucosal membranes (e.g., IUDs). The ISO standard would not require acute, sub-chronic, chronic toxicity and implantation tests. Also, for externally communicating devices, tissue/bone/dentin with prolonged and permanent contact (e.g., dental cements, filling materials etc.), the ISO standard does not require irritation, systemic toxicity, acute, sub-chronic and chronic toxicity tests. Therefore, FDA has included these types of tests in the matrix.

Although several tests were added to the matrix, reviewers should note that some tests are commonly requested while other tests are to be considered and only asked for on a case-by-case basis. Thus, the modified matrix is only a framework for the selection of tests and not a checklist of every required test. Reviewers should avoid proscriptive interpretation of the matrix. If a reviewer is uncertain about the applicability of a specific type of test for a specific device, the reviewer should consult toxicologists in ODE.

FDA expects that manufacturers will consider performing the additional tests for certain categories of devices suggested in the FDA-modified matrix. This does not mean that all the tests suggested in the modified matrix are essential and relevant for all devices. In addition, device manufacturers are advised to consider tests to detect chemical components of device materials which may be pyrogenic. We believe that ISO 10993, Part 1, and appropriate consideration of the additional tests suggested by knowledgeable individuals will generate adequate biological data to meet FDA's requirements. Reviewers in the Office of Device Evaluation will accept data developed according to the ISO-10993, Part 1, with the matrix as modified and presented in this memorandum (#G95-1).

Manufacturers are advised to initiate discussions with the appropriate review division in the Office of Device Evaluation, CDRH, prior to the initiation of expensive, long-term testing of any new device materials to ensure that the proper testing will be conducted. We also recognize that an ISO standard is a document that undergoes periodic review and is subject to revision. ODE will notify manufacturers of any future revisions to the ISO standard referenced here that affect this

document's requirements and expectations.

Effective Date: This Guidance is effective for all submissions that will be received on or after July 1, 1995. The former guidance, G87-1 entitled "Tripartite Biocompatibility Guidance," may continue to be applied until a final decision is reached on each submission received prior to July 1, 1995. Sponsors may, however, choose to follow this new memorandum immediately. After this transition period for submissions covered by the Tripartite Biocompatibility Guidance, G87-1 will be recinded and replaced by this guidance.

Susan Alpert, Ph.D., M.D.

Attachment A

Initial Evaluation Tests for Consideration

Device Categories			**Biological Effect**							
Body Contact (see 4.1)		Contact duration (see 4.2) A-limited (24h) B-prolonged (24h to 30 days) C-permanent (>30days)	**Cytotoxicity**	**Sensitization**	**Irritation or Intracutaneous Reactivity**	**System Toxicity (Acute) Sub-chronic toxicity (sub-acute toxicity)**		**Genotoxicity**	**Implantation**	**Haemocompatibility**
Surface devices	Skin	A	x	x	x	.	.	.	.	.
		B	x	x	x	.	.	.	.	.
		C	x	x	x	.	.	.	.	.
	Mucosal membrane	A	x	x	x	.	.	.	.	.
		B	x	x	x	o	o	.	o	.
		C	x	x	x	o	x	x	o	.
	Breached or compromised	A	x	x	x	o	.	.	.	.
		B	x	x	x	o	o	.	o	.

	surfaces	C	x	x	x	o	x	x	o	.
External communicating devices	Blood path, indirect	A	x	x	x	x	.	.	.	x
		B	x	x	x	x	o	.	.	x
		C	x	x	o	x	x	x	o	x
	Tissue/bone/ dentin communicating+	A	x	x	x	o	.	.	.	.
		B	x	x	o	o	o	x	x	.
		C	x	x	o	o	o	x	x	.
	Circulating blood	A	x	x	x	x	.	o^	.	x
		B	x	x	x	x	o	x	o	x
		C	x	x	x	x	x	x	o	x
Implant devices	Tissue/ bone	A	x	x	x	o	.	.	.	.
		B	x	x	o	o	o	x	x	.
		C	x	x	o	o	o	x	x	.
	Blood	A	x	x	x	x	.	.	x	x
		B	x	x	x	x	o	x	x	x
		C	x	x	x	x	x	x	X	x

X = ISO Evaluation Tests for Consideration
O = Additional Tests which may be applicable
Note + Tissue includes tissue fluids and subcutanous spaces
Note ^ For all devices used in extracorporial circuits

*See Table 2 for Supplementary Evaluation Tests

Attachment B

Supplementary Evaluation Tests for Consideration

Device Categories			Biological Effect			
Body Contact (see 4.1)		Contact duration (see 4.2) A-limited (-24h) B-prolonged (24h to 30 days) C-permanent (>30days)	Chronic Toxicity	Carcinogenicity	Reproductive/Developmental	Biodegradable
Surface devices	Skin	A	.	.	.	.
		B	.	.	.	.
		C	.	.	.	.
	Mucosal membrane	A	.	.	.	.
		B	.	.	.	.
		C	o	.	.	.
	Breached or compromised surfaces	A	.	.	.	.
		B	.	.	.	.
		C	o	.	.	.
External communicating devices	Blood path, indirect	A	.	.	.	.
		B	.	.	.	.
		C	x	x	.	.
	Tissue/bone/ dentin communicating	A	.	.	.	.
		B	.	.	.	.
		C	o	x	.	.
	Circulating blood	A	.	.	.	.
		B	.	.	.	.
		C	x	x	.	.
Implant devices	Tissue/	A	.	.	.	.

	bone	B	.	.	.	.
		C	x	x	.	.
	Blood	A	.	.	.	.
		B	.	.	.	.
		C	x	x	.	.

X = ISO Evaluation Tests for Consideration
O = Additional Tests which may be applicable

*See Table 1 for Initial Evaluation Tests.

(Updated April 12, 1996)

Attachment C

Biocompatibility Flow Chart for the Selection of Toxicity Tests for 510(k)s