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Challenges in the Biological Evaluation of the Medical Devices, the use of ISO 10993 Series of the Standard

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A B S T R A C T

Despite the various advantages of medical instruments, both are dangerous even if correctly used. For this purpose, the Biological Safety Evaluation Strategy must provide risk evaluations of medical equipment. The ISO 10993 set of criteria for Europe and the United States defines such an appraisal plan. In compliance with ISO 10993 guidelines, the biological risk should be measured for the purpose of risk assessment to be deemed biocompatible for the medical system. In order to develop a strategic and targeted approach to complying with regulatory requirements the manufacturer is responsible for assessing the biocompatibility of a final instrument at the earliest stage of the product life cycle. A new version of ISO 10993-1 was published in August 2018 which stressed the importance of deeper system awareness. Not all biological effects should be tested by biological tests in the latest edition of the standard. Any checks will now be waived if the decision is soundly endorsed. However, such a judgment will only benefit from a thorough understanding of the system, its components and its development methods. Eurofins Medical Device Testing can support manufacturers by issuing a correct Evaluation Biological Safety Plan, which collects and evaluates all available information. This plan can guide the manufacturers in finding an appropriate approach to the correct test strategy to avoid additional time and costs. The Biological Safety Evaluation Plan can assist the manufacturer in understanding the device and its biocompatibility, together with the final overall biological evaluation (the Biological Evaluation Report). In comparison, these papers are valuable for the United States. FDA submission and/or CE labeling, as regulatory authorities are more commonly working. The new intelligent approach to biological evaluation and the short overview of the corresponding ISO 10993 standards are presented in this White Paper. The biological evaluation of the medical system is carried out in accordance with the criteria set out in the ISO 10993 list. The biological assessment is an important consideration as the protection and reliability of a medical system can be shown as the manufacturer chooses to touch the patient in case of completion of the planned application.

Keywords: Standard, Assessment, Medical, Chemical

1. Introduction

In three sections, essential criteria for biological assessment and risk analysis of medical devices are clarified. The structure and basic concepts of biological assessment are given by ISO 10993-1; ISO 10993-18 offers details on qualitative and Quantitative characteristics; and ISO 10993-17 finally provides instructions for deriving the limits of leachable medical equipment components. The three main requirements will be significantly revised.

The final draft international Standard (F-DIS) was released in January 2018 for ISO 10993-1 "Evaluation and testing within a risk management process." The revision would require a modification to the flow chart explaining the biological assessment's systemic methodology and the chemical characterisation as an initial point. As a result, Annex A1 "Consideration Assessment Tests" of ISO 10993-1 was updated by introducing a new column with chemical characterisation as a test parameter. The guideline manual "ISO International Standard ISO 10993, Biological evaluation of medical devices

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Part 1: Evaluating and testing" will contain additional test criteria for some types of devices, and additional toxicological endpoints for evaluation based on the revised U.S.-FDA matrix (2016). It was addressed with additional criteria that chemical characterization is the only compulsory evaluation criterion and that all other toxicological endpoints be tested case by case within a toxicological risk assessment.

There is a significant revision to ISO 10993-17 on acceptable limits for leachable substances. TC 194 experts discuss approaches to risk assessment using the concept of TTC, which has been already established and accepted for the use of genotoxic pharmaceutical impurities. If it can be shown that impurity is below TTC, it is presumed that there is no substantial danger to the levels of the chemical material and that no further measurement of this impurity is needed. The TTC enables threshold values to be established for substances at which insufficient material is available to cause toxicological hazards and thus no further assessment is required. The definition can also be used on unidentified pollutants more generally. The introduction of TTC in Part 17 will be a considerable advance to prevent needless animal experiments if chemical characterization can appear to be below the TTC for leachables. This definition is to be incorporated in the ISO 10993-17 revisions.

ISO 10993-18 on "chemical material characterisation," given the technological and analytical knowledge of the past 10 years after its publication in 2005, will also be majorly updated. A second draft Committee (CD) has now been published in January 2018, including the selection of extraction types and a better definition of the experimental requirements for investigating extractables and leachables (exaggerated versus simulation-use extraction). It will also include a summary of the incremental method of chemical characterization and the appropriate modifications to the flow map. The analysis will include approaches to set analytical assessment thresholds (AETs) and to improve them in accordance with toxicological thresholds (TTCs).

In particular, a more complex step-by-step chemicals feature, including more complex chemical analytics for the elucidation of the structure of unknown chemicals released but also for the assessment of kinetics releases of chemical compounds from medical devices, can be predicted.

2. Need and Importance

Based on the analysis of existing science evidence and physicochemical caracterization, the evaluation has updated the biological assessment method, whereas in-vidro and in-vivo research should be performed mainly to fill gaps in our knowledge. It is important to understand that besides biocompatibility research, biological consequences can be approached in various ways. This illustrates why the evaluation of an endpoint does not mean that an extra test range is conducted. It therefore conforms to the 3Rs concept (replacement, decrease and refinement) and ISO 10993-2, which includes a minimum of discomfort, suffering, or failure for the animals in use. As stated, the latest ISO 10993-1 version emphasizes the importance of a chemical characterization before any biological examination. In addition, if the physicochemical and morphological properties of the device and of its components impair biocompatibility (see ISO/TS 10993-19), we need a clearer understanding of the physical device in the analyzes of its composite materials, packaging, sterilization and other post-production procedures before any experiments are carried out in vivo. In particular.

Based on this preliminary assessment, it is possible to recognize the inherent properties of a medical device; therefore it is possible to classify the endpoints that need more study by biological testing. Chemical characterization and toxicological assessment will provide long-term systematic impact information such that certain studies can be stopped. Additional consequences such as cytotoxicity, inflammation, and sensitization can not be sufficiently analyzed using a chemical characterization or risk evaluation method, so additional biological testing may be essential. If a test is considered appropriate, the finishing device or representative samples must be carried out and processed similarly, including sterilization, if necessary. Here is a short summary of the biological experiments that may be carried out on a medical system.

The cytotoxicity experiments, as defined in ISO 10993-5:2009, employ cell culture methods to evaluate cell lysis (cell death), cell growth inhibition, colonization and other cell-related effects of the medical device.8 Cytoxicity is considered a pilot project test as it is an important predictor of medical toxicity assessment. It is a convenient and fast in vitro test with a high sensitivity9. ISO 10993-5 lists three types of cytotoxicity tests: extract, direct and indirect touch tests. A qualitative as well as a quantitative assessment (e.g. NRU or other similar techniques) should be conducted. Cell viability losses of more than 30 percent are called a cytotoxic consequence relative to negative controls. Data on cytotoxicity should be analyzed with respect to and for the expected application of other biocompatibility test findings on the medical device. Indeed, cytotoxicity studies are mainly an example of in vivo toxicity potentials. A system should not be deemed adequate or insufficient for the therapeutic use, relying only on evidence on cytotoxicity8. Discomfort is measured in compliance with ISO 10993-10:201010. Irritation tests should be used on appropriate places of use, such as scalp, eye, and mucosal membranes, to estimate the possible irritation of medical equipment, products and/or extracts by using an appropriate model. The test(s) performed shall be suitable for the exposure or touch route and duration. Where dermal or mucous irritation is not sufficiently determined, the intracutaneous reactivity test may be performed for the localized response of tissue to the device being examined. While the new edition released in 2010 acknowledges that scientific advancement has to be followed, already using accepted approaches as established alternatives to in vivo research, the ISO 10993-10 actually defines only in vivo evaluations. Several research on in vitro assessment and evaluation of chemical Irritating Activity Determination as substitutes for in vivo annoyance tests have been published 11, 12. A new global standard is being introduced to replace the animal skin irritation experiments currently listed in ISO 10993-10, including in vitro skin irritation tests on medical devices. ISO 10993-23

3. Future Challenges

Appropriately and properly labeling biological reactions to nanodevices and tissue-engineered scaffolds that may involve different elements, such as newer materials, cells and proteins, new biological reaction tests are required. This is a major challenge and it is obvious that new, advanced biological reaction testing systems should be built to test nanodevices and fiber engineered fabrics correctly and adequately.

In the determination of biological reaction, phenotypic associations must be considered. Cytokines are now widely used for defining the involvement of different cell types in the biological response assessment, but in many situations this form of study is not adequate to offer a detailed image or understanding of the response. Examples of this involve IL-1 cell development. If macrophages and other cell type produce IL-1 the IL-1 receptor antagonist is also produced, and the biological reaction of IL-1 can be binding and inactivated. Consequently, a more complete analysis and explanation can be achieved by studying both IL-1 and IL-1ra. The detection and involvement of the fibroblast growth factor is a related example (FGF). FGF produces metalloproteinases matrix (MMPs) and produces tissue inhibitors for metalloproteinases matrix (TIMP). Thus the quantitation of both MMP and TIMP in order to assess the importance of FGF release and existence will be used in a more detailed review This is important for the remodeling of the fibrous capsule that is now considered important in the tissue response to many medical devices and biomaterials. In considering different types of controlled release systems injected or inserted, the diffusion of the fibrous capsule may be essential for the determination of the pharmacokinetics and pharmacodynamics of a provided active agent. Previous considerations of the fibrous capsule as a barrier to the diffusion of higher molecular weight active agents may prove to be false because recent experiments have shown that proteins with a weight of 4000 may produce ample blood levels for their expected reaction. Therefore, the fibrous capsule must not actually be used as a diffusion shield for active agents released from controlled release systems

4. Applicable Standards

These are the various criteria widely used by medical instruments to show biocompatibility via biological assessments.

• ISO 10993-1:2009 Medical system biological assessment — Section 1: Risk Control Evaluation and Testing (ISO 10993-1:2009) EN ISO 10993-1:2009/C:2010

• EN ISO 10993-3:2014 Medical system biological assessment – part 3: genotoxicity, carcinogenic and reproductive toxicity studies (ISO 10993-3:2014)

• EN ISO 10993-4:2009 Medical system biological assessment - Part 4: Collection of blood interplay tests (ISO 109934:2002, including Amd 1:2006)

• EN ISO 10993-5:2009 Surgical equipment biological assessment - Part 5: in vitro cytotoxicity studies (ISO 10993-5:2009)

• EN ISO 10993-6:2009 Medical device biological assessment - Part 6: local impact monitoring after implantation (ISO 10993-6:2007)

• EN ISO 10993-7:2008 Medical device biologic assessment - Section 7: Residual ethylene oxide Sterilization (ISO 10993-7:2008)

• EN ISO 10993-9:2009 Medical equipment biological assessment – Section 9: Structure for defining and quantifying possible products of degradation (ISO 10993-9:2009)

• EN ISO 10993-11:2018 Medical device biological assessment – Part 11: Structural toxicity testing (ISO 10993-11:2017)

• EN ISO 10993-12:2012 Biological assessment of medical devices - Section 12: processing of samples and products of comparison (ISO 1099312:2012)

• EN ISO 10993-13:2010 Biological assessment of medical devices, Section 13: defining and quantifying polymer medical system degradation items (ISO 10993-13:2010)

• EN ISO 10993-14:2009 Medical device bioassessment - Part 14: ceramic degradation product recognition and quantification (ISO 10993-14:2001)

• EN ISO 10993-15:2009 Medical system biological assessment — Section 15: Recognition and quantification of metal and alloy degradation items (ISO 10993-15:2000)

EN ISO 10993-16:2010 Medical system biological assessment – Part 16: Development of toxicokinetic analysis for products and leachables for degradation (ISO 10993-16:2010)

• EN ISO 10993-17:2009 Biological medical system assessment – Section 17: Setting acceptable limits for leachable substances (ISO 10993-17:2002)

• EN ISO 10993-18:2009 Medical system biological assessment — Part 18: Chemical material characterization (ISO 10993-18:2005)

• EN ISO 10993-11:2009 Medical technology biological assessment – Part 11: Structural toxicity testing (ISO 10993-11:2006)

The determination on the applicability of the standard is the type of touch and the time the medical device is contacted by the patient. The biological determination is the responsibility of the legitimate manufacturer responsible for final medical product conformity. The legal producer must pursue a risk-based approach to ensure that the correct standard/biological assessment protocol is followed and documents kept. The biological production of the substance and medical equipment must be accomplished by the risk assessment process. The assessment must be performed by appropriate qualified and experienced experts. It also ensures that the company preserves its competence and expertise and is a verifiable proof. The biological assessment is typically required on the ready-to-use completed medical product.During biological assessment, caution must be taken to test various medical instruments separately, even for different permutations and variations separately.

The following conditions must be taken into account before planning any biological examination of the medical system

Degradation: device decomposition, which results in a degradation over time of mechanical and/or physical properties of the device

Extractible: Substances released from the system because of limitations in usage (example: corrosion products)

Leachable: release from the adjuvant system developed and sterilized (example: ethylene oxide residues)

Competent, professional biological evaluators typically follow methodology:

1. Identification of biocompatibility standards and documents applied by medical equipment.
2. Formulation definition and application of medical instrument
3. Medical interface catagorization:nature and touch period
4. Material features
5. Results and literature analysts analysis process
6. Biological test systems

7. Global performance review
8. Risk file/risk management process
9. Data post-market

In the following cases, the file can be re-evaluated

If the material varies, the source, the physical configuration of the medical system, dosage manufacturing packaging and sterilization, changes in the planned application of the substance as a result of post-market monitoring data assessment if you discover any evidence of the product's adverse impact.

5. Conclusion

Under the risk control phase preceding the introduction to the market, according to the ISO 10993 set, each completed medical product must undergo a full biological safety evaluation plan assessment. This method starts with categorizing the medical device according to body touch form and length to prepare an appropriate research approach. As stated in the latest edition of ISO 10993-1, a biological safety assessment strategy should commence with the device's physical and/or chemical characterization. Following all this knowledge, further inquiries may be prepared accordingly. Eurofins Medical Device Testing will help you in this process by evaluating research literature and other available evidence, recommending a suitable testing approach, including reasons for choosing or discontinuing experiments, and offering evaluation and analysis of biocompatibility data obtained from tests.

Link with clinical evaluation:

Biological assessment is a central aspect of clinical evaluation process. Like clinical and technical compliance with medical product protection and efficacy, biological assessment also plays an important role in clinical evaluation process.

Link with first party audit:

The internal auditor may, during the internal audit of the design and production file, also review the biological assessment of the medical system as regards the materials used in its construction, which come into contact with the patient's body and may be able to cause corrosion or leaching/relief. The internal auditor will analyze the effect of the drug toxicity/impact of deterioration and leaching from the medical device of substances

Link with second party audit:

The second-party auditor may take into account during the audit the changes initiated by the supplier with respect to the impact analysis of the changes to the material regarding the expected usage of the medical device; the supplier auditor may review the biological assessment of the medical device in relation to the material used for its use. The supplier auditor will investigate the effect of toxicity of the deterioration and leaching of substances from the medical device

Link with third party audit:

During The auditor can take into consideration the improvements undertaken by an entity which must be measured in relation to the impact analysis of material changes in the planned usage of the medical device, the auditor can review the biological evaluation of the medical equipment in relation to materials used for its design. The auditor will analyze the effect of the chemical toxicity / impact of deterioration and liquidation of the substancesmedical device

Development of methods of strengthening justification, increased emphasis on optimisation, development of newer effective regulatory mechanisms and accounting for repeated examination of an individual patient all still remain challenges to meet. Continuing to repeat something in which success in implementation during decades has been minimal means lack of new ideas. Use of appropriateness criteria for justification has been one such example. Newer approachesare needed to handle issue of inappropriate examin-ation. The controls at the level of source (referrer) are likely to be more effective than at the level of those who are performing examination. Clinical decision based electronic referrals are one such good example. Creating a system of accountability for referrer for any examination that involves radiation dose to the patient of more than a defined value say 2 mSv could be another way(2)Increasing individual patient doses will need tracking of radiation exposure history as already pointedout(18 –20), but there may be a need to consider development of dose constraints, not limits, for patients an area that is taboo currently. Changing situations require changing approaches, and constraints will increase awareness on the part of referring physicians to consider radiation dose in addition to clinical considerations. Alternatively or additionally, mechanisms shall need to be developed for referrers to make them look into previous exams for clinical information.

A tendency has been emerging on passing on radi-ation dose values in an examination like a CT scan to patients in the report of the examination, and it has led to a law in a state in USA. The challenge lies in confidence building in the patient. Displays in patient waiting areas depicting system of regular monitoring of patient doses, comparing them with standards and ensuring that doses are maintained minimal without affecting quality shall be more assuring that providing mGy or other units of radiation dose figures to patients.

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7. ISO/TS 10993-19:2006, Biological evaluation of medical devices - Part 19: Physico-chemical, morphological and topographical characterization of materials.