IYAKUSHINHATSU No.0213001
February 13, 2003

To: Directors of Prefectural Pharmaceutical Divisions

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

Basic Principles for Biological Safety evaluation Required Concerning Applications for Approval for Manufacturing (Importing) of Medical Devices

Among the data to be attached when applying for approval of manufacturing (importing) of medical devices, the handling of data concerning biological safety has been managed by the "Guidelines for Biological Evaluation Required when Applying for Approval of Manufacturing (Importing) of Medical Devices'', YAKUKI No.99 of June 27, 1995, but we have recently abolished these guide lines, and stipulated a new basic concept concerning the risk evaluation of harmful biological impact (toxicity hazard) and biological safety evaluation as shown in the attached document, and we request your kind consideration in the attached document, and we request your kind consideration in providing guidance to concerned traders under your jurisdiction.

This notice shall be applied to the applications for approval to be submitted on and after April 1st of this year, however, the risk evaluation of harmful biological impact (toxicity hazard) and the testing for this can be carried out based on this notice concerning the applications for approval to be submitted from today onward.

We will also send a duplicate copy of this notice to the chairman of the board of directors of 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, ACCJ and the chairman of the Medical Devices and Diagnostics Committee of the European Business Community in Japan.

IYAKUSHINHATSU No.0213002
February 13, 2003

To: Chairman of Medical Devices and Diagnostics Subcommittee, ACCJ

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

Basic Principles for Biological Safety evaluation Required Concerning Applications for Approval for Manufacturing (Importing) of Medical Devices

This is to inform you that I have notified the Directors of Prefectural Sanitation Bureaus concerning the title shown in the attached duplicate copy.

Basic Principles for Biological Safety Evaluations

1. Purpose
   This document acts as a tool for safety evaluations of medical devices prior to marketing and provides basic principles regarding risk evaluations of adverse biological effects (toxic hazards) or their tests.

2. Definitions
   Definitions of terminology utilized in this document are as follows.
   1) Raw material
      Refers to materials for medical devices or materials used in the production processes for medical devices (including the test inspection process and sterilization process), and refers to synthetic or natural polymer compounds, metals, alloys, ceramics and other chemical substances.
   2) Final product
      Refers to post-test inspection medical devices ready for shipment and, in the case of for sterilized products, to manufactured products after sterilization. “Final product”, however, is the product in the condition in which it is actually used, after the product has been shipped and the product has been processed and adjusted for use.
   3) Hazards
      Refers to factors that can cause an adverse impact to the health of a person, such as genetic toxicity, sensitivity and chronic systemic toxicity.
   4) Risk
      Refers to a probability and the degree of such harm that causes an adverse effect to the health of a person.

3. Application of International Standards
   In general, the biological safety evaluation of medical devices conforms to the ISO 10993 “Biological Evaluation of Medical Devices” series of international standards. In particular, this generally corresponds to ISO-10993-1 “Evaluation and Testing” where the mandatory evaluation items corresponding to the nature and contact duration for the individual medical device are selected. In addition, the safety evaluation for each evaluation item is conducted by selecting an appropriate test method referenced in the ISO 10993-2 test method guidelines

   Each test method guidelines of the ISO10993 series generally lists multiple test methods for each evaluation item, but for each test method indicated, it is not clear how to apply a given test method for each medical device, and it is not clear how to use the results obtained for these tests in each medical device evaluation. Therefore, it is crucial to select an appropriate test method that addresses the following clauses.

   The international standards have been continuously revised according to scientific development so testing should be conducted after considering the most current international standards, and an appropriate test method selected accordingly.

4. Principles of Biological Safety Evaluations
    1) Biological safety evaluations of raw materials or medical devices conform to ISO14971 “Medical Equipment-Application of Medical Equipment Risk Management” and must be carried out using risk analysis. The intended use/intended purpose and the properties for the safety of the medical device must be clear, the common or foreseeable hazards stated and the risk for each hazard must be predicted. Positive results refer to detecting and characterizing hazards using this risk analysis method and does not refer to any inappropriate nature of a given medical device. The safety of a given medical device is evaluated using ongoing risk analysis.
    2) Biological safety evaluations must be carried out on safety test results conducted in accordance with this document, test results for specific safety evaluation items for a given medical device, the latest relevant scientific documents and other non-clinical and clinical tests (including post-marketing evaluation) in addition to collecting the following information and taking the risks/benefits into consideration.
        a) Information relating to raw materials
        b) Information relating to additives from the raw materials or manufacturing process or residual product from these
        c) Information relating to eluents (for example, qualitative and quantitative chemical properties of the eluent from the final product)
        d) Information regarding biodegradation
        e) Information regarding other elements and their interactions with final products
        f) Properties and characteristics of the final products
    3) Biological safety evaluations must be conducted with sufficient knowledge and training by an experienced specialist.
    4) If any of the following conditions exist, the biological safety evaluation must be carried out but there must be sufficient research if there is a need to redo tests or add test items. For example, if ignoring the amount of eluent from a toxicological standpoint or if there is a product with a known toxicity, it may not be necessary to conduct the tests a second time.
        a) Any change in the vender or in the specification of the materials used in the product.
        b) Any change in the formulation, processing, primary packaging or sterilization of the product.
        c) Any change in the final products during the storage period.
        d) Any change in the intended use of the products.
        e) Any evidence that the product many produce adverse effects.

5. Selection of Evaluation Items
   1) Selection of items that must be evaluated for the biological safety of each medical device is noted in ISO10993-1. These are categorized according to the nature of body contact and duration of contact as shown below. As a general rule, evaluations are required for the items shown in Table 1. When evaluating medical devices not addressed in any of the categories, select a category as close as possible. If there are multiple categories that apply to the medical device due to the duration of contact, evaluate the item that corresponds to the category with the longer duration. When there are categories for multiple regions of contact, evaluate the item that corresponds to each category.

   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) Body surface contact devices:

   - ○ Skin — Medical devices that contact intact skin surfaces only
   - ○ Mucous membranes — Medical devices that contact intact mucous membranes such as the oral cavity, esophagus and urethra
   - ○ Breached or compromised surfaces — Medical devices that contact breached or otherwise compromised skin or mucous membranes

   c) Devices connecting the internal to the external

   - ○ Blood vessels, indirect — Medical devices that contact blood vessels at one point and serve as a conduit for drug entry into blood vessels
   - ○ Tissue/bone/dentin system — Medical devices that contact tissue, bone or dentin system
   - ○ Circulating blood — Medical devices that contact circulating blood

   d) Internally implanted devices

   - ○ Tissue/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 up to 24 hours
   - ○ Short/mid-term contact — Medical devices whose single, multiple or long-term use has a contact duration of between 24 hours and 30 days
   - ○ Long-term contact — Medical devices whose single, multiple or long-term use has a contact duration exceeding 30 days

   2) Equivalent evaluations on previously approved medical devices or evaluations according to appropriate official documents are acceptable in lieu of evaluations for the items shown in Table 1. It is not necessary to conduct all of the test items shown in Table 1 but it is necessary to clearly determine such suitability in each case.

3) In addition to referencing Table 2 that corresponds to the medical device duration of contact, nature of contact and raw material characteristics, the need to conduct tests regarding chronic toxicity, carcinogenicity, reproductive/developmental toxicity and biodegradation should be considered.
4) Relative to acute systemic toxicity, subacute toxicity and chronic toxicity testing, if these toxicity tests include requirements for observation items and biochemical data, it is possible for implant testing or simulated use testing in lieu of such toxicity tests.
5) There are occasions when the biological safety evaluation for only those items shown in Table 1 or Table 2 may be insufficient, or when a simple application is not possible, and thus it becomes necessary to investigate evaluation items sufficiently, taking into account the properties of the medical device. For example, the tests shown here for composite resin pulp/dentin irritation testing or lens application testing for contact lens are insufficient. Thus it is necessary to conduct evaluations regarding immunological toxicity when the immunological toxicity is suspect from the acute systemic toxicity test results. There are also occasions when it is difficult to simply apply the tests shown here on medical devices for cellular tissue.

6. Test Methods
   1) In the guidelines for each test method in the ISO 10993 series, there are various test methods arranged sequentially for each evaluation item. It does not indicate which of these test methods must be selected. When there are multiple test methods for a given evaluation item, selection must be done taking into account the theories of the test, sensitivity, selectivity, quantitativity, reproducibility and test material application method based on the relevance between the objective and the significance of the biological safety evaluation for the medical device. For example, the following items should be considered relative to cytotoxicity testing, sensitivity testing and genetic toxicity testing.
      a) Methods for ISO10993-5 cytotoxicity testing (in vitro test method) include the extraction test method (colony method or sub confluent method), the indirect contact method (stratified agar method, filter diffusion method) and the direct contact method (direct contact via the subconfluent method). These test methods have varying sensitivities and quantitivity so, in order to match the hazard detection for risk evaluation, it is necessary to use a method with a certain level of quantativity if the sensitivity is high (for example, the extraction test method).
      b) Relative to sensitivity and genetic toxicity testing in particular, depending on the extraction solvents, if the eluent concentration in the test solution is high, there are limitations to the eluent liquid used in testing and thus there is a possibility of receiving false negative results. For provisions relating to extracted solvents in ISO10993-12, a strict extraction method that corresponds to risk evaluation hazard detection must be considered. To evaluate the toxicity of unknown products 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, since the results obtained from a given test method must meet the evaluations for safety in clinical use, the basis for determination and suitability must be clear.

7. Test Materials
    1) Test materials of any kind used in testing for biological safety evaluation for medical devices, such as final products, parts of final products and raw materials should be considered relative to their ability to be evaluated for final product safety and demonstrate scientific suitability for selection.
    2) Many medical devices are produced from multiple materials and the manufacturing process (including the sterilization process) can chemically alter the materials. If the manufacturing process alters the materials, testing must be conducted using test materials taken from the final product or using simulated test materials manufactured under the same conditions. If the manufacturing does not alter the materials, testing may be conducted using the raw materials as the test material.
    3) If the chemical substances of part of the raw materials are changed into new chemical substances, or if they are not chemically altered, and if it is more logical to conduct testing on such chemical substances based on the tests conducted or on the evaluation rather than conducting tests using the raw materials or final product as the test material, it is acceptable to substitute these for the raw materials and the final product testing.

8. Animal Treatment
    The treatment of animals used in animal testing is performed according to the animal welfare law and mandatory clauses regarding animal treatment referenced in ISO 10993-2.

Table 1 Guidelines for Primary Evaluation

Category of medical devices	Duration of contact		Biological test								
Nature of contact	A: Limited contact (less than 24 hours) B: Short/mid-term contact (1-30 days) C: Long-term contact (more than 30 days)		Cytotoxicity	Sensitivity	Irritation/intracutaneous reactivity	Acute systemic toxicity	Subacute toxicity	Genetic toxicity	Pyrogenousity	Implantation	Hemocompatibility
Non-contact devices											
Body surface contact devices	Skin	A	○	○	○						
		B	○	○	○						
		C	○	○	○						
	Mucous membrane	A	○	○	○						
		B	○	○	○						
		C	○	○	○		○	○			
	Breached/compromised surface	A	○	○	○						
		B	○	○	○						
		C	○	○	○		○	○			
Devices connecting the internal to the external	Blood vessels, indirect	A	○	○	○	○			○		○
		B	○	○	○	○			○		○
		C	○	○		○	○	○	○		○
	Tissue/bone/dentin system	A	○	○	○						
		B	○	○				○		○	
		C	○	○				○		○	
	Circulating blood	A	○	○	○	○			○		○
		B	○	○	○	○		○	○		○
		C	○	○	○	○	○	○	○		○
Internally implanted devices	Tissue/bone	A	○	○	○						
		B	○	○				○		○	
		C	○	○				○		○	
	Blood	A	○	○	○	○			○	○	○
		B	○	○	○	○		○	○	○	○
		C	○	○	○	○	○	○	○	○	○

Table 2 Guidelines for Supplemental Evaluation

Category of medical devices	Duration of contact		Biological test			
	A: Limited contact (less than 24 hours)					
Nature of contact	B: Short/mid-term contact (1-30 days)		Chronic toxicity	Carcinogenicity	Reproductive/ developmental	Biodegradation
	C: Long-term contact (more than 30 days)					
Non-contact devices						
Body surface contact devices	Skin	A				
		B				
		C				
	Mucous membrane	A				
		B				
		C				
	Breached/compromised surface	A				
		B				
		C				
Devices connecting the internal to the external	Blood vessels, indirect	A				
		B				
		C	○	○		
	Tissue/bone/dentin system	A				
		B				
		C		○		
	Circulating blood	A				
		B				
		C	○	○		
Internally implanted devices	Tissue/bone	A				
		B				
		C	○	○		
	Blood	A				
		B				
		C	○	○		