Comment on draft guidance:


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Introduction

These comments are provided by a group4 of technical expert members of ISO Technical Committee 194 (which writes the ISO 10993 series of standards). Our comments are presented in two parts: comments regarding the overall approaches to evaluation of biological safety of medical devices that is embodied in the guidance and comments on specific aspects of evaluation and specific technical content of the draft guidance.

About the Authors

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Biological Evaluation – a Risk Management Context

The 2009 revision of ISO 10993–1 contained significant changes to reflect the risk management paradigm of ISO 14971 – an approach to medical device evaluation which underpins all aspects of product safety. This model is described in greater detail in the supporting guidance contained in ISO TR 15499:2012 Guidance on the conduct of biological evaluation within a risk management process. Briefly, the process involves the following steps.

- Gathering of information about the materials used in the device, their toxicity and their record of use in similar clinical applications and patient contact. This includes characterization of device materials – which requires both review of formulation information and conduct of materials analysis, particularly for available extractable components.
- Evaluation of that information by suitably qualified experts to determine if there is acceptable level of biological safety. This includes review of the current toxicological knowledge for the identified materials components which are available for tissue contact taking into account the specific tissue contact route(s), the dose rate and the specific areas of biological interaction identified for consideration.
- If there is insufficient information available to determine safety, conduct of additional testing to supplement the available data for expert evaluation.

ISO 10993–1 also allows for alternative approaches to evaluation where the circumstances merit. Clauses 4.5 and 4.8 are particularly pertinent:

“4.5 All known possible biological hazards shall be taken into account for every material and final product, but this does not imply that testing for all possible hazards will be necessary or practical (see Clauses 5 and 6). ...”

“4.8 The biological evaluation shall take into account the nature and mobility of the chemical constituents 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.”

In taking this approach, the materials characterization, review of available literature and other data and determination and conduct of testing must take into account the actual user exposure and consider the specific toxicological risks both in terms of the generally considered toxicological endpoints set out in Table A1 of ISO 10993–1 as well as specific or additional risk factors that should be considered, for example because of particular tissue exposures (where modified test methods may be appropriate to take into account the particular tissues exposed).

Such an approach is more flexible and far more robust than that in the earlier versions of ISO 10993–1, the Tripartite Guidance and FDA General Program Memorandum #G95–1. These simply matched, in a matrix, toxicological endpoints to duration and invasiveness of exposure. In particular:

- The availability of strong a priori safety data relevant to the materials and identified leachables will provide a scientific framework for minimizing testing, and in particular avoidance of unnecessary animal testing. In terms of ISO 14971: low risks can be identified and confirmed, based on scientific evidence, as requiring no further mitigation.
- Careful consideration of special risks which may be present (such as specific tissue contact or presence of materials with unusual properties e.g. degradable materials, nanomaterials) will result in correct identification of additional testing and evaluations required which may go beyond the recommendations of the ISO 10993 series.
In short this approach ensures that resources are not wasted on unnecessary repeat testing of materials established as safe in the particular application, and that effort is appropriately directed to those areas of identified significant risk.

**Previous experience – application of G95–1 in FDA reviews**

It has been our joint experience that FDA CRDH ODE reviewers, especially of 510(k) submissions, tend to focus on the matrix of requirements and the additional tests required by G95–1 guidance. There is a tendency for reviewers to interpret both the ISO 10993–1 standard and FDA G95–1 guidance as a predefined, immutable list of test reports which must be delivered as part of the 510(k) dossier. This has resulted in unreasonable requests for unnecessary testing (e.g. insistence on genotoxicity testing in cases where it has been conclusively established that the device does not contain any genotoxic substances.)

Similarly we have been concerned where reviewers, in following only the matrix of tests did not consider at all other pertinent risks, such as need for modification of test protocols to address specific tissue exposures in invasive devices, or potential for interactions between devices and medicines which may have affected biological safety.

We point out that the concept of substantial equivalence should not be taken to imply a requirement for identity of testing between predicate and new device (as is often the position taken by FDA reviewers). A risk management approach implies building on prior knowledge and modifying the evaluation (and associated testing) in accordance with the evolving knowledge base, including omission of tests where safety is established for a given end point, and in some cases additional testing as knowledge of new toxicological risks emerges. Therefore the requirement should not be identity of testing but that both predicate and new devices have been established as biologically safe when evaluated according to the requirements of ISO 10993–1 and FDA guidance.

**The FDA draft guidance – comments on overall approach**

The replacement of G95–1 with a new guidance which reflects a more modern, risk based approach is a very welcome development. We note that since the publication of the G95–1 guidance, FDA CDRH has recognized, with a small number of qualifications, both ISO 14971:2007 and ISO 10993–1:2009, for the purpose of support of 510(k) and PMA submissions. Unfortunately, the specific approach taken in this draft guidance does not adequately capture the letter or the intent of the current versions of ISO 10993–1 and ISO 14971. Rather the draft guidance continues, and in some ways extends the earlier approaches embodied in G95–1 guidance, where there is undue emphasis on adherence to a predetermined list of tests to be carried out, and insufficient attention to rigorous expert evaluation of biological risks and focus on the significant risks identified in a risk management based evaluation. Manufacturers and reviewers who follow this guidance risk overemphasis on non–significant risks and, more importantly, may fail to identify and account for significant risks unique to the particular nature of the device under consideration or the specific patient exposure.

The draft guidance published by FDA certainly makes reference to the risk management approach embodied in ISO 10993–1:2009. However, there remains a considerable emphasis on the Table A1 matrix and its use as a de facto checklist for testing by review staff. Furthermore we note that the current draft further extends the endpoints to be considered beyond those of ISO 10993–1:2009 and
G95–1 guidance. It is our concern that this will simply result in longer lists of test reports required, rather than consideration of the relevance and applicability of the extra endpoints to the specific device in question.

More generally, the guidance repeatedly refers to the consideration or recommendation of testing. There appears to be a lack of understanding that ISO 10993–1 calls for evaluation of different toxicological endpoints. We emphasize that testing forms only a part of that evaluation and should only be conducted when prior materials characterization and review of existing data has failed to produce sufficient available to establish safety. The current draft is therefore contradictory to the evaluation approaches embodied in ISO 10993–1 and is confusing and ambiguous.

In summary, we believe that the draft should be revised to make it very clear to manufacturers and to review staff that a biological evaluation according to ISO 10993–1 is not simply a matter of presenting test reports according to a predetermined matrix. Rather a rigorous evaluation requires risk assessment conducted by appropriately qualified experts, which is directed at answering three questions:

1. What is the available information which allows safety to be established for specified endpoints? This may allow justification of omission of some testing identified in the Table A1 matrix.
2. What additional risks may exist which require either modified testing or consideration of additional testing – which may include testing additional evaluation or testing OUTSIDE of the matrix?
3. Based on 1 and 2, what is the required testing program to complete the knowledge base necessary to establish safety?

Specific Examples

The following specific examples highlight some of our concerns about the approach taken by the draft guidance and the potential for ambiguity or excessive prescription.

**Section 5 (E) Implantation**

The implantation test protocols defined in ISO 10993-6 and its references are designed to consider local effects of implanted materials. There is an evolving scientific consensus\(^5\)\(^,\)\(^6\)\(^,\)\(^7\)\(^,\)\(^8\)\(^,\)\(^9\)\(^,\)\(^10\)\(^,\)\(^11\)\(^,\)\(^12\) that local effects as they are evaluated according to the standard are

dominated by physical features on a macro and micro scale and that the chemical composition has a minor role in the local response. Therefore the reliance on implantation tests for evaluation of leachables is especially problematic. In particular we note that FDA recommends consideration of implant testing of externally communicating devices, where the materials never actually come into contact with tissues. We suggest that the scientific validity of such approaches is questionable. For example we are aware that FDA almost always mandates implant testing for devices in indirect contact via the air-path such as ventilators. This is notwithstanding the fact that there is limited opportunity for transmission of materials in the air path and that intramuscular or sub-cutaneous protocols (acceptable to FDA) are likely to be of limited relevance to inhalation exposure and toxicity.

In summary, while we support the use of clinically relevant implant studies for implantable devices, we question the value of implantation tests as a general approach to indirect assessment of toxicity of leachables. We suggest that this section be reworded to clarify that implantation may be of use in some circumstances, but that the validity of implant testing should be considered with regard to the actual patient contact for the device.

- **On the use of clinical data:**

The draft states (line 402): “Clinical data may be of limited utility if specific toxicology endpoints are not included in the monitoring plan.” We find this a puzzling assertion. It would be unusual indeed to conduct a clinical study where the toxicological safety of the device materials had not already been established and so there is usually no requirement to evaluate toxicology as a direct endpoint of a clinical protocol. We are not aware of any clinical study where specific toxicological endpoints have been included.

Nonetheless, clinical studies conducted according to GCP (both under US regulations and for trials conducted internationally in accordance with ISO 14155) have quite specific requirements for reporting and analysis of adverse events and it is likely that significant toxicological effects would be identified during the course of the trial and follow ups period. We are concerned that the assertion unreasonably devalues the use of previous clinical experience as an indicator for biological safety.

- **Section 7 Assessment of Known or Potentially Toxic Chemical Entities**

This section attempts to deal with several different issues and is confusing and ambiguous, and could lead to excessively prescriptive requirements. In particular, the section considers and attempts to treat in the same way both substances of unknown toxicological risk (substances used in devices for the first time) and substances of well-defined risk (such as well-known colorants). A presumably unintended consequence is that a possible interpretation is that for all substances which are bioavailable (irrespective of their potential toxicity) a full suite of testing is mandated (lines 900-909).

While we support the overall thrust of the suggested approach, this section needs clarification to set out that:

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A primary consideration should be bioavailability: if any substance (irrespective of knowledge of toxicity) is not bioavailable – then there is no requirement for any further testing or information to be provided.

For materials which are bioavailable, then the next consideration is an evaluation of toxicity based on the quantity which is available and the known toxicity at the established level of exposure. If there is established safety (after provision for appropriately protective safety factors) then there is no requirement for further testing or provision of information.

Only in the case where a substance is bioavailable and the known dose cannot be established to be safe from the known toxicity should there be need to consider additional testing. The testing should be focused on the specific toxicological endpoints of concern.

With regard to colorants, we see no reason why colorants should be treated differently to any other material. Either the colorant is bioavailable, or it is not. Either it is bio-compatible for the application, or it is not. Section 7 would provide greater consistency of scientific rationale if it addressed all materials in addition to color additives.

In consideration of toxicology of identified leachables, the guidance would benefit from explicit acknowledgement of the concepts of threshold of toxicological concern (TTC). This is well established in safety assessment of medicines (e.g. see FDA Guidance for Industry: Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches\(^\text{13}\)). If it can be established that the bioavailable dose is below either the documented safe dose relevant to the route of exposure or an established TTC, then there is no requirement for further testing or provision of information.

**Summary**

For too long, the approach to biological evaluation has been constrained by the misuse of the ISO 10993-1 standard as a simple checklist of tests. Such an approach all too often produces mediocre outcomes. Reviewers insist on only a generic list of test reports and the expedient approach for manufacturers is simply to commission the required tests and file with FDA. The result is that manufacturers often fail to engage with appropriate experts or to conduct adequate risk assessments to truly ascertain the key biological risks.

We applaud that the draft guidance is more extensive in both scope and depth compared to the previous General Program Memorandum G95-1. Biological safety evaluation is a complex field and the more detailed insight into FDA thinking is welcomed.

The approach to biological evaluation has evolved considerably in the last 20 years. The use of risk management based on rigorous evaluation of all available knowledge is well established as an approach to biological evaluation which is far more robust and effective than a simple consideration of a matrix of recommended test as according to exposure. Such an approach is far too inflexible and cannot adequately deal with the great variety of medical devices in use today, especially when the test matrix is rigidly applied by reviewers.

Given the very substantial advances in science that have occurred since the first publication of ISO 10993-1 and publication of the G95-1 guidance, an updated FDA guidance is a very welcome development. Unfortunately current draft guidance fails to provide the necessary clarity. The document requires redrafting to:

- emphasize the central role of risk management conducted by qualified experts;
- include sufficient flexibility to customize evaluations according to the actual specific risks presented by a device and
- make abundantly clear to both reviewers and manufacturers that the Table A1 matrix presents a recommendation for endpoints to be considered and **not** tests to be conducted. Actual tests should be selected to resolve outstanding questions of biological safety following review of existing materials characterization and toxicology data.

Biological safety is not best assured by a applying a list of tests (no matter how comprehensive) but by careful evaluation and risk assessment of a qualified expert taking into account 1) the intended clinical use including exposure assessment, 2) the properties of the material, 3) experience of previous clinical use of the material, as well as 4) results from preclinical tests of the base material, additives and the finished product.