Clinical Evidence Requirements

Top 10 Proposed Changes

Suzie Halliday & Ibim Tariah
September 2015
Proposed Medical Devices Regulation

Consolidated position from Council - July 2015
Proposed Regulation

- 71 Whereas … = Why
- X Chapters of 91 Articles = What
- XVI Annexes = How

- Chapter I – Scope and Definitions
- Chapter II – CE Marking, Economic Operators, Reprocessing
- Chapter III – Identification and Traceability of Devices
- Chapter IV – Notified Bodies
- Chapter V – Classification and Conformity Assessment
- Chapter VI – Clinical Evaluation and Investigation
- Chapter VII – Vigilance and Market Surveillance
- Chapter VIII – Cooperation between Member States
- Chapter IX – Confidentiality, Data Protection, Funding, Penalties
- Chapter X – Final Provisions
Proposed Regulation

• 71 Whereas … = Why
• X Chapters of 91 Articles = What
• XVI Annexes = How

- Annex I – General safety and performance requirements
- Annex II – Technical Documentation
- Annex III – EU Declaration of Conformity
- Annex IV – CE Marking of Conformity
- Annex V – European UDI System
- Annex VI – Requirements to be met by Notified Bodies
- Annex VII – Classification Criteria
- Annex VIII – Conformity Assessment – QMS Assurance and Technical Documentation
- Annex IX – Conformity Assessment – Type Examination
- Annex X – Conformity Assessment – Product Conformity Verification
- Annex XI – Procedure for Custom-made Devices
- Annex XII – Certificates issued by a Notified Body
- Annex XIII – Clinical Evaluation and Post-market clinical follow-up
- Annex XIV – Clinical Investigations
- Annex XV – Products without an intended medical purpose
- Annex XVI – Correlation Table 90/385, 93/42 and Regulation
The scope of the new Regulation includes clinical investigations on medical devices conducted in the European Union?
• This Regulation lays down rules concerning the placing on the market, making available on the market or putting into service of medical devices and accessories to medical devices for human use in the Union.

• This regulation also applies to clinical investigations on medical devices conducted in the Union.

• This regulation shall also apply to the groups of products without an intended medical purpose that are listed in Annex XV … taking into account the state of the art, and in particular existing standards for analogous devices with a medical purpose, based on a similar technology.
The definition of clinical data is almost unchanged?
Information concerning the safety or performance that is generated from the use of a device and that are sourced from the following:

- Clinical Investigation
  - device concerned

- Clinical Investigations reported in Scientific Literature
  - demonstrated equivalent devices

- Peer reviewed Scientific Literature
  - device concerned
  - demonstrated equivalent devices

+ Generated and verified from the manufacturer’s post-market surveillance system (PMCF).
Clinical Evidence, Clinical Evaluation and Clinical Data are synonymous?
Chapter I – Scope and Definitions – Article 2 – Clinical Evidence

Clinical Evidence

- the **clinical data** and **clinical evaluation report** pertaining to a medical device
- sufficient amount and quality to allow a qualified assessment of whether the device achieves the intended clinical benefit(s) and safety, when used as intended by the manufacturer

Clinical Evaluation

- a systematic and planned process to continuously generate, collect, analyse and assess the **clinical data** pertaining to a device
- to verify the safety and performance of the device when used as intended by the manufacturer

Clinical Data

- clinical investigation on the device concerned
- clinical investigation reported in the scientific literature, of a similar device for which equivalence to the device in question can be demonstrated
- peer reviewed scientific literature on other clinical experience of either the device in question or a similar device for which equivalence can be demonstrated
- generated and verified from the manufacturer’s post-market surveillance system
For Class III and implantable devices there will be a database of “summary of safety and performance?”
Chapter III – Identification and Traceability of Devices – Article 27 – European Databank

EUDAMED

Electronic System on Registration / Conformity Assessment
Applications + Summary of Safety and Clinical Performance

Electronic System on Certificates
(issued, reissued, refused, suspended, withdrawn)

Electronic System on Vigilance
/incidents, FSCA, FSN/

Electronic System on Market Surveillance
(measures taken by Member States)

Electronic System on Clinical Investigations
(sponsors, description of investigational device, comparators, purpose, status)

Electronic System on UDI

Electronic System on Registration – Manufacturers & Authorised Representatives – SRN
### Chapter III – Identification and Traceability of Devices

#### New Search

<table>
<thead>
<tr>
<th>Device Classification</th>
<th>Prosthesis Knee, Patellofemoral, Semi-Constrained, Cemented, Polymer/Metal/Polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>510(k) Number</td>
<td>K972626</td>
</tr>
<tr>
<td>Device Name</td>
<td>ADVANCE KNEE SYSTEM</td>
</tr>
<tr>
<td>Applicant</td>
<td>WRIGHT MEDICAL TECHNOLOGY, INC. 5677 Airline Rd. Arlington, TN 38002</td>
</tr>
<tr>
<td>Applicant Contact</td>
<td>Dan Regan</td>
</tr>
<tr>
<td>Correspondent</td>
<td>WRIGHT MEDICAL TECHNOLOGY, INC. 5677 Airline Rd. Arlington, TN 38002</td>
</tr>
<tr>
<td>Correspondent Contact</td>
<td>Dan Regan</td>
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<tr>
<td>Regulation Number</td>
<td>889.3560</td>
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<tr>
<td>Classification Product Code</td>
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<tr>
<td>Data Received</td>
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<tr>
<td>Decision Date</td>
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<tr>
<td>Decision</td>
<td>Substantially Equivalent (SESE)</td>
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<tr>
<td>Regulation Medical Specialty</td>
<td>Orthopedic</td>
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<td>510(k) Review Panel</td>
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<tr>
<td>Summary</td>
<td><strong>Summary</strong></td>
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<tr>
<td>Type</td>
<td>Traditional</td>
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<td>Reviewed By Third Party</td>
<td>No</td>
</tr>
<tr>
<td>Combination Product</td>
<td>No</td>
</tr>
</tbody>
</table>

#### Note

This medical device has supplements. The device description may have changed. Be sure to look at the supplements to get an up-to-date view of this device.

- **Trade Name:** CHARITE ARTIFICIAL DISC
- **Classification Name:** Prosthesis, intervertebral Disc
- **Generic Name:** Lumbar Artificial Disc
- **Applicant:** DEPUY SPINE, INC
- **PMA Number:** P040006
- **Date Received:** 02/13/2004
- **Decision Date:** 10/20/2004
- **Withdrawal Date:** 01/05/2012
- **Product Code:** NJO (Registered Establishments With NJO)
- **Docket Number:** 05M-0092
- **Notice Date:** 03/09/2005
- **Advisory Committee:** Orthopedic
- **Expedited Review Granted?** Yes
- **Combination Product** No

**Information About:**

- **Labeling, Approval Order, Summary Of Safety And Effectiveness**

#### Approval Order Statement

Approval for the charite artificial disc. The device is indicated for spinal arthroplasty in skeletally mature patients with degenerative disc disease (DDD) at one level from L-S1. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history and radiographic studies. These DDD patients should have no more than 3 mm of spondylosis or spondylolisthesis at the involved level. Patients receiving the charite artificial disc should have failed at least six months of conservative treatment prior to implantation of the charite artificial disc.

**Approval Order:** Approval Order

**Post Approval Study:** Show Report Schedule And Study Progress

**Supplements:** S001 S002 S003 S004 S005
In the case of devices classified as class III and implantable devices, the manufacturer shall draw up a summary of safety and clinical performance.

It shall be written in a way that is clear to the intended user and, if relevant, to the patient and shall be available to the public via EUDAMED.

The summary of safety and clinical performance shall include at least the following aspects:

- Manufacturer + SRN
- Device + UDI
- Intended Purpose, Indications, Contraindications
- Description, previous variant(s), differences, accessories, other products intended to be used in combination
- Suggested position in treatment options
- Harmonised Standards / Common Specifications
- Summary of the Clinical Evaluation Report + PMCF
- Suggested profile and training for users
- Information on residual risks, undesirable effects, warnings & precautions
There is no change in the number of assessments of Notified Bodies by Competent Authorities?
Chapter IV – Notified Bodies – Article 35 & 35a – Assessments of Notified Bodies

• The national authority responsible for notified bodies may in addition to regular monitoring or on-site assessments conduct short-notice, unannounced or ‘for-cause’ reviews if needed to address a particular issue or to verify compliance.

• The national authority responsible for Notified Bodies, as part of its ongoing monitoring of notified bodies shall assess an appropriate number of notified body assessments of manufacturers’ technical documentation and clinical evaluations to verify the conclusions drawn by the notified body based on the information presented by the manufacturer.

• These assessments shall be conducted both off site and during on-site assessments.

• The MDCG may recommend that the sampling, either by national authority or as part of a joint assessment activity, shall assess a greater or lesser proportion of the clinical evaluations and technical documentation assessed by a notified body.
Chapter IV – Notified Bodies

Unannounced Audits

Technical Documentation Audits

Clinical Evaluations

Quality Management System

Microbiology

Technical Documentation

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For Class III implantable devices the Notified Body’s Clinical Evaluation Report, along with the clinical evaluation documentation of the manufacturer will be subject to scrutiny from the EU Commission?
Chapter V – Classification and Conformity Assessment – Article 42

- Prior to placing a device on the market, manufacturers shall undertake an assessment of the conformity of that device.
- The conformity assessment procedures are set out in Annexes VIII to XI.

- Manufacturers of devices classified as class III, other than custom-made or investigational devices, shall be subject to a conformity assessment based on quality management system assurance and assessment of the technical documentation as specified in Annex VIII.
- Alternatively, the manufacturer may choose to apply a conformity assessment based on type examination as specified in Annex IX coupled with a conformity assessment based on product conformity verification as specified in Annex X.

- For implantable devices classified as class III, the notified body shall follow the procedure regarding clinical evaluation consultation as specified in section 6.0 of Chapter II of annex VIII or Section 6.0 of Annex IX, as applicable.

- This procedure is not required where:
  a) the device has been designed by modifications of a device already marketed by the same manufacturer for the same intended purpose if the modifications have been demonstrated by the manufacturer as not adversely affecting significantly the benefit/risk ratio; or
  b) the principles of the clinical evaluation of the device type or category have been addressed in a common specification (Article 7) and the NB confirms that the clinical evaluation of the manufacturer for this device is in compliance with the relevant common specification.
Annex VIII – Clause 6 / Annex IX – Clause 6

Notified Body Review

15 days

45 days

Notified Body Review

Implantable Class III

• Manufacturer’s Clinical Evaluation
• NB Clinical Evaluation Report
• PMCF Plan

EU Commission

• Benefit: Risk Determination
• Consistency with indications
• PMCF Plan

No ‘scientific opinion’

NB Further Review

• Restrict indications
• Limit duration of certificate
• Undertake specific PMCF studies
• Adapt IFU or Summary of Safety and Clinical Performance
• Impose other restrictions

Notified Body Certificate

• Duly justify if advice not followed

Complete Conformity Assessment

Notified Body Certificate
Peer reviewed scientific literature that has demonstrated equivalence to the device under review, can be included in any clinical evaluation?
Chapter I – Scope and Definitions – Article 2 – Clinical Data

Information concerning the safety or performance that is generated from the use of a device and that are sourced from the following:

- Clinical Investigation – device concerned
- Clinical Investigations reported in Scientific Literature
  - demonstrated equivalent devices
- Peer reviewed Scientific Literature
  - device concerned
  - demonstrated equivalent devices

+ Generated and verified from the manufacturer’s post-market surveillance system (PMCF).
Chapter VI – Clinical Evaluation and Investigation – Article 49 – Clinical Evaluation

Information concerning the safety or performance that is generated from the use of a device and that are sourced from the following:

- Clinical Investigation
  - device concerned

Clinical Investigations reported in Scientific Literature
  - demonstrated equivalent devices

In the case of implantable devices and devices falling within class III, clinical investigations shall be performed except if the device has been designed by modifications of a device already marketed by the same manufacturer ...

+ Generated and verified from the manufacturer’s post-market surveillance system (PMCF).
... and accepted by the Notified Body as being equivalent (Annex XIII), to the marketed device and the clinical evaluation is sufficient to demonstrate conformity with the relevant safety and performance requirements.

With regard to the first subparagraph a manufacturer can seek to justify use of data from a demonstrated equivalent device from another manufacturer only if they have a clear contract in place with that manufacturer allowing full access to the technical documentation on an ongoing basis.

Except for class III and implantable devices, where demonstration of conformity with general safety and performance requirements based on clinical data is not deemed appropriate, adequate justification for any such exception shall be given based on the results of the manufacturer's risk management and on consideration of the specifics of the interaction between the device and the human body, the clinical performances intended and the claims of the manufacturer.
The requirements of Regulation (EU) No 536/2014 have been included in Articles 50-60 of the new Regulation?
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<td>Annex XIV (I,2.6)</td>
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<td>Annex XIV (II,3)</td>
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Chapter VI – Clinical Evaluations and Investigations – Articles – 27 & 51-59

*Performance

ClinicalTrials.gov

- Correlation Between Alignment of Lower Limb and Clinical Outcome After Total Knee Prosthesis
- Condition: Osteoarthritis of the Knee Joint
- Intervention: Procedures: patients who undergo a total knee prosthesis

*Sponsor

- Active Knee Prosthesis Study for Improvement of Locomotion for Above Knee Amputees
- Condition: Amputation
- Intervention: Device: Active Knee Prosthesis

*Safety

Serious Adverse Events

- NexGen CR and CR-flex Knee Prosthesis
- Total, serious adverse events
  - # participants affected / at risk: 0/54 (0.00%)
Post-market surveillance shall be used to update the clinical evaluation?
Chapter VII – Vigilance and Market Surveillance – Article 60a

• For any device, proportionate to the risk class and appropriate for the type of device, manufacturers shall plan, establish, document, implement, maintain and update a post-market surveillance system which shall be an integral part of the manufacturer’s quality management system.

• The post-market surveillance system shall be suitable to actively and systematically gather, record and analyse relevant data on the quality, performance and safety of a device throughout its entire lifetime, to draw the necessary conclusions and to determine, implement and monitor any preventive and corrective actions.

• Data gathered by the manufacturer’s post-market surveillance system shall in particular be used:
  
  1. to update the risk/benefit, risk analysis and risk management, design and manufacturing information, IFU and labelling
  2. to update the clinical evaluation
  3. to update the summary of safety and clinical performance
  4. for the identification of needs for preventive, corrective or field safety corrective action
  5. when relevant, to contribute to the post-market surveillance of other devices
  6. to detect and report trends (vigilance)

The technical documentation shall be updated accordingly.
The words about ‘equivalence’ from MedDev 2.7.1 will appear in Annex VIII – Clinical Evaluation & PMCF?
Annex XIII – Clinical Evaluations & PMCF

• The clinical evaluation shall be thorough and objective, considering both favourable and unfavourable data. Its depth and extent shall be proportionate and appropriate to the nature, classification, intended use purpose, manufacturer’s claims and risks of the device in question.

• A clinical evaluation can only be based on clinical data of a similar device for which equivalence to the device in question can be demonstrated. Technical, biological and clinical characteristics shall be taken into consideration for the demonstration of equivalence:
  - Technical
  - Biological
  - Clinical

• These characteristics shall be similar to such an extent that there would be no clinically significant difference in the clinical performance and safety of the device.

• Manufacturers must be able to clearly demonstrate that they have sufficient levels of access to the data on devices to which they are claiming equivalence in order to justify that claimed equivalence.
Equivalence

Technical
- be of similar design
- used under similar conditions of use
- have similar specifications and properties (e.g. physicochemical properties such as intensity of energy, tensile strength, viscosity, surface characteristics, wavelength, software algorithms)
- use similar deployment methods (if relevant)
- have similar principles of operation and critical performance requirements

Biological
- use same materials or substances in contact with the same human tissues or body fluids
- for a similar kind and duration of contact and similar release characteristics of substances
- including degradation products and leachables

Clinical
- used for the same clinical condition or purpose (including similar severity and stage of disease)
- at the same site in the body
- in a similar population (including age, anatomy, physiology)
- have same kind of user
- have similar relevant critical performance according to the expected clinical effect for a specific intended purpose
This presentation has described all of the changes related to clinical data in the proposed Regulation?
Other changes …

- Definition of Clinical Safety, Clinical Performance, Clinical Benefit
- Prescriptive requirements for updates to Summary of Safety and Clinical Performance
- Prescriptive requirements for updates to PMCF
- No Safety & Performance Requirement for Clinical Data – but must meet #1 & #5
- Prescriptive requirements for Technical Documentation
- Identify, appraise, analyse from MedDev 2.7.1
- PMCF objectives from MedDev 2.12-2
- PMCF Plan requirements from MedDev 2.12-2

- Article 2
- Article 49
- Article 49
- Annex I
- Annex II
- Annex XIII
- Annex XIII
- Annex XIII
Questions & Answers