Successfully complying with biocompatibility requirements across the globe

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Natalia Crespo Biel, PhD
RA Specialist
Terumo Europe N.V.

Disclaimer

The content of this presentation is based on professional experience of the presenter for specific type of products and under advice of our local RA associates.

OUTLINE

- General introduction
- Discussing the differences in biocompatibility requirements when submitting applications across the globe: sharing current experiences.
  - MDD 93/42/EEC
  - FDA
  - ROW
    - Latin America: Mexico, Brazil
    - Asia: India, China, South Korea and ASEAN country members
- Conclusions
  - Is a globally harmonized biocompatibility scheme possible?

General Introduction

- Global considerations for MD registration
  - CE certification and/or FDA approval is a door opener for ROW registrations.
  - Product classification will mainly define the regulatory requirements and the content of the Technical Documentation.
  - Major markets such as US, CAN, AUS, Korea have similar classification rules as EU regulation.

MDD 93/42/EEC Certification

- Manufacturers of MD have the responsibility to demonstrate an acceptable biological safety profile for finished devices. Compliance with EN ISO 10993-1 is a preferable option as it confers a presumption of conformity with the Essential Requirements of the MDD 93/42/EEC.
- During the Technical Documentation assessment under MDD 93/42/EEC (applicable annex), the NB will audit the biological information of your MD as part of the pre-clinical evaluation. Full examination of biological data is expected for class III devices, however you cannot rule out extended examination also for Class IIa & Iib.

MDD 93/42/EEC Certification

- NB surveillance audits / review of Technical Documentation
  - Biological evaluation of the MD should be performed within a risk management process.
  - It is recommended to evaluate the totality of your biological safety data and properly document it (DHF and change control).
  - Biocompatibility test results do not provide enough evidence to have confidence on the safety and performance on the device.

MDD 93/42/EEC Certification

- NB surveillance audits / review of Technical Documentation
  - The content of your Biological Evaluation Report should cover at least the below information:
    - Categorization of the Medical Device
    - Description of materials used
    - Chemical performance
    - Biological Evaluation endpoints to be addressed
    - Any possible rationale to justify any possible deviation to the applicable standards
    - Conclusion
  - It is recommended to present data derived from testing in a clear and concise form, such as a table.

FDA

- 510(k) file clearance – Class II
  - ISO 10993-1 and most of the relative parts are recognized standards by FDA.
  - According to Guidance documents for the format of your 510(k) file – traditional submission, if your device contains components that come into contact or indirect contact with patients, biological evaluation shall be assessed based on FDA Guidance (2016) Use of International Standard ISO 10993-1 “Biological Evaluation of Medical Devices – Part 1: Evaluation and testing within a risk management process”.
  - In case biocompatibility testing shall be performed, it is recommended to include test results in your submission.

FDA

- Case example
  - Class II – 510(k) file traditional submission
    - Material characterization is based on the assumption that the predicate device is manufactured with the same materials.
    - Available Chemical performance is submitted according to the requirements of product standard.
    - Biocompatibility testing
      - Use same test performed as per MDD certification.
      - Pyrogen test as part of the Technical Documentation.
      - Cytotoxicity according ISO 10993-5 (but no MEM Elution test requested).

Latin America

Mexico

- According to COFEPRIS requirements for MD registration, your submission of the technical documentation should cover the below biocompatibility testing depending on the class of the device:
  - Class II non implantable devices: technical dossier must contain below test results:
    - In Vitro:
      - Cytotoxicity: direct contact, elution test, agar diffusion
      - Bacterial endotoxin
    - In Vivo:
      - Systemic injection
      - Intracutaneous reactivity
      - Cutaneous irritation
      - Thermic irritation
      - Pyrogens
      - Hemolysis
  - In case some of the above testing does not apply to your device, rationale shall be presented.

Latin America

- Mexico
  - The Mexican Pharmacopoeia (supplement for Medical Devices) contains 58 General Methods of Analysis and 171 Monographs of Medical Devices.
  - Case example – Class II non implantable (Third party review)
    - Submission of Technical Documentation including:
      - Same test reports performed as per MDD certification with reference to the test methods according to ISO 10993 applicable parts.
      - The raw materials specifications used for the manufacturing of the different parts/components of the finished product with direct/indirect contact with the patient.
      - Additional related test procedures under request of Third party.

Latin America

- Brazil
  - ANVISA
    - Linked to Ministry of Health.
    - Responsible for product registration in Brazil: Medicines, Cosmetics, MD, ...
    - Executes the GMP certification of the factories (when required).
    - Defines the requirements for product registration process in Brazil -> asks Inmetro to implement product certification process.
  - ISO 10993-1 is recognized by ABNT (Associação Brasileira de Normas Técnicas: ABNT NBR ISO 10993-1:2013).
  - Cadaster Regulation RDC n°40/2015 Annex II for the requirements of the Technical Documentation for Class I/II:
    - The Technical Documentation does not have to correspond to one physical or electronic file including all following information; it may be composed of reference documents and information in other files or records of the QS of the company, which ought to remain available for inspection by the National Sanitary Inspection System.

Latin America

Brazil

- This Technical Documentation will not be filed at Anvisa as part of the application for enrollment of the product, and ought to remain at the company holder of the enrollment, however Anvisa may request forwarding of the Technical Documentation for review.
- The below points should be included as part of the Technical Documentation of medical products, as applicable, considering the nature of the technology of the product and its risk class.
  - Material/Chemical Characterization
  - Biocompatibility Assessment
  - Pyrogenicity Evaluation
- All reports that compose the Technical Documentation are summarized, however complete reports can be required in situations in which more details are necessary.

ASIA

INDIA

- New regulation for MD in India will come into force Jan 2018, until now regulation for drugs and cosmetics was applicable. The new regulation will not significantly change the content of the technical dossier.
- As part of the Product Verification and Validation activities a biocompatibility study should be included:
  - The Technical documentation should contain a list of all materials in direct or indirect contact with the patient or user.
  - Where biocompatibility testing has been undertaken (as per recognized standards e.g. ISO 10993) to characterize the physical, chemical, toxicological and biological response of a material, detailed information should be included on the tests conducted, standards applied, test protocols, the analysis of data and the summary of results. At a minimum, tests should be conducted on samples from the finished, sterilised (when supplied sterile) device.

Asia

China

- ISO 10993-1 has been transposed into a Chinese national standard (Guobiao standard GB): GB/T 16886.1-2011.
- GB standards are the basis for the product testing which products must undergo during the China Compulsory Certification.
- Product Technical Requirements to be prepared before testing request.
- GB/T 16886.1-2011 is classified as “recommended” standard.
- Chinese Food and Drug Administration (CFDA) currently accepts ISO 10993-1:2009 and testing performed by a GLP-certified lab outside China.
- Case example:
  - Submission prior to New rule (Nov 2014) - Use same biocompatibility dossier as for MDD compliance and 510(k) file clearance
  - Renewal/License amendment after New rule implementation: if same materials and manufacturing process no need for biological testing
  - Material change after new rule implementation: separate biological test report required for your submission

Asia

South Korea

- Medical Devices are regulated by the Ministry of Food AND Drug Safety (MFDS) whose objective is to protect and promote the public health thorough safety control for medical devices.
- Some of the main steps for product approval by MFDS are:
  - Step 1: Appointing a license holder/distributor.
  - Step 2: If applicable, having the MD tested at the MFDS verified labs. In general MFDS has special testing requirements for some devices as such there is a general preference to use accredited test lab in Korea to do the verification testing. Alternatively, test results that meet international standards, previously performed in other countries can be used and validated under some cost.
  - Step 3 : Submission of the Technical Documentation.
- Documentation to be presented in Korean language.

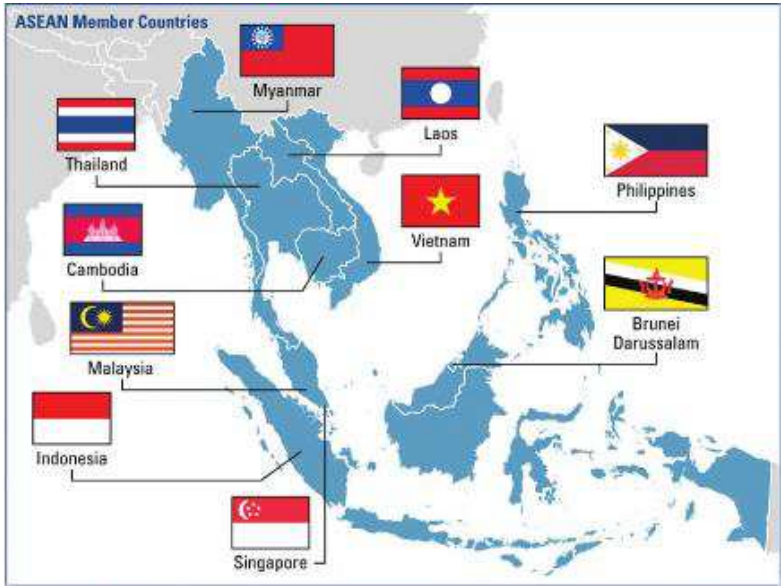
Asia

South Korea

- MFDS accepts biocompatibility testing performed in accordance with recognized international standards (ISO 10993 series and pharmacopoeias), however testing must be performed by a GLP laboratory.
- The content of the Technical Documentation should include sufficient information to prove the safety your device and its materials/components.
- Case example:
  - Class II device
    - Qualitative/quantitative information of raw materials.
    - Complete chemical/physical characterization of raw materials.
    - Proof safety profile of the raw materials: MSDS.
    - Biocompatibility testing according to ISO 10993-1 device classification:
      - » Only acceptable if performed by GLP laboratory (outside South Korea).
      - » For Cytotoxicity, only MEM elution test has been accepted.
  - Change control: new material
    - Information about the new raw material as described above.
    - Repeated biocompatibility testing with the finished product.

ASIA

- ASEAN member countries amongst others:



- Technical Documentation: CSTD
- English accepted
- In some countries the Executive Summary translated in local languages

ASEAN countries

- ASEAN member countries amongst others:
  - Singapore
    - Abridged application for MD that have been evaluated and approved in at least one of the former GHTF founding members (AUS, Canada, EU, Japan and US).
    - This route allows submission of summary data sets instead of full data with the provision that all aspects of the MD quality, shall be the same as that approved by the reference agencies.
    - The Common Submission Dossier Template (CSDT) is adopted
    - Biocompatibility testing as part of the Summary of design verification and validation documents – pre-clinical studies:
      - Test conducted on samples from the finished product, sterilized device.
      - All materials that are significantly different must be characterized.
      - Information describing the test, the results and the analysis of data should be presented.

ASEAN countries

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  - Singapore/Philippines
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Conclusions

- Is a globally harmonised biocompatibility scheme possible?
  - External communicating device
  - Contact the circulating blood
  - For limited exposure (contact can be up to 24 hours)

	US	Mexico	Brazil	India	China	South Korea	ASEAN Singapore	ASEAN Philippines
Product classification (local)	II	II	II	II	II	II	B	B
Technical dossier:								
Material Information	Yes	Yes	Yes	Yes	Yes	Yes (extended)	Yes	Yes
Biocompatibility:								
- Cytotoxicity	Yes	Yes	Yes	Yes	Yes	Yes (Elution test)	Yes	Yes
- Sensitization (Kligman maximization test)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
- Intracutaneous reactivity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
- Acute systemic toxicity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
- Haemocompatibility	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
- Pyrogen test	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

In general the ISO 10993 series are accepted, even though we cannot rule out different interpretations by Regulatory Authorities


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