Essential Principles in Japan

Essential Principles from GHTF document※1 was introduced in Japanese regulation and all *in vitro* diagnostics shall be in conformity with the EPs. Essential Principles in Japan was revised in 2014 because GHTF published the revised GHTF document※2 . Conformance to IMDRF GRRP WG/N47 can be supported by conforming to Japanese Essential Principles※3 and relevant notifications etc.

※1：GHTF/SG1/N41R9:2005 ※2：GHTF/SG1/N68:2012 ※3：Add to the requirement of the public notice of e-package inserts （2021）

Pharmaceuticals and Medical Device Agency
Office of Standards and Compliance for Medical Devices

Essential Principles in Japan:2014 （It's based on GHTF/SG1/N68:2012）		
Chapter 1 General Requirements		
(Design)		
Article1		*In vitro* diagnostics as enacted in Article 2, Paragraph 14 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960; hereinafter referred to as "the PMD Act") (excluding those to be exclusively used for animals; the same shall apply hereinafter) shall be designed and manufactured in such a way that, when used under the conditions and for the purposes intended and, where applicable, by virtue of the technical knowledge, experience, education or training, and the medical and physical conditions of intended users, they will perform as intended by the manufacturer and not compromise the clinical condition or the safety of patients, or the safety and health of users (limited to persons having the required technical knowledge when it is needed for the correct use of the *in vitro* diagnostics; the same shall apply hereinafter) or, where applicable, other persons (limited to those persons whose safety and health may be affected when using the drug for extracorporeal diagnosis; the same shall apply in Article 4), provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.
(Risk Management)		
Article2		The marketing authorization holder or manufacturer (hereinafter referred to as "MAHs") involved in design and manufacturing of *in vitro* diagnostics shall conform to safety principles, taking account of the generally acknowledged state of the art. When risk reduction is required, the MAHs shall control the risks in such a way that the residual risk associated with each hazard is judged to be within an acceptable range. In this case, the MAHs shall apply the following principles to the management of risk in the priority order listed:
		(1) To identify known or foreseeable hazards and estimate the associated risks arising from the intended use method and foreseeable misuse;
		(2) to eliminate risks estimated in the previous item as far as reasonably practicable through inherently safe design and manufacture;
		(3) to reduce as far as reasonably practicable the residual risks after eliminating the risks based on the previous item by taking adequate protection measures; and
		(4) to indicate any residual risks after eliminating the risks based on item 2.
(Performance and function of *in vitro* diagnostics)		
Article3		*In vitro* diagnostics shall achieve the performance intended by the MAHs and be designed and manufactured in such a way that they may perform their functions as *in vitro* diagnostics.
(Term of validity of the products)		
Article4		The characteristics and performance shall not be adversely affected by deterioration, etc. to such a degree that the health and safety of the patient, user, and other persons are threatened during the term of validity of the *in vitro* diagnostic established by the MAHs, when the *in vitro* diagnostic is subjected to the stresses which may occur under normal conditions of use and has been properly maintained in accordance with the MAHs' instructions.
(Transport and storage, etc.)		
Article5		*In vitro* diagnostics shall be designed, manufactured, and packaged in such a way that their characteristics and performance will not be adversely affected when transported and stored under the conditions subject to the instructions and information provided by the MAHs and used in accordance with their intended usage.
(Benefits of *in vitro* diagnostics)		
Article6		All known or foreseeable risks and undesirable effects shall be minimized as far as reasonably practicable and be acceptable when weighed against the intended benefits of *in vitro* diagnostics under normal conditions of use.

Chapter 2 Requirements for design and manufacture		
(Chemical properties, etc. of *in vitro* diagnostics)		
Article7	1	Regarding the selection of materials used, *in vitro* diagnostics shall be designed and manufactured, where necessary, with attention given to the matters provided in each of the following items.
		(1) Toxicity and flammability,
		(2) Reduction in performance due to incompatibility between the materials used and the samples or analyte (including biological tissues, cells, body fluids, microorganisms, etc.), and
		(3) Other necessary items.
	2	*In vitro* diagnostics shall be designed, manufactured, and packaged in such a way as to minimize the risk posed by contaminants and residues (hereinafter referred to as "contaminants, etc.") to the persons involved in the transport, storage, and use of the *in vitro* diagnostics and to patients, according to their purpose of use, and attention shall be paid to the biological tissues that come into contact with the contaminants, etc., contact duration, and contact frequency.
	3	*In vitro* diagnostics shall be designed and manufactured in such a way as to reduce, appropriately and as far as reasonably practicable, the risks posed by substances that may leach or leak from the *in vitro* diagnostics. Special attention shall be given to substances which are carcinogenic, mutagenic, or reproductively toxic.
	4	*In vitro* diagnostics shall be designed and manufactured in such a way as to reduce, appropriately and as far as reasonably practicable, risks posed by the unintentional ingress or egress of certain substances into or from the *in vitro* diagnostic, taking into account the *in vitro* diagnostic and its intended use environment.
(Prevention of microbial contamination, etc.)		
Article8	1	*In vitro* diagnostics and their manufacturing processes shall be designed in such a way as to eliminate or reduce, appropriately and as far as reasonably practicable, the risk of infection to patients, users, or other persons (limited to those persons at risk of infection during use of the *in vitro* diagnostic; the same shall apply in this Article.), taking the following items into account.
		(1) To allow easy handling;
		(2) to reduce, where necessary, appropriately as far as reasonably practicable, any microbial leakage or exposure from using *in vitro* diagnostics; and
		(3) to prevent, where necessary, microbial contamination of *in vitro* diagnostics or specimens by the patient, user, or other persons.
	2	The MAHs shall ensure the optimal level of safety for the patient, user, or other persons in the processing, preservation, testing and handling of tissues, cells and substances of animal origin (hereinafter referred to as "animal origin tissues, etc.") incorporated into *in vitro* diagnostics, and ensure safety by elimination or inactivation of viruses and other infectious pathogens in the manufacturing process of the *in vitro* diagnostic using validated methods, to take preventive measures against the viruses and other infectious pathogens. Provided, however, that this does not apply to those *in vitro* diagnostics which require viruses and other infectious pathogens for use or the performance of which is reduced by their elimination or inactivation.
	3	The tissues, cells, and substances of human origin which are incorporated into *in vitro* diagnostics (hereinafter referred to as "human origin tissues, etc.") shall be obtained from appropriate sources. The MAHs shall ensure the optimal level of safety for the patient, user, or other persons in the selection of donors or human origin substances, and in the processing, preservation, testing and handling of human origin tissues, etc., and ensure safety by elimination or inactivation of viruses and other infectious pathogens in the manufacturing process of the *in vitro* diagnostic using validated methods, to take preventive measures against the viruses and other infectious pathogens. Provided, however, that this does not apply to those *in vitro* diagnostics which require viruses and other infectious pathogens for use or the performance of which is reduced by their elimination or inactivation.
	4	The MAHs shall ensure the optimal level of safety for the patient, user, or other persons in the processing, preservation, testing and handling of microbial origin tissues, etc. (meaning cells and substances originating from microorganisms) incorporated into *in vitro* diagnostics. The MAHs shall ensure safety by elimination or inactivation of viruses and other infectious pathogens in the manufacturing process of the *in vitro* diagnostic using validated methods, to take preventive measures against the viruses and other infectious pathogens. Provided, however, that this does not apply to those *in vitro* diagnostics which require viruses and other infectious pathogens for use or the performance of which is reduced by their elimination or inactivation.
	5	*In vitro* diagnostics labelled as sterile or having a special microbiological state shall be designed, manufactured, and packaged to ensure that they maintain their special microbiological state, unless the package is damaged or until opened, when placed on the market or when transported and stored under the conditions indicated by the MAHs.
	6	*In vitro* diagnostics labelled as sterile or having a special microbiological state shall be manufactured upon being sterilized by appropriate, validated methods or processed to create the special microbiological state, and where necessary, shall be sterilized.
	7	*In vitro* diagnostics to be sterilized shall be manufactured under appropriately controlled conditions.
	8	Packaging for non-sterile *in vitro* diagnostics shall maintain the specified cleanliness of the *in vitro* diagnostics in order that their qualities are not adversely affected.

(Consideration of use environment)		
Article9	1	If the *in vitro* diagnostic is used in combination with other *in vitro* diagnostics, medical devices, other equipment, etc., the *in vitro* diagnostic concerned shall be safely connected to the equipment, etc. concerned and the performance of the *in vitro* diagnostic concerned and the equipment, etc. concerned shall not be impaired by combined use.
	2	Any restrictions on use in the case of the previous item shall be made a public notice as an e-package inserts, or described in the document attached to the *in vitro* diagnostic (referred to as "paper-based package inserts" in Article 11) or indicated on its container or encapsulation (these descriptions and indications are referred to as "indication of package inserts, etc." in Article 14).
	3	*In vitro* diagnostics shall be designed and manufactured in such a way as to eliminate or reduce, appropriately and as far as reasonably practicable, the risks to the patient, user, or other persons (limited to persons who may be subject to any of the risks listed in the following items during their use) during their use as listed in the following items.
		(1) The risk of injury in connection with their physical and ergonomic features;
		(2) the risk of misuse due to the ergonomic features, human factors and the use environment in which the *in vitro* diagnostic is intended to be used;
		(3) the risk associated with rationally predictable influence of surrounding or environmental conditions;
		(4) the risk associated with the use of the *in vitro* diagnostic when it comes into contact with substances, liquids, or gases to which it is exposed under normal conditions of use;
		(5) the risk of accidental penetration of substances into *in vitro* diagnostics;
		(6) the risk of incorrect identification of specimens; and
		(7) the risks of reciprocal interference with other *in vitro* diagnostics or medical devices normally used in studies or for treatment.
	4	*In vitro* diagnostics shall be designed and manufactured in such a way as to minimize the risk of fire or explosion during normal use and under single fault conditions. Particular attention shall be paid to the design and manufacturing of *in vitro* diagnostics, the intended use of which includes use in association with flammable substances or substances which could cause combustion (including cases where *in vitro* diagnostics are exposed or used with these substances).
	5	*In vitro* diagnostics shall be designed and manufactured in such a way that calibration, where such is necessary to achieve the performance intended, can be performed safely.
	6	*In vitro* diagnostics shall be designed and manufactured in such a way as to facilitate the safe disposal of all waste substances.
(Consideration of measuring or diagnostic function)		
Article10	1	*In vitro* diagnostics shall be designed and manufactured in such a way that the performance is coincident with the purpose of use, based on appropriate scientific and technical methods. In designing *in vitro* diagnostics, appropriate attention shall be paid to trueness and precision (including repeatability and reproducibility) associated with sensitivity, specificity, and accuracy, and control of known interference factors and limits of detection. The performance characteristics shall be maintained during the term of validity of the *in vitro* diagnostics indicated by the MAHs.
	2	If the performance of *in vitro* diagnostics depends on the use of calibrators or reference materials, the traceability of values assigned to such calibrators or reference materials shall be assured through available reference measurement methods or available reference materials of a higher order.
	3	In principle, the values expressed numerically shall be standardized units as far as possible, and understood by the users of *in vitro* diagnostics.
(Protection against radiation)		
Article11	1	*In vitro* diagnostics shall be designed, manufactured, and packaged in such a way that exposure of patients, users, or other persons to radiation (limited to persons at risk of exposure to radiation during use of the *in vitro* diagnostics; the same shall apply in Paragraph 3) shall be appropriately reduced as far as reasonably practicable, while not restricting the level of irradiation required for measurement, etc. consistent with the purpose of their use.
	2	If *in vitro* diagnostics emit hazardous or potentially hazardous levels of visible or invisible radiation, they shall be designed and manufactured in such a way that the characteristics and the dose of radiation emitted can be appropriately controlled or adjusted, as far as reasonably practicable. They shall be additionally fitted, as far as reasonably practicable, with visual displays or audible warnings to check such emissions.
	3	*In vitro* diagnostics shall be designed and manufactured in such a way that exposure of patients, users, or other persons to the emission of unintended, secondary or scattered radiation is reduced as far as reasonably practicable.
	4	E-package inserts or paper-based package inserts for *in vitro* diagnostics emitting radiation shall provide detailed information on the characteristics of the radiation emitted, the protective measures for patients and users, the methods for prevention of misuse, and the methods for eliminating the specific risks during handling.
(Consideration of mechanical risks)		
Article12	1	*In vitro* diagnostics shall be designed and manufactured in such a way as to protect the patient, user, or other persons (limited to persons exposed to a mechanical risk during use of the *in vitro* diagnostics) against mechanical risks associated with resistance to movement, instability, and moving parts.
	2	If there are risks due to moving parts, risks due to break-up or detachment, or leakage of substances, appropriate measures to prevent risks arising shall be incorporated into the *in vitro* diagnostics.

(Consideration of *in vitro* diagnostics intended for self-testing)		
Article13	1	*In vitro* diagnostics for self-testing (meaning *in vitro* diagnostics which are intended to be used by persons who may not always have specialized knowledge regarding their use; the same shall apply hereinafter) shall be designed and manufactured in such a way that they can be appropriately operated, in consideration of the technique and methodology available to their users and technical and environmental changes affecting the user that may be expected to normally occur.
	2	*In vitro* diagnostics for self-testing shall be designed and manufactured in such a way as to reduce, as far as reasonably practicable, the risk of misuse by the users during the use of the *in vitro* diagnostic, use of the specimens, and interpretation of test results.
	3	For *in vitro* diagnostics for self-testing, as far as reasonably practicable, procedures by which users can verify whether the *in vitro* diagnostics are performing their functions as intended by the MAHs shall be provided.
(Information provision to users by the public notice of e-package inserts or indication of package inserts, etc.)		
Article14		The MAHs shall provide, when *in vitro* diagnostics are placed on the market, necessary information to ensure the name of MAHs, the methods for safe use, and their performance in the public notice of e-package inserts or the indication of paper-based package inserts, etc. of the *in vitro* diagnostics, in a manner that users can easily understand such information, in consideration of the degree of training and knowledge that the users have on the *in vitro* diagnostics.
(Performance evaluation and clinical performance studies)		
Article15	1	All data collected to evaluate the performance of *in vitro* diagnostics shall be collected in accordance with the PMD Act and other relevant laws and regulations.
	2	*In vitro* diagnostics shall be continuously evaluated by the test results, data and other records required for the *in vitro* diagnostics based on the data from clinical performance studies and the Ministerial Ordinance on Good Vigilance Practice for Drugs, Quasi-Drugs, Cosmetics, Medical Devices, and Regenerative Products (MHLW Ordinance No. 135 of 2004) in addition to the data mentioned in the preceding paragraph.