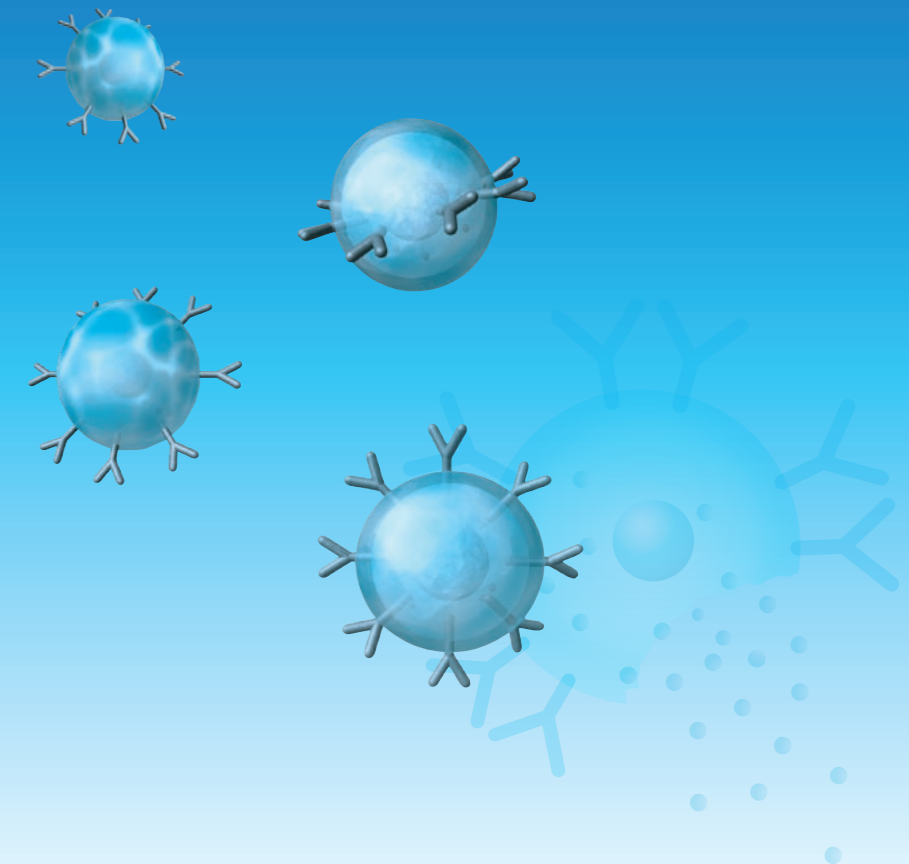




YAMAMOTO PRECIOUS METAL CO., LTD.
OSAKA, JAPAN

The Pursuit of International Standards in Quality and Safety



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ISO 9001/13485
ISO 14001
CERTIFIED



Scope:
Headquarters and Kochi Plant



QAIC/JP/0455
Scope: Kochi Plant



Our Mission: Keywords for Safety

From Production Skills to Scientific Knowledge, and onward to Fusion with Medical Science

Over the course of history, dental materials of various kinds have been used in multi-purpose ways, and new materials have constantly been researched and developed in order to achieve better quality and meet the demand for new products. Treatment methods combining multiple materials have also become widely used.

On the other hand, the advance in sophistication of dental treatment has seen the demands placed on the materials' properties changing from their physical chemistry to their biological properties. There has been a notable increase in public interest in the area. This change has occurred along with the development of dental materials and their associated treatment methods. Even if new materials are developed with excellent properties, they must be strictly non-toxic.

It is absolutely vital to ensure the safety of dental materials, no matter whether they are used domestically or overseas, and as a matter of course manufacturers must give priority to safety.

It is an undeniable fact that manufacturers have been prone to focus on mechanical properties such as handling and strength in their R&D, without considering product development from a deeper medical standpoint. This is a point which manufacturers need to fully understand.

By contrast, the research and development approach we propose constitutes a new system – more focused on safety, and also with a fresh R&D stance which fuses scientific functionality and medical safety.

From this viewpoint, our mission is to provide the kind of safe, reliable, high-performance dental materials that can accompany the future development of dental treatment to higher levels of sophistication.

Hirohisa Yamamoto
Chairman and CEO of
Yamamoto Precious Metal Co., Ltd.

Pursuing Safety: Offering Safety and Peace of Mind...

Dental Materials have been developed with an eye to functionality over a long period of time. However, is it enough that only functionality is called for, even though these materials are to be used in our patients' mouths?

Material dissolution caused by chewing and saliva expulsion has an incalculable effect on the human body. Dental materials are, of course, classified as medical devices, and there are guidelines regulated by the government.

However, our corporate mission is to transcend national guidelines and pursue safety at global standards, offering long-standing Safety in terms of the human physique and to provide safe, reliable, high-performance products. The pursuit of safety is the abiding concern in our ongoing research and development.



Biological Safety I: the Pharmaceutical Affairs Law and International Organization for Standardization

— Evaluation of Biological Safety through ISO10993 —

What is required for the evaluation?

Safety is absolutely required from medical devices in terms of their functional materials. Safety is examined under The Pharmaceutical Affairs Law in Japan and ISO 10993 globally; however, the evaluation method is different depending on the parts of devices to be used and also on use period. Here are some examples of evaluations that we have implemented for biocompatibility in R&D:

Systemic Toxicity Test

Purpose of the Test:

A wide range of substances produce toxicity by impacting the human body. Because of this, it is necessary in advance to expect risk when medical devices come into close contact with the human body. The purpose of the test is to analyze the quality and quantity of the toxicity in a subject by taking a solution (a test sample of raw material of chemical substances) from the mouth.

Summary of the Test

The test sample is orally administered in a single dose or multiple doses, and the subject's reactions, such as changes in health condition and weight, are observed. If the test sample shows no reaction during the observation period, there is deemed to be no toxicity; on the other hand, if there is toxicity, depression, notable weight reduction, or death may be observed. Assessment has generally been based on the median lethal dose (LD50) value - an estimate of the dose of a test substance that kills 50% of test animals. However, LD50 increasingly tends not to be used because it is actually possible to determine whether there is toxicity or not by simply checking weight change; there are also concerns from the animal welfare standpoint.

In Vitro Cytotoxicity Test

Purpose of the Test

The test is performed to analyze whether or not the human body is at risk of being subject to toxicity from material devices or their raw materials or chemical constituents thereof. It is carried out by measuring how cultured cells react in terms of survival rate and reproduction rate.

Summary of the Test

Approximately 100 cultured cells are distributed on a test plate, a test sample is added, and incubation is performed for six days. The colonies will comprise the same number as the number of cells in the original colony if the test sample is non-toxic. (For example, if 100 cultured cells are distributed, a hundred colonies will form.) The smaller the number of colonies which form, the higher toxicity the test sample has.

The colony-forming assay, in which the index is the number of colonies formed during cell reproduction, is recommended by Japanese Ministry of Health, Labour and Welfare guidelines. For medical devices, the method of processing cells with sample extract and the method of distributing cells directly on a test sample are recommended, and these methods must be backed up by control experiments.

In ISO 10993-5, both processing with sample extract and exposing test sample to cells directly or indirectly are stipulated. However, the agar overlay technique or direct contact method is generally employed in western countries.



Keeping lab mice



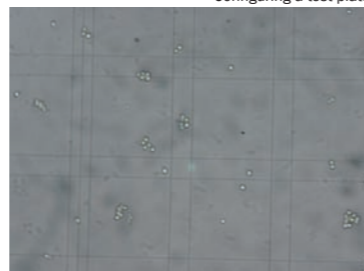
Measuring a test sample



Confirming health conditions of mice



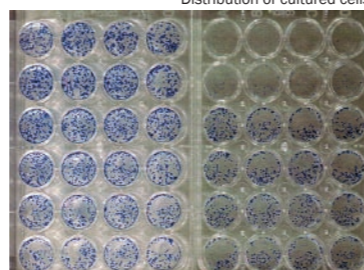
Configuring a test plate



Observation of cells



Distribution of cultured cells



Observation of colonies

Biological Safety II: the Pharmaceutical Affairs Law and International Organization for Standardization

— Evaluation of Biological Safety through ISO10993 —

Mutagenicity Test

Purpose of the Test

Some chemical substances react with human DNA and mutate DNA. A mutation may cause cancer in general somatic cells; moreover, the mutation may affect its descendant cells. Therefore, it is important to examine whether the chemical constituents of raw materials in dental devices cause mutations or not. The purpose of this test is to ascertain whether a test sample affects DNA or not.

Summary of the Test

Mutated bacteria, with genes related to their amino acid metabolism which live only where amino acid exists, such as histidine-dependent salmonella and tryptophan-dependent colon bacillus, are used for the test. In cases where a test sample has an impact on the genes, the bacterial genes revert to normal (Reverse Mutation); the colony is then able to form even on a culture medium where there is not sufficient amino acid.

If the number of colonies increases to more than double as many as the negative control group, and confirms dose-dependency, we confirm the test sample as positive. In this case, the chemical substances used in the test cause cancer or have an impact on the genes.

Skin Sensitization Test

Purpose of the Test

This test is performed to inspect if a test sample results in allergic contact dermatitis when dental devices come into contact with the human body, and also to evaluate the level of such dermatitis.

Summary of the Test

A test sample is attached on the skin of a subject and left for 48 hours; a result is obtained by observing how the skin changes over time. (This is generally called Skin Patch Test.) Reddening of the skin is seen as a light symptom and scab or necrosis of the skin is seen as a severe symptom. There are other irritation tests in addition to the skin sensitization test: Eye Irritation Test for ocular tissue, Oral Mucosa Irritation Test for oral mucosa, and Vaginal Irritation Test for vaginal mucosa. Those tests are appropriately chosen depending on the method of use of the relevant medical devices. However, skin sensitization tests are not always sufficient for full evaluation, because allergies are understood to be a still-developing contemporary medical problem, and they appear differently from individual to individual.

Oral Mucosa Irritation Test

Purpose of the Test

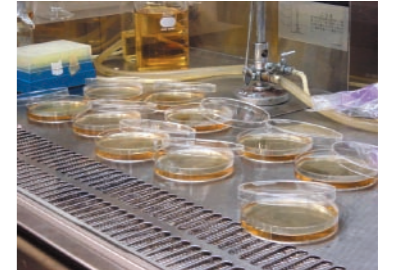
From a medical standpoint, the test is performed to analyze impact on oral mucosa from medical devices, where the medical devices are used in the mouth.

Summary of the Test

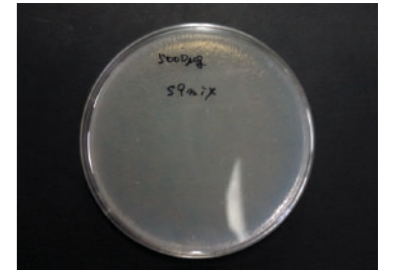
The entire medical device or the chemical constituents thereof are placed as a test sample into cheek pouches in a subject, and left for two weeks. Afterward, the pouches are observed histologically so as to be able to predict how the use of the medical devices in question impacts the human body from a medical standpoint. In normal cases, the tissue sequence will be regular; on the other hand, it will be random in abnormal cases.



Setting culture medium



Developing enriched culture mediums in petri dishes



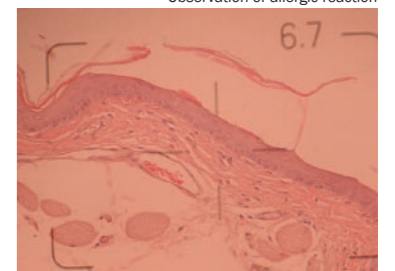
Observation of colony formation



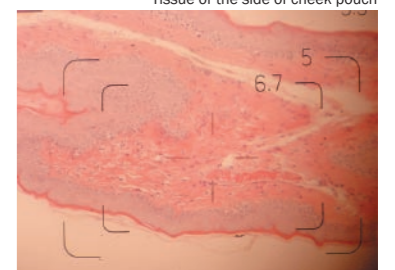
A test sample for skin sensitization test



Observation of allergic reaction



Tissue of the side of cheek pouch



Tissue of the bottom of cheek pouch

Biological Safety

Collaboration with Medical Science

Department of Kochi University in Japan

— Biological Evaluation of Safety Based on Cell, Cell Structure, Genetic Engineering —

To the Next Stage...

It is of course mandatory for professionals involved in medical treatment to practice properly regulated Safety Evaluation; however, we always look for the “next stage”. We are working on research and development from multiple aspects, such as allergies, carcinogenicity, the impact on our offspring, and those risks which cannot be proven by a single evaluation.

Cell Growth Inhibition Test

Purpose of the Test:

The purpose of the test is to predict toxic presence in the living body by measuring the impact of whole medical devices or the chemical constituents thereof on the growth rate of cultured cells.

Summary of the Test

A test sample is placed on cultured cells and incubated for 48 hours. After the incubation, it is possible to ascertain whether there is inhibitory action on the growth of cultured cells by comparing the number of cells obtained when a test sample is added or not added. In normal cases, the growth speed is fixed. In abnormal cases, the growth speed is inhibited, or sometimes the cells may be exterminated.

DNA Synthesis Test

Purpose of the Test

When cells divide, they perform DNA synthesis. By examining DNA synthesis and its impact, the test is performed to make a prediction of the toxicity of entire medical devices or the chemical constituents thereof in the human body.

Summary of the Test

A test sample is added to cultured cells and incubated for 48 hours. Six hours before completing the incubation, it is marked by adding a test liquid that will be incorporated into the newly synthesized DNA. Afterward, it is possible to ascertain the impact on the DNA synthesis of the test sample by measuring its beta-ray emissions and the synthetic quantity.

Cytotoxicity Test

Purpose of the Test

The test is performed to predict if the human body is at risk of being subject to toxicity by measuring how many cells are damaged or have been exterminated after placing an entire medical device or the chemical constituents thereof into cultured cells.

Summary of the Test

A test sample is placed on cultured cells marked by a radioactive substance, and incubated for 48 hours. After the incubation, it is possible to ascertain how much damage the cells have sustained by measuring the activity of the radioactive substance which was isolated from the supernatant of the incubation.

DNA Fragmentation Test

Purpose of the Test

Electrophoresis is induced in the cell DNA, and the toxicity or lack thereof in the cell of a test sample is observed. The test is performed to analyze whether the form of toxicity is apoptosis or necrosis when toxicity is found in the cell.

Summary of the Test

A test sample is added into cultured cells, and the cell DNA is removed after 48 hours of incubation; electrophoresis is then induced to observe the movement pattern in order to obtain a result. If the cells survive, the DNA has not dissolved. For apoptosis cases, the DNA divides in a regular manner, and for necrosis cases, in an irregular manner.

Protein Synthesis Test

Purpose of the Test

When cells are in normal condition, protein synthesis is performed by the action of DNA and RNA for purposes of cell division. Because of this, the test is performed to analyze if a test sample has toxicity by measuring amount of protein synthesis after placing entire medical devices or the chemical constituents thereof into cultured cells.

Summary of the Test

A test sample is added to cultured cells and incubated for 48 hours. The protein is then extracted from the cells and the absorptivity is measured to determine the impact on protein synthesis.



Observing cells under microscope



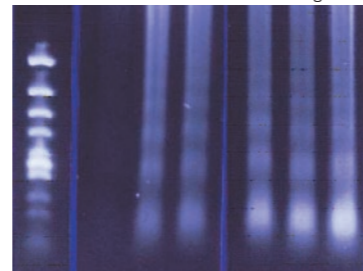
Measuring test samples



Distribution of cultured cells



Staining of cells



DNA Fragmentation image



Measuring the amount of cell



Controlling temperature of culture media

Collaboration with External Organizations

Industry-University Collaboration

The Pursuit of Safety

In 2005, The Biological Science Safety Laboratory was established in the Department of Oral and Maxillofacial Surgery, Kochi Medical School, Kochi University, Japan. We are working on research and development from multiple aspects, such as Cell Structure and Genetic Engineering, in addition to performing general safety examinations (Dissolution Test, In Vitro Cytotoxicity Test).



Quality Management System

ISO 9001, ISO 13485, and the CE marking certifications obtained

Our Company has been continuously working on obtaining ISO certifications in order to pursue international standards for quality and safety. As a first step, we obtained ISO 9002 certification in September, 2000. As a second step, in May, 2003, we obtained ISO 9001 and ISO 13485 certifications, and also the CE marking for our products in the EU. While continuing to obtain those international standards, we intend to move forward by offering products and services, always thinking from the customers' point of view.



– Terms and Definitions –

What is the ISO?

The ISO stipulates various kinds of standards, such as the “Company Standards (Manufacturer Standards)” used at the business level, “Organizational/Industrial Standards,” “National Standards” used at the national level and “Regional Standards” used in designated areas, for example in Europe. In addition to these standards, “International Standards” are used in common in all countries. The ISO (International Organization for Standardization) is the organization that establishes such international standards.

What is ISO 13485?

ISO 13485 (“Comprehensive Management System for the Design and Manufacture of Medical Devices”) is an ISO standard, and it also is a quality management system just like ISO 9001. A fundamental difference, however, is that ISO 13485 is applied only to medical devices. ISO 13485 is generally harmonized with ISO 9001 in terms of quality management systems; ISO 13485 contains specific requirements for each medical device and regulatory requirements concerning the pharmaceutical affairs legislation of each country.

What is ISO 9001?

ISO 9001 (Quality Management System) is an ISO standard designed to help organizations wishing to achieve the ISO standards ensure that they can meet the relevant requirements in order to obtain good and/or improved quality, and to publically demonstrate that they have accommodated to the standards. They receive certificate issued by the certification body.

What is the CE Marking?

The CE marking means that the product conforms to essential requirements; it is a mandatory conformity mark for products placed on the market in the EU. With the CE marking, the product can be proven to comply with these requirements, and the mark is also obligatory for export outside the EU.