The legal framework for medical devices in the European Union with emphasis on the assessment of biocompatibility

Dissertation proposal

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under the supervision of Professor Dr. rer. nat. habil. Harald G. Schweim
at the Department of Drug Regulatory Affairs,
Rheinische Friedrich-Wilhelms-University Bonn

prepared by

Jaqueline Schierhuber

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1. Introduction

Biocompatibility evaluations are an ongoing process for manufacturers and distributors of medical devices. Generally, materials that come into contact with tissue/skin/blood have to be biologically compatible i.e. do not induce any host response upon contact. Nevertheless, the release of medical devices that are not biocompatible and/or biodurable is still an issue and has recently provoked a proposal of the European Commission for the amendment of the Medical Device Directive in order to close regulatory gaps concerning e.g. implantable or invasive products for cosmetic purposes[1].

Biocompatibility has to be proven on different stages during the lifecycle of a medical device. This process already starts in the development phase, where biocompatible and biodurable materials have to be selected. Used chemicals have to be assessed based on their chemical, physical and toxicological properties. Further on, the production process including all production equipment (leakage/corrosion), additives and the final product have to be regarded as well. Based on the inputs of these steps which can be based on a risk analysis, biocompatibility has to be determined on all levels. Rather than solely testing the final products, chemical analysis has to be performed in advance in order to assess the requirements of *in vitro* and especially *in vivo* tests. A comprehensive risk analysis can reduce animal testing to an essential minimum which is an advantage concerning animal welfare and has also economical advantages by reducing the costs of biocompatibility evaluations.

Manufacturers have to prove that their medical devices are biocompatible before a clinical evaluation can be initiated. For this purpose the essential requirements of the council directive 93/42/EEC[2], outlined in Annex I have to be followed. As outlined in chapter 2.1, for biocompatibility especially point 7: “Chemical, physical and biological properties” plays a major role.
Where applicable harmonized standards have to be applied, throughout the production (e.g. EN ISO 17665-1[i]) - and testing of the medical device (e.g. EN ISO 10993-1[ii]). One of the most important standards for medical devices is EN ISO 14971[iii] on the application of risk management to medical devices. In this standard the approach to risk management is outlined with respect to identified possible hazards and their initiation which can also be found in the essential requirements. Biological risks are also covered in this standard. Therefore this standard already provides the framework for further biocompatibility tests. Regarding biocompatibility the EN ISO 10993-series for biological evaluation of medical devices have to be followed.

However, some of these standards (EN ISO 10993-1 and EN ISO 10993-4[iv]) are recommendations and can be interpreted on a case by case basis. Defining a generalized procedure is hardy possible due to the variety of medical devices on the market.

[i] Sterilization of health care products - Moist heat - Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices
[ii] Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process
[iii] Medical devices - Application of risk management to medical devices
[iv] Biological evaluation of medical devices - Part 4: Selection of tests for interactions with blood

Nevertheless, based on EN ISO 10993-1 and -17[v], a generalized approach for a risk management concerning the safety of chemicals, raw materials and the final product can be attained. The application of a generalized procedure allows notified bodies to assess the efforts of medical device manufacturers in terms of biological safety on a standardized level. Thus, showing conformance to the essential requirements can be unified at least in the case of biocompatibility.

2. Current legal background

In the European Union the legal framework for medical devices consists of three directives as outlined in Table 1.

Table 1: *Parts of the Medical Device Directive (Council Directives) with information on classification*

Active implantable medical devices (AIMD) 90/385/EEC[3]	**Medical devices (MD)** (general) 93/42/EEC[2]	***In-vitro*-diagnostic medical devices (IVD)** 98/79/EC[4]
No further classification (fall *de facto* into MD class III)	Classification according to Annex IX into class I, IIa, IIb or III	Assignment according to Annex II into List A or B
e.g.: pacemakers	e.g.: sticking plasters, dialyzers	e.g.: reagents for diagnostics

The process of marketing medical devices relies on the conformity assessment. For the conformity assessment, first the risk class has to be identified. For medical devices according to Annex IX of 93/42/EEC, this is based on the degree of invasiveness, the application period and on systematic risks – 18 rules lead to the appropriate classification. For the conformity assessment of medical devices different approaches as regulated in the corresponding Annexes of the directives can be chosen. The range of methods depends on the classification and provides that for higher risk devices notified bodies are also involved[2]. As mentioned in Table 1, Active implantable medical devices (AIMD) are not subject to classifications since these are already considered as high risk medical devices[3]. In the case of in-vitro diagnostic medical devices, Annex II of 98/79/EC defines the products of List A and list B, where list A covers “higher risk” IVD[4].

Based on the conformity assessment in which compliance to the essential requirements has to be shown, the CE mark is applied. Medical devices with CE mark can circulate freely in the European Economic Area (EU/EFTA countries and Turkey). Most importantly for the customer, the CE mark offers a certain degree of confidence that the device is safe to use and functions as outlined in the description.

2.1 Approach of the MDD to biocompatibility

In the 93/42/EEC directive a legal framework for the manufacturers of medical devices is provided by the definition of essential requirements that have to be fulfilled in order to attain a CE mark – the prerequisite to market medical devices in the EU. The essential requirements

[v] Biological evaluation of medical devices - Part 17: Establishment of allowable limits for leachable substances

include e.g. general requirements on the product safety and design and construction requirements which also include requirements on the chemical, physical and biological properties of the device.
In terms of biocompatibility, the main focus is in the “Requirements regarding design and construction”[2]:

7. Chemical, physical and biological properties
7.1 Design and manufacturing: toxicity, flammability and compatibility to biological tissue
7.2 Contaminants and residues – particular attention must be paid to the tissues exposed and to the duration and frequency of exposure
7.3 Design and manufacturing to be compatible with medicinal products
7.4 Risks associated with substances that leak or leach that are carcinogenic, mutagenic or toxic to reproduction (e.g. acc. to REACH)
7.5 Leachables
7.6 Unintended ingress of substances

In order to fulfill the essential requirements harmonized standards have to be followed throughout the development, production and marketing of the medical device. Harmonized standards are standards which have been published in the “Official Journal of the European Communities”[2]. Advantage of this approach is general recognition of the procedures and methods in the EU which may also accelerate the licensing process.
Requirements for biocompatibility tests are summarized in the EN ISO 10993-series for biological evaluation of medical devices. This set of standards includes an overview of the different testing methods and provides a framework for producers and distributors of medical devices in the single European market for material testing.

2.2 Regulation of chemical substances (REACH)

As mentioned before, an important part of medical device safety and the evaluation of biocompatibility are the utilized chemicals. REACH, which stands for Registration, Evaluation, Authorization and Restriction of Chemicals is a regulation that came into force in 2007[5]. Based on this regulation, only chemicals which were previously registered can be marketed in the EU. For a successful registration especially possible carcinogenic, reproductive or teratogenic effects of the chemical have to be understood. REACH thereby also restricts the use of certain substances. The use of so called substances of very high concern (SVHC) shall be limited due to their possible adverse impact on human health. Where possible, these chemicals shall be replaced by alternative substances[6]. Article 60 of the REACH regulation excludes under explained conditions health risks associated with the use of a substance in medical devices[5]. Nevertheless, the REACH regulation has strong impact on the manufacturing of medical devices.

Prominent examples for restrictions by REACH which also impacts a number of medical devices are plasticizers (phthalates) which are used in polyvinylchloride tubings to improve their flexibility. Phthalates e.g. di(2-ethylhexyl) phthalate (DEHP) can be released from PVC under special conditions (e.g. in contact with blood)[7]. DEHP impacts the reproductive system and is therefore categorized as toxic for reproduction by REACH. The use of DEHP in medical devices should be avoided and suitable alternatives used. An example for an alternative is Tris (2-Ethylhexyl) Trimellitate (TOTM) which is less susceptible to migration and offers good hemocompatibility[8].

The REACH regulation provides harmonization and transparency in terms of safety and also biocompatibility of chemicals. The example of DEHP shows that regulations of certain chemicals can influence medical device production profoundly. Therefore the evaluation of the used chemicals is an important part of biocompatibility evaluations since suitable alternatives can already be considered during development.
The example of DEHP also reflects the close relation of the REACH regulation and the medical device directive – an amendment (Directive 2007/47/EC) provides medical devices containing phthalates to be labeled as such (Section 7.5)[9].

2.3 The EN ISO 10993-series on the Biological Evaluation of Medical Devices

Biological evaluation of medical devices is covered by EN ISO in a set of standards, the 10993-series. Each of the standards provides either detailed routine testing procedures or gives a framework of possible methods for different areas to cover. The areas cover all parts of biological evaluation of medical devices ranging from a generalized risk management process over methods for the assessment of genotoxicity or cytotoxicity, etc. to chemical and physical characterization of materials. A list of all standards is provided in chapter 6.
In the framework of this dissertation proposal, the emphasis will be on EN ISO 10993-1 (Evaluation and testing within a risk management system) and EN ISO 10993-17 (Establishment of allowable limits for leachable substances).

2.3.1 Risk assessment (EN ISO 10993-1)

This part of the series includes the process of risk evaluation and subdivides the use of medical devices based on three parts:
- Category (Surface device, external communicating device, implant device)
- Contact (e.g. for implant devices: tissue/bone or blood)
- Contact duration (A- limited ≤ 24 h, B- prolonged > 24 h to 30 d, C- permanent > 30 d)

Based on the categorization of the medical device, different tests are recommended by the standard. Which tests are actually performed should be determined on a case by case base supported by a structured risk analysis. This risk analysis can cover literature review or clinical experience.

2.3.2 Procedure for biocompatibility assessment (EN ISO 10993-17)

- **Development of standard operating procedure (SOP) for the evaluation and assessment of biocompatibility of medical devices**

The assessment of biocompatibility is a substantial part of the development of a medical device. As soon as during the development of the medical device the allowable limit of extractables and leachables shall be determined to provide a basis for the establishment of specification limits. In the current version of the EN ISO 10993-17 a procedure to assess the allowable limit of leachable substances is given. These recommendations are not concretized and leave room for interpretation by the users. Nevertheless it is advantageous that users stick to certain procedure for all devices to avoid misunderstandings with authorities and notified bodies.

A standardized procedure can provide a more detailed code of practice than the ISO standard is capable of. This is mainly due to the fact that ISO standards attempt to offer a set of standards that can be applied universally to all medical devices.
Thus, a target of the dissertation will be to provide an overview of the establishment of biocompatibility evaluations for a broad set of medical devices. This includes the following parts:

- Identification of the substances of concern
    - Literature research on physical and chemical properties of identified compounds – standardized literature review/data collection procedure
    - Overview of toxicological properties including LD_{50}, NOAEL, etc.
- Using the toxicity data for determination of the allowable limits for extractables and leachables
    - Establishment of the tolerable intake (TI)
        - TI for endpoint carcinogenicity
    - Determination of the proportional and concomitant exposure factor (CEF/PEF)
    - Use of a beneficial factor (BF) in the determination of the allowable limit (AL)
    - Calculation of the margin of safety (MoS)

3. Proposal for a regulation on medical devices and *in-vitro* diagnostic medical devices

On 26th September 2012 the European Commission published two proposals for regulations on medical devices[1] and for *in vitro* diagnostic medical devices[10]. The proposed regulation on medical devices covers both, active implantable medical devices (AIMD) and medical devices (MD), which are currently subject to two separate directives as outlined in chapter 2. In contrast to directives, which are implemented into national law, regulations become directly in force in the EU member states[11].
The objectives of the regulations as outlined here are adopted from: “Executive summary of the impact assessment on the revision of the regulatory framework for medical devices”[12].
Objectives of the regulation for medical devices (AIMD and MD):

- *Uniform control of notified bodies*
- *Enhanced legal clarity and coordination in the field of post-marked safety*
- *Cross-sectorial solution of “borderline” cases*
- *Enhanced transparency regarding medical devices on the EU marked including their traceability*
- *Enhanced involvement of scientific and clinical expertise*
- *Clear obligations and responsibilities of economic operators including in the fields of diagnostic services and intended sales*
- *Governance – efficient and effective management of the regulatory system*

The objectives of the regulation for in-vitro diagnostic medical devices (IVD):

- *Covering of legal gaps and loopholes*
- *Appropriate and robust classification and conformity assessment of IVD*
- *Clear and updated legal requirements for enhanced safety and performance of IVD*

Incentives for the proposed regulations were gaps in the existing regulatory framework. Especially after revealing that a French manufacturer of breast implants used industrial silicone rather than biocompatible and biodurable medical grade silicone the existing law

came under criticism. Based on this case, the main weaknesses of the current legal basis were identified. The changes include besides of re-classifications of certain medical devices also a broadened scope by the inclusion of borderline products such as non-corrective contact lenses. Another important part of the regulation is the oversight of notified bodies. This change is also partial due to the French breast implant scandal which may have been detected earlier if unannounced audits would have been performed. Furthermore, uniform control of Notified Bodies shall ensure that these work consistently at a high level standard and differences between Notified Bodies especially in terms of competence and consistency shall be eliminated.

Currently the proposal is still in the process of revision. Thus expert committees can still raise objections which might be regarded in the final version of the regulation. This process is followed throughout the anticipated timeframe of the dissertation.

4. Aim of the dissertation

Content of the dissertation will be a comprehensive assessment of the legal background in the marketing of medical devices. Thereby the focus will be on the importance of biocompatibility in the life-cycle of medical devices.
The proposal for the amendment of the Medical Device Directive aims to enhance consumer protection and medical device safety. Manufacturers and distributors of medical devices will have to adapt to these changes. One target of the proposed dissertation is to scrutinize the anticipated amendments and the possible impact on the licensing of medical devices. All amendments will be summarized and critically evaluated based on expert opinions and if applicable compared to approaches from other countries. Case Studies will be included to further show amendments in legislation targeting safety in the manufacturing and use of medical devices.
Furthermore, triggered by the PIP silicone case, the term “biocompatibility” and especially its evaluation will be evaluated. Generally, biocompatibility evaluations are a crucial part in the licensing of medical devices. The existing standards strive to regulate this procedure. However, difficulties arise in their practical application. Thus, the importance of harmonized standards in the course of biocompatibility evaluations – especially the EN ISO 10993-series for the biological evaluation of medical devices – shall be outlined.

Planned outcome of the dissertation is beside an overview of the legal framework for medical device marketing also a standard operating procedure for biocompatibility evaluations as explained in chapter 2.3.2.

5. Time Schedule

Anticipated duration of this dissertation is approximately two years:

Literature research will be an ongoing process throughout the dissertation but is intensified for the first six months. Recent updates in laws and the actual implementations of the proposed amendments of 93/42/EEC, 90/385/EEC and 98/79/EC will be considered.

Preparation of the dissertation is planned from Jan. 2014 onwards.

6. References

[1] Proposal for a regulation of the European Parliament and of the council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009; 26.09.2012

[2] Council Directive 93/42/EEC of 14 June 1993 concerning medical devices; 1993L0042

[3] Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices; 1990L0385

[4] Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices; 1998L0079

[5] Regulation (EC) No 1907/2006 of the European Parliament and the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC; L396/1

[6] REACH in brief; European Commission; October 2007 (http://ec.europa.eu/environment/chemicals/reach/pdf/2007_02_reach_in_brief.pdf)

[7] Phthalates: http://toxtown.nlm.nih.gov/text_version/chemicals.php?id=24; request date: 27.04.2013

[8] Flaminio LM, De Angelis L, Ferazza M, Marinovich M, Galli G, Galli CL; Leachability of a new plasticizer tri-(2-ethylhexyl)-trimellitate from haemodialysis tubing; Int J Artif Organs. 1988 Nov;11(6):435-9.

[9] Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007 amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices and Directive 98/8/EC concerning the placing of biocidal products on the market

[10] Proposal for a regulation of the European Parliament and of the council on *in vitro* diagnostic medical devices; 26.09.2012

[11] http://ec.europa.eu/eu_law/introduction/what_regulation_en.htm; request date: 27.04.2013

[12] Commission Staff Working Document: Executive summary of the impact assessment on the revision of the regulatory framework for medical devices; 26.09.2012

EN ISO 10993-series for biological evaluation of medical devices:

- EN ISO 10993-1 - Evaluation and testing within a risk management system
- EN ISO 10993-2 - Animal welfare requirements
- EN ISO 10993-3 - Tests for genotoxicity, carcinogenicity and reproductive toxicity
- EN ISO 10993-4 - Selection of tests for interactions with blood
- EN ISO 10993-5 - Tests for in vitro cytotoxicity
- EN ISO 10993-6 - Tests for local effects after implantation
- EN ISO 10993-7 - Ethylene oxide sterilization residuals
- EN ISO 10993-9 - Framework for identification and quantification of potential degradation products
- EN ISO 10993-10 - Tests for irritation and skin sensitization
- EN ISO 10993-11 - Tests for systemic toxicity
- EN ISO 10993-12 - Sample preparation and reference materials
- EN ISO 10993-13 - Identification and quantification of degradation products from polymeric medical devices
- EN ISO 10993-14 - Identification and quantification of degradation products from ceramics
- EN ISO 10993-15 - Identification and quantification of degradation products from metals and alloys
- EN ISO 10993-16 - Toxicokinetic study design for degradation products and leachables
- EN ISO 10993-17 - Establishment of allowable limits for leachable substances
- EN ISO 10993-18 - Chemical characterization of materials
- ISO/TS 10993-19 - Physico-chemical, morphological and topographical characterization of materials
- ISO/TS 10993-20 - Principles and methods for immunotoxicology testing of medical devices