ISO は、IEC と密接に協力して国際的な標準化を進めている。1976 年には IEC は電気工学と電子工学の分野を扱い、その他の部分を全て ISO が扱うとする協定を結んでいる。その協力関係を具体化したのが ISO と IEC の共通専門委員会 JTC1（Joint Technical Committe1；情報技術専門委員会）である。これを契機として、相互の作業手順が IEC/ISO Directive、規格に関連した項目を捕捉する多くのガイドが ISO/IEC Guide として共通に発行され、両者の規格策定課程に至るまでの強調関係が進展している。更に JTAB（ISO・IEC；合同技術諮問会議）が設置され、共同作業案件の調整が行われている。

②CEN

CEN（European Committee for Standardization）はヨーロッパにおける電気工学、電子工学を除くすべての分野の標準化を進めている地域標準化機関である。CEN はイギリス、フランス、ドイツなどの 19 カ国の加盟国を擁しているが、各国の加盟機関である BSI、AFNOR、DIN などが ISO の加盟機関であるため、CEN は ISO に準じた規格開発を行うこととなっている。

③JISC

ISO には 1 国から 1 標準化機関のみが参加することとなっており、日本では日本工業規格（JIS）の調査、審議を行っている JISC が 1952 年に加入している。1979 年の総会において、JISC は DIN（ドイツ）とともに、常任理事会メンバーとなっている。

（2）規格の具体的内容

1）関連する TC

上述した医療機器に関する TC や SC のうち、再生医療に関わる規格や基準を検討している TC としては、TC194 及び、TC150 がある。

表 2 TC194(医療機器等の生物学的評価) [3]

Committee	Title
TC 194/WG 1	Systematic approach to biological evaluation and terminology
TC 194/WG 2	Degradation aspects related to biological testing
TC 194/WG 3	Animal protection aspects
TC 194/WG 4	Clinical investigations of medical devices in humans
TC 194/WG 5	Cytotoxicity
TC 194/WG 6	Mutagenicity, cancerogenicity and reproductive toxicity
TC 194/WG 7	Systemic toxicity
TC 194/WG 8	Irritation, sensitization
TC 194/WG 9	Effects on blood
TC 194/WG 10	Implantation
TC 194/WG 11	Allowable limits for leachable substances
TC 194/WG 12	Sample preparation and reference materials
TC 194/WG 13	Toxicokinetic study
TC 194/WG 14	Material characterization
TC 194/WG 15	Strategic approach to biological assessment

表 3 TC150(外科用インプラント)[4]

Committee	Title
TC 150/WG 7	Fundamental standards
TC 150/WG 8	Breast implants
TC 150/WG 10	Data on implanted and retrieved devices
TC 150/WG 11	Tissue engineered implants
TC 150/SC 1	Materials
TC 150/SC 2	Cardiovascular implants and extracorporeal systems
TC 150/SC 3	Neurosurgical implants
TC 150/SC 4	Bone and joint replacements
TC 150/SC 5	Osteosynthesis and spinal devices
TC 150/SC 6	Active implants

2) ISO10993

①概要

再生医療に関連する規格としては、医療機器等の生物学的評価を取り扱っている TC194 の検討によって制定された ISO10993 がある。ISO10993 では、医療機器や医療材料に対する生物学的な安全性を評価するための試験法にいて定められており、下表の項目が含まれている。

[3] ISO ウェブサイト参照。
[4] ISO ウェブサイト参照。

表 4　ISO10993 Biological evaluation of medical devices[5]

ISO 10993-1:2003	Evaluation and testing
ISO 10993-2:1992	Animal welfare requirements
ISO 10993-3:2003	Tests for genotoxicity, carcinogenicity and reproductive toxicity
ISO 10993-4:2002	Selection of tests for interactions with blood
ISO 10993-5:1999	Tests for in vitro cytotoxicity
ISO 10993-6:1994	Tests for local effects after implantation
ISO 10993-7:1995	Ethylene oxide sterilization residuals
ISO 10993-9:1999	Framework for identification and quantification of potential degradation
ISO 10993-10:2002	Tests for irritation and delayed-type hypersensitivity
ISO 10993-11:1993	Tests for systemic toxicity
ISO 10993-12:2002	Sample preparation and reference materials (available in English only)
ISO 10993-13:1998	Identification and quantification of degradation products from polymeric
ISO 10993-14:2001	Identification and quantification of degradation products from ceramics
ISO 10993-15:2000	Identification and quantification of degradation products from metals
ISO 10993-16:1997	Toxicokinetic study design for degradation products and leachables
ISO 10993-17:2002	Establishment of allowable limits for leachable substances
ISO 10993-18	Chemical characterization of materials

[5] ISO ウェブサイト参照。

②個別規格の内容

以下では、表 4 で掲げた項目の内いくつかを例としてあげ、その具体的内容を示す。

(a) ISO10993-1

ISO10993 の Part1 では、ISO10993 の概要として、各種生物学的試験法の定義が説明され、また、接触時間と対象部位毎に医療機器を分類し、その分類毎にどのような生物学的試験が適用されるのかを説明している。以下では、その内容を示す。

INTERNATIONAL STANDARD ISO 10993-1:2003(E)

Biological evaluation of medical devices —

Part 1:
Evaluation and testing

1 Scope

This part of ISO 10993 describes

a) the general principles governing the biological evaluation of medical devices;

b) the categorization of devices based on the nature and duration of their contact with the body;

c) the selection of appropriate tests.

This part of ISO 10993 does not cover testing of materials and devices that do not come into direct or indirect contact with the patient's body, nor does it cover biological hazards arising from any mechanical failure.

NOTE Other parts of ISO 10993 cover specific tests (see also the rationale in A.2).

2 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

2.1
medical device
any instrument, apparatus, appliance, material or other article, including software, whether used alone or in combination, intended by the manufacturer to be used for human beings solely or principally for the purpose of:

— diagnosis, prevention, monitoring, treatment or alleviation of disease;

— diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;

— investigation, replacement or modification of the anatomy or of a physiological process;

— control of conception;

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means

NOTE 1 Devices are different from drugs, and their biological evaluation requires a different approach.

NOTE 2 Use of the term "medical device" includes dental devices.

2.2
material
any synthetic or natural polymer, metal, alloy, ceramic or other nonviable substance, including tissue rendered nonviable, used as a medical device or any part thereof

2.3
final product
medical device in its "as-used" state

3 General principles applying to biological evaluation of medical devices

3.1 The selection and evaluation of any material or device intended for use in humans requires a structured programme of assessment.

In the design process, an informed decision shall be made and documented that weighs the advantages/disadvantages of the various choices of material and test procedure. To give assurance that the final product will perform as intended and be safe for human use, the programme shall include a biological evaluation.

The biological evaluation shall be planned, carried out and documented by knowledgeable and experienced individuals capable of making informed decisions based on the advantages and disadvantages of the various materials and test procedures available.

3.2 In the selection of materials to be used in device manufacture, the first consideration should be fitness for purpose with regard to characteristics and properties of the material, which include chemical, toxicological, physical, electrical, morphological and mechanical properties.

3.3 The following should be considered for their relevance to the overall biological evaluation of the device:

a) the material(s) of manufacture;

b) intended additives, process contaminants and residues;

c) leachable substances;

d) degradation products;

e) other components and their interactions in the final product;

f) the properties and characteristics of the final product.

NOTE If appropriate, identification and quantification of extractable chemical entities of the final product should precede biological evaluation (see ISO 10993-9).

3.4 Tests to be used in biological evaluation, and the interpretation of the results of such tests, should take into account the chemical composition of the materials, including the conditions of exposure and the nature, degree, frequency and duration of exposure of the device or its constituents to the body. By following these principles, devices can be categorized to facilitate the selection of appropriate tests (see Clause 4). This part of ISO 10993 is concerned with the tests to be carried out on materials and/or the final product.

The range of potential biological hazards is wide and may include:

a) short-term effects (e.g. acute toxicity, irritation to the skin, eye and mucosal surfaces, sensitization, haemolysis and thrombogenicity);

b) long-term or specific toxic effects [e.g. subchronic and chronic toxic effects, sensitization, genotoxicity, carcinogenicity (tumorigenicity) and effects on reproduction including teratogenicity].

3.5 All potential biological hazards should be considered for every material and final product, but this does not imply that testing for all potential hazards will be necessary or practical (see Clause 6).

3.6 Any *in vitro* or *in vivo* tests shall be based on end-use applications and appropriate good laboratory practice followed by evaluation by competent informed persons. Whenever possible, *in vitro* screening should

be carried out before *in vivo* tests are commenced. Test data, complete to the extent that an independent analysis could be made, shall be retained (see A.2, "Subclause 3.6").

3.7 The materials or final product shall be considered for biological re-evaluation if any of the following occurs:

a) any change in the source or in the specification of the materials used in the manufacture of the product;

b) any change in the formulation, processing, primary packaging or sterilization of the product;

c) any change in the final product during storage;

d) any change in the intended use of the product;

e) any evidence that the product may produce adverse effects when used in humans.

3.8 The biological evaluation performed in accordance with this part of ISO 10993 should be considered in conjunction with the nature and mobility of the ingredients in the materials used to manufacture the device and other information, other non-clinical tests, clinical studies and post-market experience for an overall assessment (see A.2, "Subclause 3.8").

4 Categorization of medical devices

4.1 General

Following the general principles laid down in Clause 3, medical devices can be categorized to facilitate the selection of appropriate tests.

The testing of any device that does not fall into one of the categories described should follow the general principles contained in this part of ISO 10993. Certain devices may fall into more than one category, in which case testing appropriate to each category should be considered.

Medical devices shall be categorized according to the nature and duration of body contact as described in 4.2 and 4.3.

4.2 Categorization by nature of body contact

4.2.1 Non-contact devices

Medical devices that do not contact the patient's body directly or indirectly are not included in the scope of ISO 10993.

4.2.2 Surface-contacting devices

These include medical devices in contact with the following surfaces:

a) **skin**: devices that contact intact skin surfaces only; examples include electrodes, external prostheses, fixation tapes, compression bandages and monitors of various types;

b) **mucosal membranes**: devices that contact intact mucosal membranes; examples include contact lenses, urinary catheters, intravaginal and intraintestinal devices (stomach tubes, sigmoidoscopes, colonoscopes, gastroscopes), endotracheal tubes, bronchoscopes, dental prostheses, orthodontic devices and intrauterine devices;

c) **breached or compromised surfaces**: devices that contact breached or otherwise compromised body surfaces; examples include dressings, healing devices and occlusive patches for ulcers, burns and granulation tissue.

4.2.3 External communicating devices

These include medical devices in contact with the following application sites:

a) **blood path, indirect:** devices that contact the blood path at one point and serve as a conduit for entry into the vascular system; examples include solution administration sets, extension sets, transfer sets and blood administration sets;

b) **tissue/bone/dentin:** devices that contact tissue, bone or pulp/dentin systems; examples include laparoscopes, arthroscopes, draining systems, dental cements, dental filling materials and skin staples;

c) **circulating blood:** devices that contact circulating blood; examples include intravascular catheters, temporary pacemaker electrodes, , oxygenators, extracorporal oxygenator tubing and accessories, dialysers, dialysis tubing and accessories, haemoadsorbents and immunoadsorbents.

4.2.4 Implant devices

These include medical devices in contact with the following application sites:

a) **tissue/bone:**

   1) devices principally contacting bone; examples include orthopaedic pins, plates, replacement joints, bone prostheses, bone cements and intraosseous devices;

   2) devices principally contacting tissue and tissue fluid; examples include pacemakers, drug supply devices, neuromuscular sensors and stimulators, replacement tendons, breast implants, artificial larynxes, subperiostal implants and ligation clips;

b) **blood:** devices principally contacting blood; examples include pacemaker electrodes, artificial arteriovenous fistulae, heart valves, vascular grafts, internal drug-delivery catheters and ventricular assist devices.

4.3 Categorization by duration of contact

Medical devices shall be categorized according to the duration of contact as follows:

a) **Limited exposure (A):** devices whose single or multiple use or contact is likely to be up to 24 h;

b) **Prolonged exposure (B):** devices whose single, multiple or long-term use or contact is likely to exceed 24 h but not 30 days;

c) **Permanent contact (C):** devices whose single, multiple or long-term use or contact exceeds 30 days.

If a material or device may be placed in more than one duration category, the more rigorous testing requirements shall apply. With multiple exposures to the device, the decision into which category a device is placed should take into account the potential cumulative effect, bearing in mind the period of time over which these exposures occur.

5 Testing

5.1 General

In addition to the general principles laid down in Clause 3, the following shall apply to biological testing of medical devices.

a) Testing shall be performed on the final product, or on representative samples taken from the final product or from materials processed in the same manner as the final product.

b) The choice of test procedures shall take into account:

1) the nature, degree, duration, frequency and conditions of exposure to or contact of humans with the device in the normal intended use;

2) the chemical and physical nature of the final product;

3) the toxicological activity of the chemical elements or compounds in the formulation of the final product;

4) that certain tests (e.g. those designed to assess systemic effects) may not be applicable where the presence of leachable materials has been excluded, or where leachables have a known and acceptable toxicity profile;

5) the relationship of device surface area to recipient body size;

6) the existing information based on the literature, experience and non-clinical tests;

7) that the protection of humans is the primary goal of this document, a secondary goal being to ensure animal welfare and to minimize the number and exposure of test animals.

c) If extracts of the devices are prepared, the solvents and conditions of extraction used shall be appropriate to the nature and use of the final product.

d) Positive and negative controls shall be used where appropriate.

e) Test results cannot ensure freedom from potential biological hazard, thus biological investigations shall be followed by careful observations for unexpected adverse reactions or events in humans during clinical use of the device.

A bibliography of International Standards and guidelines on biological-response test methods is given at the end of the text.

5.2 Initial evaluation tests

5.2.1 *General*

The tests that shall be considered for initial biological response are given in 5.2.2 to 5.2.10.

5.2.2 Cytotoxicity

With the use of cell culture techniques, these tests determine the lysis of cells (cell death), the inhibition of cell growth, and other effects on cells caused by medical devices, materials and/or their extracts. Cytotoxicity tests are described in ISO 10993-5.

5.2.3 *Sensitization*

These tests estimate, using an appropriate model, the potential of medical devices, materials and/or their extracts for contact sensitization. These tests are appropriate because exposure or contact to even minute amounts of potential leachables can result in allergic or sensitization reactions. Sensitization tests are described in ISO 10993-10.

5.2.4 Irritation

These tests estimate the irritation potential of medical devices, materials and/or their extracts, using appropriate sites for implant tissue such as skin, eye and mucous membrane in a suitable model. The test(s) performed should be appropriate for the route (skin, eye, mucosa) and duration of exposure or contact to

determine irritant effects of devices, materials and potential leachables. Irritation tests are described in ISO 10993-10.

5.2.5 Intracutaneous reactivity

These tests assess the localized reaction of tissue to medical device extracts. These tests are applicable where determination of irritation by dermal or mucosal tests are inappropriate (e.g. medical devices having access to the blood path). These tests may also be useful where extractables are hydrophobic. Intracutaneous reactivity tests are described in ISO 10993-10.

5.2.6 Systemic toxicity (acute toxicity)

These tests estimate the potential harmful effects of either single or multiple exposures, during a period of less than 24 h, to medical devices, materials and/or their extracts in an animal model. These tests are appropriate where contact allows potential absorption of toxic leachables and degradation products.

Pyrogenicity tests are included to detect material-mediated pyrogenic reactions of extracts of medical devices or materials. No single test can differentiate pyrogenic reactions that are material-mediated from those due to endotoxin contamination. Systemic toxicity tests are described in ISO 10993-11.

Immunotoxicity tests should be considered only for devices where data from other sources is suggestive of immunotoxicological effects.

Systemic toxicity tests may be included in subacute and subchronic toxicity test protocols and implantation test protocols.

5.2.7 Subacute and subchronic toxicity

These tests determine the effects of either single or multiple exposures or contact to medical devices, materials and/or their extracts for a period not less than 24 h but not greater than 10 % of the total life-span of the test animal (e.g. up to 90 days in rats). These tests may be waived for materials with chronic toxicity data. The reason for waiving of the tests should be included in the final report. These tests should be appropriate for the route and duration of contact. Subchronic toxicity tests are described in ISO 10993-11.

5.2.8 Genotoxicity

These tests use mammalian or non-mammalian cell culture or other techniques to determine gene mutations, changes in chromosome structure and number, and other DNA or gene toxicities caused by medical devices, materials and/or their extracts. Genotoxicity tests are described in ISO 10993-3.

5.2.9 Implantation

These tests assess the local pathological effects on living tissue, at both the gross level and microscopic level, of a sample of a material or final product that is surgically implanted or placed in an implant site or in a tissue appropriate to the intended application (e.g. special dental usage tests). These tests should be appropriate for the route and duration of contact. For a material, these tests are equivalent to subchronic toxicity tests if systemic effects are also investigated. Implantation tests are described in ISO 10993-6.

Implantation test protocols may be expanded to include systemic toxicity tests, subacute and subchronic toxicity tests, and chronic toxicity tests.

5.2.10 Haemocompatibility

These tests evaluate, using an appropriate model or system, the effects of blood-contacting medical devices or materials on blood or blood components. Specific haemocompatibility tests may also be designed to simulate the geometry, contact conditions and flow dynamics of the device or material during clinical applications.

Haemolysis tests determine the degree of red blood cell lysis and the release of haemoglobin caused by medical devices, materials and/or their extracts *in vitro*. Haemocompatibility tests are described in ISO 10993-4.

5.3 Supplementary evaluation tests

5.3.1 General

The supplementary biological evaluation tests that shall be considered are given in 5.3.2 to 5.3.5.

5.3.2 Chronic toxicity

These tests determine the effects of either single or multiple exposures to medical devices, materials and/or their extracts during at least 10 % of the life-span of the test animal (e.g. more than 90 days in rats). These tests should be appropriate for the route and duration of exposure or contact. Chronic toxicity tests are described in ISO 10993-11.

Chronic toxicity tests may be included in subacute and subchronic toxicity test protocols and implantation test protocols.

5.3.3 Carcinogenicity

These tests determine the tumorigenic potential of medical devices, materials and/or their extracts from either single or multiple exposures or contacts during the major portion of the life-span of the test animal. These tests may be designed in order to examine both chronic toxicity and tumorigenicity in a single experimental study. Carcinogenicity tests should be conducted only if there are suggestive data from other sources. These tests should be appropriate for the route and duration of exposure or contact. Carcinogenicity tests are described in ISO 10993-3.

5.3.4 Reproductive and developmental toxicity

These tests evaluate the potential effects of medical devices, materials and/or their extracts on reproductive function, embryonic development (teratogenicity), and prenatal and early postnatal development. Reproductive/developmental toxicity tests or bioassays should only be conducted when the device has potential impact on the reproductive potential of the subject. The application site of the device should be considered. Reproductive and developmental toxicity tests are described in ISO 10993-3.

5.3.5 Biodegradation

Where the potential for resorption and/or degradation exists, corresponding tests may determine the processes of absorption, distribution, biotransformation and elimination of leachables and degradation products of medical devices, materials and/or their extracts. Biodegradation tests are described in ISO 10993-9.

6 Selection of biological evaluation tests

Evaluation may include both a study of relevant experience and actual testing. Such an evaluation may result in the conclusion that no testing is needed if the material has a demonstrable history of use in a specified role that is equivalent to that of the device under design.

Table 1 identifies the initial evaluation tests that shall be considered for each device and duration category. Table 2 identifies the supplementary evaluation tests that shall be considered for each device and duration category.

Due to the diversity of medical devices, it is recognized that not all tests identified in a category will be necessary or practical for any given device. It is indispensable for testing that each device be considered on its own merits: additional tests not indicated in the table may be necessary.

The tests considered and the rationale for selection and/or waiving of tests shall be recorded.

7 Assurance of test methods

7.1 Test method assurance

The test methods used in the biological evaluation shall be sensitive, precise and accurate. The test results should be reproducible (interlaboratory) as well as repeatable (intralaboratory).

7.2 Continued assurance

The assurance that a material is initially acceptable for its intended use in a medical device, and its continued acceptability in the long term, is an aspect of a quality management system (see A.2, "Subclause 7.2").

NOTE ISO 9001 specifies the requirements for such quality management systems. ISO 9004 provides more detailed guidance for designing and manufacturing products.

Table 1 — Initial evaluation tests for consideration

Medical device categorization by			Biological effect							
Nature of body contact (see 4.2)		Contact duration (see 4.3) A — Limited (< 24 h) B — prolonged (24 h to 30 days) C — permanent (> 30 days)	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Systemic toxicity (acute)	Subacute and sub-chronic toxicity	Genotoxicity	Implantation	Haemocompatibility
Category	Contact									
Surface device	Skin	A	x	x	x					
		B	x	x	x					
		C	x	x	x					
	Mucosal membrane	A	x	x	x					
		B	x	x	x					
		C	x	x	x		x	x		
	Breached or compromised surface	A	x	x	x					
		B	x	x	x					
		C	x	x	x		x	x		
External communicating device	Blood path, indirect	A	x	x	x	x				x
		B	x	x	x	x				x
		C	x	x		x	x	x		x
	Tissue/bone/dentin	A	x	x	x					
		B	x	x	x	x	x	x	x	
		C	x	x	x	x	x	x	x	
	Circulating blood	A	x	x	x	x				x
		B	x	x	x	x	x	x	x	x
		C	x	x	x	x	x	x	x	x
Implant device	Tissue/bone	A	x	x	x					
		B	x	x	x	x	x	x	x	
		C	x	x	x	x	x	x	x	
	Blood	A	x	x	x	x	x		x	x
		B	x	x	x	x	x	x	x	x
		C	x	x	x	x	x	x	x	x

NOTE This table is a framework for the development of an assessment programme and is not a checklist (see Clause 6).

Table 2 — Supplementary evaluation tests for consideration

Medical device categorization by			Biological effect			
Nature of body contact (see 4.2)		Contact duration (see 4.3) A — Limited (< 24 h) B — prolonged (24 h to 30 days) C — permanent (> 30 days)	Chronic toxicity	Carcinogenicity	Reproductive/developmental	Biodegradation
Category	Contact					
Surface device	Skin	A				
		B				
		C				
	Mucosal membrane	A				
		B				
		C				
	Breached or compromised surface	A				
		B				
		C				
External communicating device	Blood path, indirect	A				
		B				
		C	x	x		
	Tissue/bone/dentin	A				
		B				
		C	x	x		
	Circulating blood	A				
		B				
		C	x	x		
Implant device	Tissue/bone	A				
		B				
		C	x	x		
	Blood	A				
		B				
		C	x	x		

NOTE This table is a framework for the development of an assessment programme and is not a checklist (see Clause 6).

2．米国における規格（ASTM）

（1）規格の概要[6]

1）概要

ASTM (ASTM International：米国試験材料協会)は、ASTM 規格を策定している米国にある民間の規格制定機関である。ASTM は 1898 年に American Society for Testing and Materials として設立され、後に国際標準化への動向に応じ、2001 年に国際標準化機関を示す ASTM International へ改称された。ASTM は独立した非営利の団体で、材料、製品、サービスなどに関する規格を、会員の自発的な発案と総意によって作成している。現在では、100 ヵ国以上から 32,000 名以上の製造業者、使用者、最終消費者、政府、学会代表者等が会員として参加しており、製造、調達、規定に関する活動の基本となる文書を作成している。

2）運営体制

ASTM は約 130 の分野における標準試験方法、仕様、作業方法、ガイド、分類、用語集を作成している。それらの分野の例としては、プラスチック、金属、塗料、繊維、石油、建設、エネルギー、環境、消費財、医療サービス・機器、コンピュータシステム、電子などがある。また、ASTM の本部は技術研究施設や試験設備を持っておらず、実際の作業は世界各地の ASTM メンバーによって自主的に行われている。

規格作成のメンバーは、130 を超える専門委員会のいずれかに所属しており、専門委員会は更に分科委員会、タスク・グループに分かれている。

タスク・グループは規格のドラフトを作成し、分科委員会で投票により検討される。分科委員会で承認された後、同文書は専門委員会と本部に同時に提出されることになる。規格の最終承認は、規格委員会によって行われ、規格の開発が正当な手順・手続きを踏んでなされたことが確認される。

また、規格の開発においては ASTM のウェブサイト上のフォーラムにおいて、規格のドラフトを発表することができ、開発の手順が迅速に行える体制が整っている（ASTM International http://www.astm.org/参照）。

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6 日本規格協会編『ASTM 規格の基礎知識』（2001 年）、日本貿易振興機構「米国 ASTM について」（http://www.jetro.go.jp/jpn/regulations/importproduct_04/04A-011014）参照。

（2）企画の具体的内容

1）概要

ASTM の規格は、下表に示すような分類が行われている。心筋シートなどの再生医療に関する具体的な製品の規格は、主に特定用途材料で取り扱われている。

表 5　ASTM 規格分類

A	鋼、鋳物、メッキ等
B	非鉄金属、導線、冶金等
C	セメント、セラミック、床材、ガラス等
D	ペンキ、石油類、紙、ゴム、プラスチック等
E	金属関連の試験方法等
F	特定用途材料
G	金属の腐食、疲労、劣化等
PS	暫定規格

2）規格の内容

①概要

上述した規格の分類において、医療用の特定用途材料に分類される規格のうち、再生医療に関連する規格としては、医療機器等の生物学的評価を取り扱った規格が存在する。下表がその例である。

表 6　HealthCare に分類される規格（抜粋）

ASTM F701-81(2002)	Standard Practice for Care and Handling of Neurosurgical Implants and Instruments
ASTM F702-98a(2003)	Standard Specification for Polysulfone Resin for Medical Applications
ASTM F703-96(2002)	Standard Specification for Implantable Breast Prostheses
ASTM F719-81(2002)e1	Standard Practice for Testing Biomaterials in Rabbits for Primary Skin
ASTM F720-81(2002)e1	Standard Practice for Testing Guinea Pigs for Contact Allergens Guinea Pig Maximization Test
ASTM F732-00	Standard Test Method for Wear Testing of Polymeric Materials for Use in Total Joint Prostheses
ASTM F745-00	Standard Specification for 18 Chromium-12.5 Nickel-2.5 Molybdenum Stainless Steel for Cast and Solution-Annealed Surgical Implant
ASTM F746-04	Standard Test Method for Pitting or Crevice Corrosion of Metallic Surgical Implant Materials
ASTM F748-04	Standard Practice for Selecting Generic Biological Test Methods for Materials and Devices
ASTM F749-98(2002)e2	Standard Practice for Evaluating Material Extracts by Intracutaneous Injection in the Rabbit
ASTM F75-01	Standard Specification for Cobalt-28 Chromium-6 Molybdenum Alloy Castings and Casting Alloy for Surgical Implants (UNS R30075)
ASTM F750-87(2002)e1	Standard Practice for Evaluating Material Extracts by Systemic Injection in the Mouse
ASTM F754-00	Standard Specification for Implantable Polytetrafluoroethylene (PTFE) Polymer Fabricated in Sheet, Tube, and Rod Shapes
ASTM F755-99(2005)	Standard Specification for Selection of Porous Polyethylene for Use in Surgical Implants
ASTM F756-00	Standard Practice for Assessment of Hemolytic Properties of Materials
ASTM F763-04	Standard Practice for Short-Term Screening of Implant Materials
ASTM F799-02	Standard Specification for Cobalt-28 Chromium-6 Molybdenum Alloy Forgings for Surgical Implants (UNS R31537, R31538, R31539)
ASTM F813-01	Standard Practice for Direct Contact Cell Culture Evaluation of Materials for Medical Devices
ASTM F86-04	Standard Practice for Surface Preparation and Marking of Metallic Surgical Implants
ASTM F881-94(2000)	Standard Specification for Silicone Elastomer Facial Implants
ASTM F882-84(2002)	Standard Performance and Safety Specification for Cryosurgical Medical Instruments
ASTM F895-84(2001)e1	Standard Test Method for Agar Diffusion Cell Culture Screening for

②個別規格の内容

以下では、表 6 で掲げた項目の内、再生医療、特に心筋再生に関連すると考えられる規格のいくつかについて、その具体的内容を示す。

(a) ASTM F748

ASTMF748 では、医療機器に対して必要な生物学的試験が説明されている。これは、ISO10993-1 と同様な位置づけを持つ規格である。以下、その内容を示す。

Standard Practice for Selecting Generic Biological Test Methods for Materials and Devices[1]

This standard is issued under the fixed designation F 748; 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 practice recommends generic biological test methods for materials and devices according to end-use applications. While chemical testing for extractable additives and residual monomers or residues from processing aids is necessary for most implant materials, such testing is not included as part of this practice. The reader is cautioned that the area of materials biocompatibility testing is a rapidly evolving field, and improved methods are evolving rapidly, so this practice is by necessity only a guideline. A thorough knowledge of current techniques and research is critical to a complete evaluation of new materials.

1.2 These test protocols are intended to apply to materials and medical devices for human application. Biological evaluation of materials and devices, and related subjects such as pyrogen testing, batch testing of production lots, and so on, are also discussed. Tests include those performed on materials, end products, and extracts. Rationale and comments on current state of the art are included for all test procedures described.

1.3 The biocompatibility of materials used in single or multicomponent medical devices for human use depends to a large degree on the particular nature of the end-use application. Biological reactions that are detrimental to the success of a material in one device application may have little or no bearing on the successful use of the material for a different application. It is, therefore, not possible to specify a set of biocompatibility test methods which will be necessary and sufficient to establish biocompatibility for all materials and applications.

1.4 The ethical use of research animals places the obligation on the individual investigator to determine the most efficient methods for performing the necessary testing without undue use of animals. Where adequate prior data exists to substantiate certain types of safety information, these guidelines should not be interpreted to mean that testing should be unnecessarily repeated.

1.5 *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 and health practices and determine the applicability of regulatory limitations prior to use.*

2. Referenced Documents

2.1 *ASTM Standards:* [2]

E 1202 Guide for Development of Micronucleus Assay Standards

E 1262 Guide for Performance of the Chinese Hamster Ovary Cell/Hypoxanthine Guanine Phosphoribosyl Transferase Gene Mutation Assay

E 1263 Guide for Conduct of Micronucleus Assays in Mammalian Bone Marrow Erythrocytes

E 1280 Guide for Performing the Mouse Lymphoma Assay for Mammalian Cell Mutagenicity

E 1397 Practice for the *in vitro* Rat Hepatocyte DNA Repair Assay

E 1398 Practice for the *in vivo* Rat Hepatocyte DNA Repair Assay

F 619 Practice for Extraction of Medical Plastics

F 719 Practice for Testing Biomaterials in Rabbits for Primary Skin Irritation

F 720 Practice for Testing Guinea Pigs for Contact Allergens: Guinea Pig Maximization Test

F 749 Practice for Evaluating Material Extracts by Intracutaneous Injection in the Rabbit

F 750 Practic for Evaluating Material Extracts by Systemic Injection in the Mouse

F 756 Practice for Assessment of the Hemolytic Properties of Materials

F 763 Practice for Short-Term Screening of Implant Materials

F 813 Practice for Direct Contact Cell Culture Evaluation of Materials for Medical Devices

F 895 Test Method for Agar Diffusion Cell Culture Screening for Cytotoxicity

F 981 Practice for Assessment of Compatibility of Biomaterials for Surgical Implants with Respect to Effect of

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

Current edition approved May 1, 2004. Published June 2004. Originally approved in 1982. Last previous edition approved in 1998 as F 748 – 98.

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

Materials on Muscle and Bone
F 1027 Practice for Assessment of Tissue and Cell Compatibility of Orofacial Prosthetic Materials and Devices
F 1408 Practice for Subcutaneous Screening Test for Implant Materials
F 1439 Guide for Performance of Lifetime Bioassay for the Tumorigenic Potential of Implant Materials
F 1877 Practice for Characterization of Particles
F 1903 Practice for Testing for Biological Responses to Particles *in vitro*
F 1904 Practice for Testing the Biological Responses to Particles *in vivo*
F 1905 Practice for Selecting Tests for Determining the Propensity of Materials to Cause Immunotoxicity
F 1906 Practice for Evaluation of Immune Responses In Biocompatibility Testing Using ELISA Tests, Lymphocyte Proliferation, and Cell Migration
F 1983 Practice for Assessment of Compatibiltiy of Absorbable/Resorbable Biomaterials for Implant Applications
F 1984 Practice for Testing for Whole Complement Activation in Serum by Solid Materials
F 2065 Practice for Testing for Alternative Pathway Complement Activation in Serum by Solid Materials
F 2147 Practice for Guinea Pig: Split Adjuvant and Closed Patch Testing for Contact Allergens
F 2148 Practice for Evaluation of Delayed Contact Hypersensitivity Using the Murine Local Lymph Node Assay (LLNA)
F 2151 Practice for Assessment of White Blood Cell Morphology After Contact with Materials

2.2 *Other Referenced Documents:*

ISO/AAMI/ANSI 10993-1 Biological Testing of Medical and Dental Materials and Devices - Part 1: Guidance on Selection of Tests[3]
EN 30993–1 Biological Testing of Medical and Dental Materials and Devices - Part 1: Guidance on Selection of Tests[3]
General Program Memorandum #G95-1 FDA[4]
Immunotoxicity Testing Guidance-FDA[4]

3. Summary of Practice

3.1 A matrix listing biological test methods versus materials (devices) and their applications is included in Table 1. The expected duration of use of the device is also considered. Intraoperative is less than 24 h, short-term is up to and including 30 days, chronic is greater than 30 days. The position of row and column intersection is marked to indicate whether the test is recommended for a material or device for the specific application indicated. The terms relating to device or material type and application are addressed in Section 5. Discussion of applicability, current state of the art, and rationale for individual test methods also appears in that section.

[3] Available from American National Standards Institute (ANSI), 25 W. 43rd St., 4th Floor, New York, NY 10036.
[4] Available from CDRH, 5600 Fishers Ln., Rockville, MD 20857.

4. Significance and Use

4.1 The objective of this practice is to recommend sufficient biological testing to establish a reasonable level of confidence concerning the biological response to a material or device, while at the same time avoiding unnecessary testing.

4.2 This practice is intended to provide guidance to the materials investigator in selecting the proper procedures to be carried out for the screening of new or modified materials. Because each material and each implant situation involves its own unique circumstances, these recommendations should be modified as necessary and do not constitute the only testing that will be required for a material nor should these guidelines be interpreted as minimum requirements for any particular situation. While an attempt has been made to provide recommendation for different implant circumstances, some of the recommended testing may not be necessary or reasonable for a specific material or application.

5. Classification of Materials and Devices by End-Use Applications

5.1 *General:*

5.1.1 When new materials are sought for a medical application for use on humans, the material(s) may comprise the whole final device product, or may be one of many component materials in the device. The first step is a thorough literature search for previous use of the material or biocompatibility testing studies to ensure that it has not been known to produce an adverse biological response that exceeds the expected benefit in the use of the device. Note that the final fabricated product may differ chemically, physically, or biologically from the raw materials used to fabricate the product due to processing and this has to be considered when designing test protocols. For some devices, it may be necessary or desirable to take material test samples directly from the final device product. Samples should be fully representative of the finished product in terms of processing, cleaning, packaging, sterilization, and any other procedures that are performed on the materials before the device is used.

5.1.2 At this point, preliminary material screening may be employed, depending on the expertise of the organizations evaluating the materials. Since preliminary screening is normally an option to minimize the economic impact of a candidate material failing final biological tests after extensive time and effort, it is not a required procedure. The investigator should be aware that, should an adverse tissue response be observed with a final product, it may be impossible to determine which component or process is responsible without these initial screening tests.

5.1.3 This practice addresses two dimensions of tissue-material interactions: duration and tissue type. A third dimension, which should be considered, is the relative size difference between the host and the material, that is, to how much material surface area is the host exposed. The material surface area to body weight ratio may become a significant factor for porous materials, and devices of repeated short-term applications (for example, dialysis products). While this practice does not address the issue of "intensity factor" of increased surface

TABLE 1 Applicable Tests

Classification of Material or Device and Application	Cell Culture Cytotoxicity	Sensitization	Skin Irritation or Intracutaneous	Mucous Membrane Irritation	Systemic Toxicity, Acute or Subchronic	Blood Compatibility	Hemolysis	Pyrogen Test	Short-term Implantation	Long-term Implantation	Immune Response	Genotoxicity	Carcinogenicity
External devices													
Intact surfaces (all time periods)	x	x	x										
Breached surfaces													
Intraoperative	x	x	x										
Short-Term	x	x	x		x								
Chronic	x	x	x		x							x	
External Devices Communicating with:													
Intact Natural Channels													
Intraoperative	x	x	x	x									
Short-term	x	x	x	x	x				x				
Chronic	x	x	x	x	x				x		x	x	x
Body Tissues and Fluids													
Intraoperative	x	x	x		x			[A]					
Short-term	x	x	x		x			[A]	x		x		
Chronic	x	x	x		x			[A]	x		x	x	x
Blood Path, indirect													
Intraoperative	x	x	x		x	x	x	x					
Short-term	x	x	x		x	x	x	x					
Chronic	x	x	x		x	x	x	x			x	x	
Blood Path, direct													
Intraoperative	x	x	x		x	x	x	x					
Short-term	x	x	x		x	x	x	x	x		x		
Chronic	x	x	x		x	x	x	x	x	x	x	x	x
Implanted Devices principally contacting													
Bone/Tissue/tissue fluid													
Intraoperative	x	x	x		x								
Short-term	x	x	x		x			x	x				
Chronic	x	x	x		x			x	x	x	x	x	x
Blood													
Intraoperative	x	x	x		x	x	x	x					
Short-term	x	x	x		x	x	x	x	x			x	x
Chronic	x	x	x		x	x	x	x	x	x	x	x	x

[A] (i) Pyrogenicity testing may be considered for all devices contacting the central nervous system.

area, the biocompatibility testing facility personnel should consider it in their material screening and testing protocol design.

5.1.4 For the purposes of this practice, devices and the materials that comprise them are classified as to end-use human application as outlined in 5.2-5.4.

5.2 *External Devices*:

5.2.1 *Devices That Contact Intact Body Surfaces Only*—examples include electrodes, splints, external prostheses, certain dressings, monitors of various types, or ostomy appliances.

5.2.2 *Devices That Contact Breached Body Surfaces*—examples include ulcer, burn, and granulation tissue dressings, or healing devices.

5.3 *Externally Communicating Devices*:

5.3.1 *Devices Communicating with Intact Natural Channels*:

5.3.1.1 *Intraoperative (<24 hours)*—examples include intraintestinal devices (such as sigmoidoscopes, colonoscopes, stomach tubes, or gastroscopes), tracheal tubes, bronchoscopes and any parts of ancillary equipment that are in contact with materials entering the body, and irrigation sets.

5.3.1.2 *Short-term (up to and including 30 days)*—examples include contact lenses, urinary catheters, and intravaginal devices.

5.3.1.3 *Chronic (>30 days)*—examples include urinary catheters for chronic use and intrauterine devices.

5.3.2 *Devices Communicating with Body Tissues and Fluids*:

5.3.2.1 *Intraoperative (<24 hours)*—examples include hypodermic needles, penetrating electrodes, biopsy instruments, arthroscopes, laparoscopes, irrigation equipment, surgical instruments, trochars, and any parts of ancillary equipment that are in contact with materials entering the body.

5.3.2.2 *Short-term (up to and including 30 days)*—examples include cranial calipers, perfusion apparatus, drainage apparatus, stabilizing orthopedic devices, and any parts of ancillary equipment that are in contact with material entering the body.

5.3.2.3 *Chronic (>30 days)*—examples include percutaneous electrodes, active penetrating electrodes, stapedectomy prostheses, partial and total ossicular replacement prostheses, or tympanoplasty ventilation tubes.

5.3.3 *Blood Path, Indirect*—Products contacting blood path at one point for usually less than 24 hours, and serves as a conduit for fluid entry into the vascular system. Examples include solution administration sets, extension sets, transfer sets, or blood administration sets.

5.3.3.1 Products that are used for >24 hours or that are used repeatedly in the same patient will be considered as chronic usage and should undergo extended testing.

5.3.4 *Blood, Path, Direct*—Single recirculating blood exposure or product is in blood path generally less than 24 hours. Examples include intravenous catheters, oxygenators, extracorporeal oxygenator tubing and accessories.

5.3.5 *Blood Path, Direct, Short Term, or Chronic, or repeated exposure*—Examples include dialyzers or dialysis tubing and accessories, shunts.

5.4 *Implanted Long-Term Devices*:

5.4.1 *Devices Principally Contacting Bones*—examples include orthopedic pins, screws, replacement joints, bone prostheses, cements, or dental implants.

5.4.2 *Devices Principally Residing in the Subcutaneous Space*—examples include pacemakers, neuromuscular stimulators, facial augmentation devices, tissue expander devices, and breast prostheses.

5.4.3 *Devices Principally Contacting Soft Tissue and Tissue Fluids*—examples include drug supply devices, neuromuscular sensors, replacement tendons, penile, and other implants, cerebrospinal fluid drains, artificial larynx, vas deferens valves, or ligation clips.

5.4.4 *Devices Principally Contacting Blood*—examples include pacemaker leads, artificial arteriovenous fistulae, heart valves, vascular grafts, stents, blood monitors, internal drug delivery catheters, or ventricular assist pumps.

6. Selection of Test Procedures

6.1 *General*:

6.1.1 Biocompatibility testing involves tests of either the material itself, or an extract from it, or both, depending on the nature of the end-use application. While this practice does not address specific chemical methods for evaluating the extractable substances or residuals from implant materials, several of the recommended tests (see 6.2, 6.7, 6.6, and 6.3) utilize extracts rather than the original material for testing. If sensitive chemical assay techniques (such as GC, HPLC, and AA) should reveal no detectable substances being extracted into the medium, consideration may be given to deletion of these tests from the test battery. The investigator is cautioned, however, that the detection limit of the analytical chemistry procedures may not be adequate to detect trace extractables that may generate a tissue response. Before analysis of extracts is substituted for actual biocompatibility testing of the extracts, validation procedures may be necessary to show the relative tissue response to levels of extractable which are slightly above the detection limit. It is particularly appropriate that animal testing involving extracts be considered for deletion if there are no detectable substances being extracted.

6.1.2 If the material to be tested is being tested in the form of particles, characterization of the particles in accordance with Practice F 1877 should be performed so that the particles can be fully described and their relevance to clinical usage situations evaluated.

6.2 *Cell Culture Cytotoxicity Assays*—This test evaluates *in vitro* toxicity of substrate materials to cultured cells.

6.2.1 Generally, materials that do not pass the cytotoxicity assays are not considered for further biocompatibility testing and are not used in devices for human application. Thus, the direct relation between results of cytotoxicity testing and biocompatibility of materials has not been documented and there is some controversy as to the value of the testing since some good materials may be excluded and some others that are not biocompatible may pass this test. Cytotoxicity testing is recommended as an early screening test and also to provide information that will aid in the development of cytotoxicity tests predictive of *in vivo* performance.

6.2.2 Several different tests are included under this heading, such as Agar Diffusion, Fluid Medium, Agar Overlay, Flask