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Joint EU-US Industry Contribution to EU and US call for input on opportunities to promote greater regulatory compatibility in the medical technology sector

Safety of medical devices is one of the common goals for regulators, patients, and healthcare professionals, next to high quality, performance, easy access and cost effectiveness. Our industry remains highly committed to provide such devices at the earliest possibility.

COCIR, MITA, EUCOMED, EDMA and ADVAMED welcome the opportunity to present key topics on how to achieve greater regulatory compatibility between the United States and Europe in the medical technology sector. This contribution presents the priorities for the medical technology sector and supplement earlier contributions by COCIR and MITA on 31 October 2012¹, and of EUCOMED, EDMA and ADVAMED.

Those priorities are:

- A. Single Audit of Medical Technology Manufacturer Quality Management Systems**
- B. Single Harmonized Standard for Marketing Application Format**
- C. Unique Device Identification**

A. Single Audit of Medical Technology Manufacturer Quality Management Systems

1. What is the situation today?

The current regulatory requirements for medical device manufacturer quality management systems (QMS) are similar, but not identical. Continued efforts to reduce or eliminate those differences over time (i.e., regulatory convergence), at bilateral and international levels, should be encouraged.

European national regulatory authorities, European conformity assessment bodies (i.e., "Notified Bodies"), and the US Food and Drug Administration (FDA) do not today mutually accept reports of each other's audits of manufacturer QMS and/or certificates of conformity with the QMS requirements. As a result, when marketing the same product in the United States and the European Union (i.e., a product manufactured by the same process at the same facility), a manufacturer must comply with, and be audited or inspected repeatedly by, two different auditing bodies despite the similar requirements:

¹ http://www.cocir.org/uploads/documents/-79-cocir_mita_joint_contribution_to_eu_us_public_consultation_on_regulatory_convergence_31_october_2012.pdf



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- ***In the European Union:***

- The European Commission has recognized international standard ISO 13485, Medical devices – Quality management systems – requirements for regulatory purposes as a basis on which the manufacturer may demonstrate conformity with the QMS requirements of European directives.
- Depending on the risk-based classification of the device, the EU legislation relies on Notified Bodies, appointed and overseen by Member States according to EU requirements, to periodically audit manufacturing facilities to verify compliance to ISO 13485, as one means of conformity assessment for CE marking under the Medical Devices Directives. Notified Bodies perform follow-up inspections and may take other measures if facilities are found to be noncompliant. In coordination with the European Commission, national regulatory authorities also have enforcement powers to assure compliance with the requirements.

- ***In the United States:***

- FDA has established *21 CFR 820 Quality System Regulation (QSR)* for medical device manufacturers.
- Most inspections of manufacturer QMS are performed by FDA. FDA allows certain accredited third parties to perform facility audits only for certain types of inspections. FDA performs follow-up inspections if facilities are found to be noncompliant.

2. How could greater compatibility/convergence of the EU and US regulations and standards be achieved?

- Greater compatibility and convergence of the EU and US regulatory systems can be achieved by a common audit process or, better, even a single quality system, with:
 - Common auditing procedures having consistency in quality system requirements, content (type of audit) and levels of detail assessed
 - Use of common audit reporting templates/formats
 - Application of common criteria by which auditors rank non-conformances, and common pathways for refuting non-conformances
 - Co-development of training for auditors
 - Joint training of auditors
 - Mutual use of Notified Body/Conformity Assessment Body (NB-CAB) auditing reports (i.e., as a basis for setting auditing priorities and/or as full or partial evidence of conformity with the respective QMS regulatory requirements)



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3. How should the European Union and the US authorities address the reported issues?

- Regulators from the United States and the European Union, along with regulators in other countries, both participate in the International Medical Device Regulators Forum (IMDRF)².
- IMDRF has accepted the single audit of medical device quality systems as one of its five work items and is developing related guidance documents. Through IMDRF and other channels, the US and EU medical device regulators have the opportunity to enhance transatlantic regulatory compatibility in this field and industry supports this effort.
- The EU should sign up for the work program on Medical Device Single Audit Program (MDSAP).
- Once the IMDRF guidance documents are developed and tested in pilot programs, EU and US authorities should work to fully and timely adopt them in their respective regulatory and administrative systems.
- Once adopted and implemented, those practices should be deemed to generally allow the mutual acceptance of reports of QMS audits as demonstrating compliance with regulatory requirements.
- The US and EU should use the present revision of ISO 13485 to introduce solutions to currently diverging elements in the respective requirements for manufacturers quality management systems.

4. What could be the timeline to achieve those objectives?

Once the above-cited IMDRF guidance documents are available, a single multi-purpose QMS audit program acceptable to both the EU and US could reasonably be in place within 2 years of an executed Transatlantic Trade and Investment Partnership. We propose that such a program be implemented in stages, including a reduced scale pilot. Industry is committed to participate in the development of such program which will bring mutual benefits to industry and regulators.

5. What will be the impact of the proposed measures?

There is a continuing regulatory burden for industry due to routine multiple audits, according to very similar requirements, disrupting day-to-day operations and diverting resources. In addition there is the uncertainty related to scheduling and allocation of resources needed for multiple regulatory and quality system audits.

² For more information, see <http://www.imdrf.org/index.asp>



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Based on the findings of prior pilot audit programs conducted by FDA, an average savings of time in person-days of 33%³ can be expected in most instances when compared to the estimated combined time of previously separate audits/inspections that were performed to satisfy the respective regulatory and quality system requirements of two different regulatory authorities. Also substantial cost saving in travel cost for audit teams is expected.

It should also be noted that manufacturers are often also subject to audits by other regulators beyond those of the EU and US. These proposed measures would help reduce the cumulative burden of multiple QMS audits if US and EU regulators, as well as others, would use the audits performed by the other regulators to determine whether separate audits are needed.

The use of single audit reports to satisfy requirements for both regulatory systems would enhance the regulatory dialogue between the EU and the US, ensuring that for instance whenever an issue is detected with a quality system a single solution would be acceptable for both EU and US regulators.

B. Single Harmonized Standard for Marketing Applications Format

1. *What is the situation today?*

• *In the European Union:*

- Europe requires a single submission to the relevant notified body or regulatory authority following a risk-based classification.
- For all classes of device, the manufacturer must demonstrate, and have documented evidence, that the device conforms to the relevant “essential requirements” of safety and performance. That evidence includes technical and clinical safety, along with risk assessment, information, and is often based on demonstrated conformity with recognized European harmonized standards.
- For class I (low risk) products, affixing the required CE-marking is based on the manufacturer’s self-declaration of compliance with the relevant Essential Requirements of the appropriate Medical Devices Directives. When these devices have a measuring function, or when they are supplied sterile, a Notified Body will check these aspects only. For the highest risk devices, class III and active implantable devices, effectively a full formal review by the Notified Body of the manufacturer’s technical and clinical dossier is required. Only when those reviews are completed, and necessary certificates issued, does the manufacturer complete the declaration and affix the CE Marking.

³ FDA Final Report:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ThirdPartyInspection/ucm232806.htm>



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- When a Notified Body is involved, documentation –be it QMS or device design related technical documentation- can be inspected on-site or submitted to the Notified Body for desk audit.
- In all cases, and before or after marketing, when considered necessary by the competent authorities, the technical documentation or parts of that can be requested for further review.
- ***In the United States:***
 - The US system requires a single submission to the FDA, for the evaluation of the safety and effectiveness of a medical device. The details of the submission depend on the novelty and risk presented by the device.
 - As partial evidence of conformity with the regulatory requirements, the manufacturer may demonstrate that a device conforms to certain national and international standards recognized by FDA.

The format and contents of required submissions are currently not the same in the US and EU.

2. How could greater compatibility/convergence of the EU and US regulations and standards be achieved?

- Insofar as the elements of the respective regulatory submissions allow for common data sets, the regulatory burden on manufacturers would be reduced if differences in format and contents were further reduced or eliminated. This would allow substantially similar compliance evidence to be submitted in both jurisdictions. This, for example, could apply to the information on compliance with international standards that have been harmonized or recognized by the regulatory authorities.
- Recommended guidance on a harmonized format and general contents of pre-market submissions has been developed by the Global Harmonization Task Force (GHTF), the predecessor to IMDRF, and in which both the EU and US participated. It is known as the Summary Technical Documentation ("STED"). The use of STED should be encouraged in both jurisdictions and should be continued and encouraged.
- A single protocol and program for the electronic exchange of compliance evidence would be helpful. IMDRF has already begun work on internationally harmonized guidance and standards for the format and use of such electronic formats for the submission and management of regulatory information (Regulatory Product Submissions (RPS)).



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3. How should the European Union and the US authorities address the reported issues?

- In the context of their respective revision processes for their medical device regulation, explicit attention must be paid to integrate the future capabilities for electronic information exchange, with the proper provisions for safeguarding intellectual property.
- As the IMDRF RPS work is completed and endorsed, the EU and US should work to fully and timely adopt those guidance documents in their respective regulatory and administrative systems.

4. What could be the timeline to achieve those objectives?

The timeline will depend upon progress in the IMDRF RPS harmonization effort, along with timely adoption by the EU and US of the resulting guidance.

5. What will be the impact of the proposed measures?

If successful, adoption by the EU and US of IMDRF RPS guidance would allow the manufacturer to prepare and submit common datasets, in substantially similar form, to the regulators and/or conformity assessment bodies in both jurisdictions.

C. Unique Device Identification

1. What is the situation today?

It needs to be emphasized that the Unique Device Identification (UDI) is a project with global ambition. Yet, it is running at different speeds: the US is well ahead of the EU in developing legislation. Nevertheless, both regions are committed to global harmonisation. For this reason, if the EU/US Trade agreement could stimulate harmonisation, this would give a huge boost to the global objective.

There are two aspects to UDI which will benefit from regulatory convergence: the marking/labelling requirements for UDI, including implementation timelines, and the UDI database.

• In the European Union:

- UDI requirements for device marking/labelling: The requirements for the marking/labelling of the devices with a unique device identifier needs to be consistent. To date there has been no clear decision from the European Commission that a risk based approach will be considered for marking/labelling requirements at the various packaging levels. Marking all packaging levels with the Device Identifier and Production Identifier could then be a requirement independently of the product risk-based classification for class II and class III products (class I to be clarified, could



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be exempted based upon information included in GHTF guidance). Additionally consistency would be needed for those devices which are excluded from the labelling requirements. This remains work in progress.

- **UDI database:** To date, the European Union has not developed a specific database for capturing medical device characteristics associated with an assigned device identifier. EUDAMED is a system currently in use to capture general regulatory information and the intention is that it will be the designated system to capture UDI data. This might suggest the US FDA's global UDI Database would not be used but that possibility cannot be ruled out. The EU UDI database will contain all core data elements defined with the IMDRF draft guidance. As yet there has been no discussion in the EU as to whether further EU specific data elements will be included. Divergence from a common standard would lead to increased complexity in data handling, data transmission and interfacing presenting the manufacturers with a challenge to manage country-specific data. However the EU Commission will issue guidance to Member States to ensure that they conform to the proposed legislation.
- ***In the United States:***
 - **UDI requirements for device marking/labelling:** FDA expects to exempt most or all class I products from the requirement for UDI at the Unit of Use. There is no requirement for a production identifier for class I products. Additionally, a special consideration is expected for over the counter devices. The proposed rule is asking for specific data into device labelling which are diverging from provisions of recognized standards (e.g. format of expiry date).
 - **UDI database (UDID):** The US FDA is developing a database for listing medical device characteristics associated with a unique device identifier. The FDA engaged multiple manufacturers and other industry users to test the database during the early development period. The focus was on the usability of the technology platform. Several administrative and FDA-specific regulatory requirements create a less than perfect fit with other potential regional regulatory models. FDA has committed to GMDN as the nomenclature, and HL7/SPL for the messaging standard for data submission into the UDI Database.
 - FDA's UDID contains all core data elements defined within the IMDRF draft UDI Guidance.
 - Further US-specific data elements (incl. administrative) have been supplemented.
 - FDA's UDID is the first existing UDI database worldwide which is fully aligned with general principles described within the draft IMDRF UDI Guidance.
 - FDA's UDID has implemented the globally harmonized HL7 messaging standards for data submission into the UDID.

2. How greater compatibility/convergence of the EU and US regulations and standards could be achieved?



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Greater convergence of UDI marking/labelling can be established by ensuring common rules on the information which needs to be contained in the UDI marking/labelling and by then allowing the different manufacturers to select the optimal technological solution to present that information in a machine readable format.

Greater compatibility can be achieved by establishing a common standard for the format and elements in the core data required from manufacturers; the core data set should only identify the device and its manufacturer and not associated product characteristics. In addition, non-core data elements should avoid country specific permutations and dependency on language variations by promoting the development of a single UDI database in the EU.

To optimize compatibility of the EU and US UDI database, a globally harmonized messaging standard and protocol for electronic data submissions into UDID is necessary. FDA has already developed the HL7/SPL messaging standard for all electronic submissions of UDI data into the UDID.

- Industry and regulators must make available necessary resources to ensure the development of a database that meets the UDI objectives. Critical elements of a standardized database include: data element attributes (metadata), e.g. Boolean, or fixed/closed vocabulary with an attribute list that contains definitions, data values, relationships and specifications.
- UDI marking/labelling requirements: Including the production identifier data (variable data) at the unit of use level for class I products is considered as a major burden for industry because the expected use of this information at unit level is limited. EU legislation should be framed with this in mind.

3. How should the European Union and the US authorities address the reported issues?

- Marking/labelling requirements: Consistency of requirements between the US and the EU should be achieved by providing guidance on how UDI marking/labelling can be implemented at the different packaging levels of medical devices using a risk-based approach. While device identifier should be a requirement at unit of use level, using the risk based approach should leave the production identifier at the unit of use level at the discretion of the manufacturer.
- UDI database: The EU should establish a high level group to engage with the US FDA to learn of the FDA development process in order to avoid known problems. The EU group should engage database experts, medical device industry experts, and regulators to establish the user requirements for a harmonized EU UDI database. The specifications of all core data elements should be exactly the same in the US and EU (and ideally in other UDI databases around the world as well). The data element list, relationships between attributes, definitions and value sets must be agreed upon by industry and regulators and made available for public review and comment prior to



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delivery of requirements. The data set established for the device identification should be the smallest core list possible, remain stable and pertain to identification purposes only.

4. What could be the timeline to achieve those objectives?

Given that the FDA has a UDI regulation close to final publication and a database that has been developed and initially tested. The timeline is urgent and needs to be in the short-term.

5. What will be the impact of the proposed measures?

- Achieving convergence between EU and US in terms of UDID and UDI marking/labelling requirements.
- Keep the cost for UDID implementation and daily operation as low as possible, on regulators as well as on industry side.
- Implementation of UDI databases in EU and US and ensure interoperability.
- If implemented in the short-term, the UDI database can facilitate traceability systems which are urgently required.
- US and EU have the opportunity to set the stage for global harmonization of UDI.

###

The Advanced Medical Technology Association (AdvaMed) represents medical device and diagnostics manufacturers in the United States.

COCIR is the voice of the European Radiological, Electromedical and Healthcare IT Industry.

EDMA is the industry association that represents the interests of the In Vitro Diagnostic (IVD) industry throughout Europe.

Eucomed represents the medical technology industry in Europe.

MITA is the collective voice of medical imaging equipment, radiation therapy and radiopharmaceutical manufacturers in the United States.