22 October 2012

A white paper by Emergo Group

- The proposed Regulation on medical devices sets forth more stringent rules on Noified Bodies.
- As a Regulation, the proposed document would apply as-is to all Member States.
- Promotes a shift to a life-cycle approach, similar to the view advocated by the US FDA.
- A new regulatory body, the MDCG, would foster cooperation between the Member States

Europe's Proposed Medical Device Regulation

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The European Community has expanded into a behemoth union with 27 Member States. It now encompasses 32 stakeholders and over 500 million inhabitants. This ill-managed expansion impeded the governability, and led to disharmonization in the implementation of the Medical Devices Directive (MDD) 93/42/EEC.

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Background

Since 1987 and the inception of the first Directive concerning medical devices, the European Community has expanded into a behemoth union with 27 Member States. Considered in the broader sense, the Community now encompasses 32 stakeholders and over 500 million inhabitants.[1] This ill-managed expansion impeded the governability, and led to disharmonization in the implementation of the Medical Devices Directive (MDD) 93/42/EEC. Tension between the desire to harmonize and Member States' refusal to relax their sovereign rights, paired with differences in interpretation of the MDD, further led to discrepancies between Competent Authorities (CAs). These factors also contributed to a non-level playing field for Notified Bodies (NBs).

Many of the weaknesses of the MDD were identified as early as 2002 by the Medical Device Expert Group.[2] Directive 2007/47/EC modified the MDD and Active Implantable Medical Devices Directive (AIMDD) 90/385/EEC in an attempt to address these concerns. Among other elements, this Directive inserted a definition for clinical data and greatly expanded Annex X on Clinical Evaluation. However, the EU Commission seemed to believe this was insufficient, as evidenced by the rather close release of the amendment (October 2007) and the public recast (May 2008) of the MDD.[3]

Member States made desperate attempts to improve their coordination and enforcement efforts through the MDEG, CMC, COEN and MSOG. Member States also attempted to harmonize NBs in several key areas (e.g. clinical evaluation) through NBOG and NB-MED, and to create an operationally sound essential European data base (EUDAMED). Nevertheless, these endeavors were only partially successful. The Notified Bodies also championed a Code of Conduct[4] in the hopes of self-policing; however, at the time of the release of the proposed Regulation, only a small proportion of the 78 NBs had endorsed the document.

In addition, the amazingly rapid development of hybrid technologies and highly bureaucratic procedures for adjudication made the Medical Devices Directives obsolete much more rapidly than anticipated. Finally, for the EU Commission, the PIP fraud scandal in France came at a very opportune time. The concerns raised in the PIP scandal expedited the necessary process of renewal and mollified the ardent proponents of subsidiarity.

Overview of proposed changes

The European Commission recently published the Proposal for a Regulation.[5] (The Commission also published an analogous document for In Vitro Diagnostic Medical Devices.[6]) The proposed Regulation on medical devices sets forth more stringent rules on NBs which reflects the Member States' lack of consistent implementation of existing rules and regulations in regard to NBs. As the proposed Regulation relates to

1 This includes the 27 official EU member states, Norway, Iceland, Lichtenstein, Switzerland, and Turkey by way of a Customs Union Agreement.

2 http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:52003DC0386:EN:HTML

3 http://ec.europa.eu/health/medical-devices/files/recast_docs_2008/responses/responses_public_consultation_recast_en.pdf

4 http://www.team-nb.org/index.php?option=com_docman&task=cat_view&gid=17&Itemid=38&lang=en

5 "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" http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_542_en.pdf

6 http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_541_en.pdf

post-market surveillance (PMS), it is noted that CAs currently do not have sufficient mechanisms to monitor information on vigilance and implement market surveillance. The proposal also emphasizes the administrative burden of specific member state registration requirements[7] (e.g. Italy, France, Spain, and Portugal) and countries which have imposed traceability requirements on economic operators.[8]

The proposed Regulation promotes a shift from the pre-approval stage (i.e. the path to CE-marking) to a life-cycle approach similar to the view advocated by the US FDA.

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The proposed Regulation is an "evolution of the current regime." While the EU Parliament (April 2012) proposed a central marketing authorization for medical devices, the proposed Regulation does not. Centralized marketing authorization would have involved a "new public body with a sufficiently skilled staff to assess devices, similar to [that of] the US FDA."[9]

The legislation also incorporates the New Legislative Framework, [10]and in particular, the economic operators (manufacturer, Authorized Representatives, distributors, and importers). The New Legislative Framework replaced the New Approach and is the overarching legislative framework for medical devices. The revision also supports and reinforces innovation and competition of small and medium sized enterprises. As a Regulation, the proposed document would apply as-is to all Member States. Unlike the MDD, it would not require national transposition. The accompanying explanatory memorandum of the proposed Regulation extols the benefits of a Regulation as a legal instrument: A Regulation "imposes clear and detailed rules which will become applicable in a uniform manner and at the same time throughout the Union."[11]

Other stakeholders are mentioned only tangentially, which may annoy users and patients.

Main themes of the Regulation

Compared to the MDD, the proposed Regulation promotes a shift from the pre-approval stage (i.e. the path to CE-marking) to a life-cycle approach. This approach is similar to the life-cycle view advocated by the US FDA. [12]The life-cycle approach is illustrated by the incorporation of European guidance (MEDDEVs) into the regulation:[13] Guidance on Authorized Representation, Clinical Evaluation, Vigilance, and Post-Market Clinical Follow-Up has been integrated into the proposed Regulation. According to the draft document, NBs would be placed under a strict regimen of supervision, although it remains unclear whether the intended sanctions could be implemented against the will of a Member State, should the need occur. The qualification requirements for auditing and reviewing NB staff are steeply increased.

Mandatory Unique Device Identification (UDI) is introduced with the intention to facilitate the traceability of devices. Various databases for clinical investigations, product registration, and vigilance are introduced, under the aegis of the EU Commission. The

7 MDD Article 14(1) permitted member states to transpose the "member states may" to require notification of Class IIa, IIb, and III medical devices.

8 For examples, Poland, Act of May 20, 2010 on Medical Devices, Official Journal Laws 2010, No. 107, Item 679.

9 This is a pleasant compliment by the EU Commission of the US FDA after the verbal exchanges between Shuren (Jan 2011) about EU patients as "guinea pigs". Paola Testori Coggi (2/18/2011) expressed dismay that "senior official FDA should publically discredit the EU regulatory system." Hopefully, this has culminated with the FDA Report (May 2012), Unsafe and Ineffective Devices Approved in the EU that were Not Approved in the US.

10 http://ec.europa.eu/enterprise/policies/single-market-goods/regulatory-policies-common-rules-for-products/new-legislative-framework/

11 http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_542_en.pdf

12 This is also a concept noted globally among many regulatory authorities.

13 http://ec.europa.eu/health/medical-devices/documents/guidelines/index_en.htm

In the proposed Regulation there are 50 definitions put forth. The MDD only contained 14 definitions. Significant changes include the extension of the definition of "medical device" to include aesthetic implantable devices and invasive devices used in humans.

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proposal attempts to professionalize the implementation of compliance by mandating a Qualified Person (QP) similar to the requirement placed upon manufacturers under the Medicinal Products Directive.

The proposed Regulation attempts to make more transparent the time frames for review by various parties for different activities. In general, greater details are inserted into the document, and information from guidance and standards are codified. Finally, an attempt is made to concentrate the harmonization efforts between the Member States by means of a new regulatory body called the Medical Device Coordination Group (MDCG). The objective of the MDCG would be to foster cooperation between the Member States while at the same time increasing the Commission's power to act as needed in acute cases.

Organization of the proposed Regulation

The draft Regulation combines medical devices and active implantable medical devices into one document (194 pages).[14] The proposed Regulation commences with an explanatory memorandum and the recitals which are explanatory material that lack legal merit. One recital of particular interest, (4) acknowledges the guidance of the now almost defunct Global Harmonization Task Force (GHTF) and the International Medical Device Regulators Forum (IMDRF). It emphasizes the importance of "global convergence of regulations" and UDI as well as other areas which would benefit from global regulatory harmonization. There are 71 recitals in all.

The proposed Regulation is further organized into ten Chapters which are comprised of Articles. The Chapters address the important concepts and identify weaknesses. The Articles reference 16 Annexes.

Chapter I — Descriptions about the scope of the legislation

With the 50 definitions put forth in the proposed Regulation, this section is significantly expanded. (The MDD only contained 14 definitions.) The definition of medical device is extended to include aesthetic implantable devices and invasive devices used in humans. There is also a corresponding Annex (Annex XV) that provides examples of such products.

The definition of accessory is expanded to "assist" and not just "enable" [a device to be used]. Thus, the understanding of products which could be classified as accessories to medical devices is broadened. The term label is defined (Art 2(1)(11)). The label is the physical label on the device or on the package. Common Technical Specifications (CTS) (which is borrowed from the *In Vitro* Diagnostic Devices Directive IVDD 98/79/EC) prescribes technical specifications which will be a mechanism to augment standards.

Chapter II — Placing product on the market

This chapter provides substantial definitions and responsibilities of the respective economic operators (EOs).[15] This chapter delineates a demarcation between the responsibilities of the Authorized Representative (AR), the distributor and the importer. The MEDDEV on ARs is essentially incorporated into the Regulation, which

14 The IVD Proposed Regulation is 143 pages. http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_542_en.pdf

15 Previously, only the manufacturer and AR were defined terms.

highlights the complementary, but incompatible roles of the AR and the two other EOs (distributor and importer).

Art 3 of the MDD is retained as Art 4 (2); medical devices must be compliant to relevant Annex I, General safety and performance requirements. Similarly, Art 5(1)of the MDD exists as Art 6 (1), compliance to EN harmonized published in OJEU presumes compliance to Annex I. Furthermore, Art 16 requires that patients with implantable medical devices be provided an implant card.

General Safety and Performance Requirements (Annex I)

Chapter 1, General Requirements, resembles the Essential Requirements (ER) of the current MDD. Chapter 1, Section 1, remains identical except for an important insertion: "taking account the generally acknowledged state of the art." Of course one appreciates that the use of current standards and published literature facilitates addressing this requirement, however, otherwise, who determines what this is? Section 2 has some additional comments about risk. MDD ER #3-5 are consolidated into Section 3. MDD ER#6a has been deleted. Chapter 2 has added the following Sections: Devices incorporating medicinal product and devices composed of substances or combination of substances intended to be ingested, inhaled or administered rectally or vaginally; Devices incorporating materials biological origin; Software in devices and standalone software; and Risks medical devices for lay person. Chapter 3, Information supplied with the device, is extensive. In particular, 19.1(b) "information required on the label shall be provided on the device itself…." Of course, there is the "not practicable and appropriate" exemption.

Qualified Person

Similar to requirements placed on medicinal products, Art 13 introduces the Qualified Person (QP). This highly educated and experienced person is intended to safeguard the regulatory compliance within the manufacturer. Similar qualifications are demanded for the QP in an AR organization.

As NBs are also required to have similarly qualified staff for Tech File reviews and Audits, it is easy to foresee a structural deficit in numbers of candidate QPs.

Chapter III — UDI and Databases

The challenge[16] posed about how to keep track of devices placed on the EU's "borderless," but nationally fragmented market is addressed by a combination of mandatory inputs by Notified Bodies, Economic Operators and Member States (Member States into EUDAMED and other databases). There will be an extensive amount of information collected and transmitted electronically as well as a mandate to use UDI. Class III medical device manufacturers must generate a summary of safety and clinical performance (Art 42).

Chapter IV — Notified Bodies

By far the greatest change is the metamorphosis of the NBs from an industry partner into a police-like extension of the Competent Authorities' market surveillance apparatus. Some items:

The widely published unannounced audits[17] (Chapter V) will likely be possible only for countries without

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16 The problems of who owns and manages the data, as well who has access to them now are going to be addressed. However, the funding, language, adjudication of problems and irregularities, and who has the jurisdiction has not been addressed in the Proposal.

17 DG SANCO Commissioner, John Dalli (IP/12/96) had indicated the following would occur as a result of PIP: unannounced inspections, enhanced controls NBs, and sample testing."

pre-visit visa requirements, if sourced from Notified Bodies' HQ. This means that Notified Bodies will have to establish subsidiaries in major non-EU markets. The cost will be borne by the manufacturer. NBs will also be expected to perform sample checks (Chapter V) as foretold by John Dalli in February 2012.

Although on legal grounds the formal designation and assessment of NBs is left up to Member States, in practice the power to notify, manage the scope and notification and the corrective measures is transferred from the CAs to "peer-reviews" by multi-national teams (ref Arts 28, 29 32 and 33). NBs are monitored to ensure they are capable and honest. Most importantly, this would create the level playing field for NBs so badly needed.

For Class III implantable, and undoubtedly an array of other products, the Notified Body will be obliged to notify them MDCG (through the EU Commission) of the intent to review. The notification must, oddly enough, be accompanied by the Summary of Safety and Clinical Performance (generated by the manufacturer, Art 42), which seems a document that many manufacturers will not have completed at that stage. Where an ensuing review by a new Member State-only body will occur, the MDCG (Art 78-80) is undoubtedly going to pose a hurdle and delay, but is unlikely to offer a shield against products that do not meet the required standards, as these should have been pre-filtered out by the NB.

Under the proposed conditions, the real challenge for the majority of NBs will be to gain and retain highly qualified staff with the education and experience mandated in Annex VI. Both Chapter IV and Annex VI abound with language describing the demise of NBs and how to monitor the competence of the remaining ones. The competition with EOs for QPs and similar persons will be intense until such a time that universities and industry deliver more post-graduate QPs.

Unannounced audits will be impracticable in non-EU jurisdictions unless the NB has an in-country subsidiary. Even then, countries may consider this espionage. Much higher costs for NBs will probably not be completely offset by economies of scale, so in all likelihood, regulatory compliance in EU including, but not limited to, Notified Body intervention will become much more expensive.

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Chapter V and Annex VII — Conformity Assessment

Classification is kept essentially the same, with some extensions. The Classification Criteria (Annex VII) includes 21 rules. Rule 17 non-viable tissue or cells human or animal will be considered Class III. Rule 19 nanomaterial Class III. Rule 20 devices apharesis Class III (upclassification by request of France). Rule 21 devices ingested, inhaled, administered rectally or vaginally absorbed or dispersed Class III. Dispute resolution has been codified at a higher level of course the effectiveness of this mechanism remains to be proven.

The MDCG is expected to provide expeditious conclusion of difficult cases, but it is unclear how industry will be able to share its views.[18] Conformity assessment has been simplified (routes to conformity assessment Annexes VIII through X), with many instances

18 To date, industry has participated in Medical Device Expert Group Meetings as well as in the Working Group on Borderline and Classification.

Focus is on the reporting of Serious Adverse Events during clinical studies, input by Notified Bodies about certificates, Summaries of Safety and Clinical performance, Vigilance Reports, and Market Surveillance.

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for mandatory Quality Management Systems. There is better correlation between risk and data requirements.

The Technical documentation (elements) specified in Annex II mentions STED and is largely based upon GHTF STED guidance.[19] Annex III describes the Declaration of Conformity (DoC).

Class I self-certified medical devices do not have a route to conformity assessment (Art 42(5)); the manufacturer compiles the technical documentation and signs the DoC.

Annex VIII, Conformity Full Quality Assurance and Design Examination

This is the equivalent of MDD, Annex II. Section 3.3 Audits, and Section 4, Surveillance Assessments.

Section 4.3 states NB audits and assessment at least yearly, on the quality management system and PMS. Section 4.4 ads that the NB is to perform unannounced factory inspections of manufacturer and manufacturer's suppliers or subcontractors. The NB will be mandated to check samples from the production or manufacturing process. NBs are also encouraged to analyze samples from the market. Nevertheless, it is unclear who will pay for these samples.

Chapter VI and Annex XIV — Clinical Evaluation and Investigation

As expected, the roles of clinical evaluation and clinical investigation become far more prominent. Inclusion of MEDDEV 2.7/1 and parts of ISO 14155 into the draft Proposal is to be applauded. Even though defined in detail, the regulatory pathway to study approval may not be defined well enough in case of multi-country approach (Art 58), though there is a designated "coordinating Member State."

Again, the database is emphasized, and clinical data is to be collected herein. Art 54 (PMCF) is very important, but leaves the details to MEDDEV 2.7/2.

CHAPTERS VII and IX — EUDAMED and other databases, communications and information exchanges between Member States (Art 56 -59, Annex XIV, etc.)

The information modalities focus on the reporting of Serious Adverse Events during clinical studies, input by NBs about certificates, Summaries of Safety and Clinical performance, Vigilance Reports, and Market Surveillance.

Manufacturers are required to report a serious incident or Field Safety Corrective Action (FSCA) to the database within 15 days (Art 61). The EU database will be used to share these vigilance reports to the following (Art 62(5)): Member State where the incident occurred, Member State where FSCA is undertaken, Member State manufacturer is based in the EU, or Member State where the NB is established.

The draft Field Safety Notice (FSN) needs to be submitted for review "except in case of urgency" (Art 63(5)). In practice, our experience has been that all manufacturers treat the release of the FSN as urgent and have not shared the draft for review. For FSCAs and similar serious incidents in more than one Member State, a coordinating CA would be designated (Art 63(5)). In view of the complexity and scope of the information streams and the

19 http://www.ghtf.org/documents/sg1/sg1final-n11.pdf

dismal record in EU for getting even one data base going, this seems a very ambitious program. Yet the need for it is evident.

Chapter VIII and MDCG — Art 78-80

The intended use for the MDCG seems intended to replace the proliferating Member State-only bodies (CMC, COEN, MSOG) structures that are trying to coordinate the CAs.[20] Apart from the fact that it has proven impossible to find even a 75% consensus in all but a few MDEG meetings, the difficulty to find truly "independent" experts (as witnessed by the FDA in its expert panels!) and the lack of sanctions for exceeding the review periods do not bode well. In any case an appeal procedure is sorely missing.

The role of the MDEG is probably going to be retained, but it would behoove the Commission to be explicit on this issue since the MDCG is tasked with providing guidance.

Role of standards

Seems to be maintained rather unscathed, which is good (Art 6(1)), Art 7(2) and 7(3), states that if there are standards and CTS and the manufacturer is compliant, the manufacturer is presumed to be compliant to the relevant aspects of the Regulation.

Remaining remarks

In conclusion, Art 87 is interesting in that it defines the need for penalties, but not against whom. Neither does it define the penalty for Member States if they transgress their powers or violate their obligations. This would be a good addition. It is evident that this Regulation is vastly more "legal" in nature than its predecessor, which had more of a "good will" approach in many ways. This will have consequences for staffing at Competent Authorities, Notified Bodies, and the Economic Operators, manufacturers included.

The proposed Regulation largely resembles the MDD and retains some of the positive elements therein, such as classification criteria. The proposed Regulation codifies many of the MEDDEVs and GHTF guidance, but also introduces many more provisions. The draft is now circulated for review by the EU Parliament and EU Council.[21] Interestingly, at the recent EUCOMED meeting, Commissioner Dalli[22] expressed his desire to pass this proposal through the sitting European Parliament rather than risk a delayed passage with unknown changes in the wake of the 2014 European Parliament elections.

When the proposal is finally accepted by all parties involved, the Regulation would apply three years (Art 97(2)) after publication in the OJEU. The actual implementation and enforcement will be practically dictated by the availability of sufficiently competent NBs and a functioning supranational adjudication Committee (MDCG).

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20 Art. 78(2), each MS appoints one member and one alternate member to the MDCG.

21 http://ec.europa.eu/health/medical-devices/documents/revision/index_en.htm

22 Unfortunately, Commissioner John Dalli tendered his resignation October 16, 2012. http://europa.eu/rapid/press-release_MEMO-12-788_en.htm

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