Provisional Translation (as of March 2010) *

PFSB/ELD (*Iyakushin*) Notification No.0213001
February 13, 2003

To: Directors of Pharmaceutical Affairs Divisions
Prefectural Governments

From: Director of Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Basic Principles of Biological Safety Evaluation Required for Application for Approval to Manufacture (Import) Medical Devices

Among data to be submitted when applying for approval to manufacture (import) medical devices, the data relating to biological safety have been handled according to the PAB/MDD (*Yakuki*) Notification No.99, dated June 27, 1995, "Guidelines for Biological Tests Required for Application for Approval to Manufacture (Import) Medical Devices." However, the guidelines have been abolished, and the basic principles for risk evaluation of adverse biological effects (toxic hazards) and biological safety evaluation have newly been stipulated as shown in the attached sheets. Accordingly, you are requested to provide your guidance to relevant business parties and organizations under your jurisdiction.

This Notification shall apply to medical devices for which applications for approval are to be submitted on and after April 1, 2003; however, the risk evaluation of adverse biological effects (toxic hazards) and testing for that purpose may be performed, based on this Notification, with respect to medical devices for which applications for approval are to be submitted from February 13, 2003 onwards.

Please note that copies of this Notification will be sent to the Board Chairperson of the Japan Association for the Advancement of Medical Equipment; the Chairman of the Japan Federation of Medical Devices Associations; the Chairman of Medical Devices and Diagnostics Subcommittee, the American Chamber of Commerce in Japan; and the Chairman of the Medical Equipment Committee, the European Business Council in Japan.

* This English version of the Japanese Notification is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

Basic Principles for Biological Safety Evaluation

1. Purpose

   This document, as a tool for safety evaluation of medical devices prior to marketing, provides basic principles for risk evaluation of adverse biological effects (toxic hazards) and biological safety evaluation/test.

2. Definitions

   Definitions of terminology utilized in this document shall be as follows:

   1) Material

      Refers to a material for medical devices or a material used in the manufacturing processes for medical devices (including test/inspection process and sterilization process), such as synthetic or natural polymer compounds, metals, alloys, ceramics and other chemical substances.

   2) Finished product

      Refers to a post-test/inspection medical device ready for shipment and, in the case of a sterile product, refers to a product after sterilization. However, in the event that the shipped product is to be processed and prepared for use, "finished product" is a product in a state where it is actually used.

   3) Hazard

      Refers to a factor that may cause adverse effects on human health, such as genotoxicity, sensitization or chronic systemic toxicity.

   4) Risk

      Refers to a probability and a degree of such a hazard that causes an adverse effect on human health.

3. Adoption of International Standards

   As a rule, biological safety evaluation of medical devices shall be performed in compliance with the ISO 10993 "Biological Evaluation of Medical Devices" series as international standards. Specifically, based on the framework and principles of ISO 10993-1 "Evaluation and Testing," the necessary evaluation items shall be selected corresponding to the nature and duration of contact of individual medical devices with the body. In addition, safety evaluation is conducted through the selection of appropriate test methods for each evaluation item by referring to the guidelines for test methods described in the ISO 10993-2 and other parts.

   The test method guidelines in the ISO 10993 series generally include lists of multiple test methods for each evaluation item. For those test methods indicated, it is not clearly specified how to apply a given test method to each medical device or how to use the results obtained using such test methods when evaluating each medical device. Before conducting the tests, therefore, it is important to select an appropriate test method based on the following clauses 4 to 8.

   The international standards have been continuously revised according to the development of science and technology. Accordingly, an appropriate test method must be selected, considering the most current international standards at the time when testing is conducted.

4. Principles of Biological Safety Evaluation

1) Biological safety evaluation of materials or medical devices must be carried out using risk analysis techniques specified in ISO 14971 “Medical Devices - Application of Risk Management to Medical Devices.” The intended use/intended purpose and the safety properties of a medical device must be clarified, known or foreseeable hazards must be identified, and the risk of each hazard must be anticipated. If such a risk analysis technique is employed, its positive results represent detection and identification of some hazards and do not necessarily mean non-conformity of the medical device. The safety of such medical device must be evaluated through continued risk analyses.

2) Biological safety evaluation must be comprehensively carried out based on the results of safety tests conducted in accordance with this Notification and the following information, test results for safety evaluation items specific to such medical device, the latest relevant scientific literature and other non-clinical studies and clinical experiences (including post-marketing surveillances), taking the risk-benefit profile into consideration.
   a) Information relating to materials
   b) Information relating to contaminants generated from materials or during the manufacturing processes or their residues
   c) Information relating to leachable substances (for example, qualitative and quantitative chemical properties of the substances leached from the finished product)
   d) Information relating to biodegradation
   e) Information relating to other components and their interactions in a finished product
   f) Properties and characteristics of the finished product

3) Biological safety evaluation must be conducted by experienced specialists with sufficient education and training.

4) If the case falls under any of the following conditions, biological safety evaluation must be performed, however, the necessity to carry out re-tests or add test items must be considered thoroughly. For example, if the amount of leached substances is negligible from a toxicological standpoint or if their toxicity is known and acceptable, it is not necessarily required to conduct the re-tests.
   a) Change of suppliers or any change in the specifications of the materials used for the product.
   b) Any change in the materials, formulation, manufacturing processes, sterilization or primary packaging of finished products.
   c) Any change observed in the finished products during the storage period.
   d) Any change in the intended use of the finished products.
   e) Any evidence that the product may cause adverse events.

5. Selection of Evaluation Items

1) Items to be evaluated for the biological safety of each medical device shall be selected by following the requirements specified in ISO 10993-1. As a general rule, evaluation must be made for the items shown in Table 1, depending on the categorization in accordance with the nature of body contact and the duration of contact as described below. When evaluation is made for a medical device that does not fall into any of the categories, the closest category should be selected. If multiple categories for the duration of contact apply to the medical device, the item that corresponds to the category with the longer duration should be evaluated. When there are categories applicable to multiple regions of contact, the items that correspond to each category should be evaluated.

i) Categorization by Nature of Body Contact of Medical Device

a) Non-contact devices:	Medical devices that do not contact the patient's body directly or indirectly
b) Surface devices:	
○ Skin	Medical devices that contact intact skin surfaces only
○ Mucous membranes	Medical devices that contact intact mucous membranes such as oral cavity, esophagus and urethra
○ Breached or compromised surfaces	Medical devices that contact breached or otherwise compromised skin or mucous membranes
c) External communicating devices	
○ Blood path, indirect	Medical devices that contact blood path at one point and serve as a conduit for drug entry into the vascular system
○ Tissue, bone, or dentin	Medical devices that contact tissue, bone, or pulp and dentin system
○ Circulating blood	Medical devices that contact circulating blood
d) Implant devices	
○ Tissue or bone	Medical devices that contact tissue and/or bone
○ Blood	Medical devices that principally contact blood

ii) Categorization by duration of contact

○ Limited contact	Medical devices with a contact duration of less than 24 hours
○ Prolonged contact	Medical devices of which single, multiple or longer-term use has a contact duration of not less than 24 hours and up to 30 days
○ Permanent contact	Medical devices of which single, multiple or long-term use has a contact duration exceeding 30 days

2) Evaluation of equivalence to already approved medical devices or evaluation according to appropriate published literature is acceptable in lieu of the evaluation for the items shown in Table 1, and it is not necessarily required to conduct all of the test items shown in Table 1. In this case, however, it is necessary to clearly determine such appropriateness.

3) Table 2 should be referred based on the duration of contact, nature of contact with the medical device and characteristics of materials, and then it should be considered whether there is a need to conduct tests regarding chronic toxicity, carcinogenicity, reproductive/developmental toxicity and biodegradation.

4) As for acute systemic toxicity, subacute toxicity and chronic toxicity, if the implant testing or simulated use testing includes observation items and biochemical data that are needed for those toxicity tests, it is possible to use the testing results in lieu of those of such toxicity tests.

5) The biological safety evaluation with only those items shown in Table 1 or Table 2 may be insufficient in some cases or in other cases, a simple application of substitute tests may not be possible, and thus evaluation items must be investigated, taking the properties of the medical device into account adequately. For example, the below mentioned tests are insufficient for tooth pulp stimulation testing for composite resin or contact lens trials. It is necessary to conduct the evaluation on immunotoxicity if the immunotoxicity is suspected from the results of toxicity tests and other data. Also, it may be difficult to simply apply the below mentioned tests to cell/tissue engineered medical devices.

6. Test Methods

1) In the guidelines for test methods specified in the ISO 10993 series, various test methods for each evaluation item are listed in parallel, but which test method should be selected from among them is not indicated. When there are multiple test methods for a given evaluation item, selection must be done taking into account the principles, sensitivity, selectivity, quantitative capability, and reproducibility of the test methods as well as application method and limitation of test samples, with respect to the significance of the biological safety evaluation for the medical device in question. For example, the following items should be considered as to tests for cytotoxicity, sensitization and genotoxicity.

a) In the case of cytotoxicity, ISO 10993-5 “Tests for In Vitro Cytotoxicity” includes the extraction test method (colony method or subconfluent method), the indirect contact method (agar overlay method, filter diffusion method) and the direct contact method (direct contact via the subconfluent method). Since the sensitivity, quantitative capability, etc. of these test methods are varied, in order to detect potential hazards for risk evaluation, it is necessary to use a quantitative test method with high detection sensitivity (for example, the extraction test method).

b) Regarding tests for sensitization and genotoxicity, in particular, if the concentration of leached substances in the test solution is low for some extraction solvents, the volume of leached substances used in testing is limited, which may lead to false negative results. The provisions relating to extraction solvents in ISO 10993-12 state that a stressed extraction method must also be considered to detect potential hazards for risk evaluation. To evaluate the toxicity of unknown substances contained in a medical device, a solvent with a high extraction rate must be selected.

2) It is not logical to establish a uniform test method nor is it necessary to adhere to a specific test method. However, it is essential to clarify the basis and justification for the judgment that the results obtained using the selected test methods meet the requirements for evaluating safety in clinical use.

7. Test Samples
   1) Test samples used in testing for biological safety evaluation of medical devices include finished products, parts of a finished product and materials. Among them, a suitable test sample must be selected by investigating its ability to evaluate the safety of a finished product and by demonstrating scientific justification for the selection.

   2) Many medical devices are manufactured by combining multiple materials, and the manufacturing processes (including the sterilization process) can chemically alter the materials. If the manufacturing processes chemically alter the materials, testing must be conducted using test samples taken from the finished product or using simulated test samples manufactured under the same conditions. If the manufacturing processes do not alter the materials chemically, testing may be conducted using the materials as the test sample.

   3) When the chemical substances as part of the materials are changed to new chemical substances but are not chemically altered, and if it is more reasonable to conduct tests on such chemical substances than tests using the materials or finished product as the test sample, from a viewpoint of conducting both the tests and the evaluation, the former tests can replace the latter.

8. Animal Welfare
   The treatment of animals used in animal testing is performed according to the Law for the Humane Treatment and Management of Animals and ISO 10993-2 “Animal Welfare Requirements.”

Table 1 Guidelines for Primary Evaluation

Category	Duration of contact		Biological test								
	A: Limited contact (< 24 hours)										
Nature of contact	B: Prolonged contact (24 hours - 30 days)		Cytotoxicity	Sensitization	Irritation/intracutaneous reactivity	Acute systemic toxicity	Subacute toxicity	Genotoxicity	Pyrogenousity	Implantation	Hemocompatibility
	C: Permanent contact (> 30 days)										
Non-contact devices											
Surface devices	Skin	A	○	○	○						
		B	○	○	○						
		C	○	○	○						
	Mucous membrane	A	○	○	○						
		B	○	○	○						
		C	○	○	○		○	○			
	Breached or compromised surface	A	○	○	○						
		B	○	○	○						
		C	○	○	○		○	○			
External communicating devices	Blood path, indirect	A	○	○	○	○			○		○
		B	○	○	○	○			○		○
		C	○	○		○	○	○	○		○
	Tissue/bone/dentin	A	○	○	○						
		B	○	○				○		○	
		C	○	○				○		○	
	Circulating blood	A	○	○	○	○			○		○
		B	○	○	○	○		○	○		○
		C	○	○	○	○	○	○	○		○
Implant devices	Tissue/bone	A	○	○	○						
		B	○	○				○		○	
		C	○	○				○		○	
	Blood	A	○	○	○	○			○	○	○
		B	○	○	○	○		○	○	○	○
		C	○	○	○	○	○	○	○	○	○

Table 2 Guidelines for Supplemental Evaluation

Category	Duration of contact		Biological test			
	A: Limited contact (< 24 hours)					
Nature of contact	B: Prolonged contact (24 hours - 30 days)		Chronic toxicity	Carcinogenicity	Reproductive/ developmental toxicity	Biodegradation
	C: Permanent contact (> 30 days)					
Non-contact devices						
Surface devices	Skin	A				
		B				
		C				
	Mucous membrane	A				
		B				
		C				
	Breached or compromised surface	A				
		B				
		C				
External communicating devices	Blood path, indirect	A				
		B				
		C	○	○		
	Tissue/bone/dentin	A				
		B				
		C		○		
	Circulating blood	A				
		B				
		C	○	○		
Implant devices	Tissue/bone	A				
		B				
		C	○	○		
	Blood	A				
		B				
		C	○	○		