

Letter from the Editor

Welcome to the first edition of the medical devices newsletter for 2010.

2010 already looks set to be another interesting year for medical devices in Ireland and on a European level.

In this edition, we feature articles regarding the changes that have been introduced in the recent revisions of MEDDEV 2.7/1 Rev 3 Clinical Evaluation: A Guide for Manufacturers and Notified Bodies and MEDDEV 2.12/1 Rev 6 Guidelines on a Medical Devices Vigilance System.

We also feature articles on some of the different IMB projects that have

taken place, including the IVD information day that was held by the IMB in February and the new system being applied by the IMB in placing manufacturers' field safety notices on the IMB website.

Updates on European meetings attended by the IMB are also provided.

As always, readers are encouraged to provide feedback particularly in relation to articles that may be of interest by contacting us at medicaldevices@imb.ie.



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MEDDEV 2.7/1 Rev 3 Clinical Evaluation: A Guide for Manufacturers and Notified Bodies

The latest revision (revision 3) of MEDDEV 2.7/1, entitled 'Clinical Evaluation: A Guide for Manufacturers and Notified Bodies' was published in December 2009. This revision of these guidelines has:

- amended the document according to the most recent amendment to the Medical Device Directives (Directive 2007/47/EC) and in the light of experience
- considered and transposed into the European context the Global Harmonisation Task Force (GHTF) international regulatory guidance document on clinical evaluation (SG5/N2R8:2007).

The primary purpose of the MEDDEV is to provide manufacturers and notified bodies with guidance on how to conduct and document the clinical evaluation of a medical device as part of the conformity assessment procedure prior to placing a medical device on the market as well as to support its ongoing marketing. It is also intended to provide guidance to regulators and other stakeholders when assessing clinical evidence provided by manufacturers in support of a medical device.

The MEDDEV provides the following guidance:

- general principles of clinical evaluation;
- how to identify relevant clinical data to be used in a clinical evaluation;
- how to appraise and integrate clinical data into a summary; and
- how to document a clinical evaluation in a clinical evaluation report.

The guidance contained within the MEDDEV is intended to apply to medical devices and the device component of combination products. It is not intended to cover *in-vitro* diagnostics.

This latest revision of the MEDDEV is a more substantial document (46 pages) in comparison to MEDDEV 2.7/1 Rev.2.

The number of terms defined and their definitions has been significantly increased to include, for example the current ISO 14155 definitions of *adverse event* and *serious adverse event*:



Adverse event: Any untoward medical occurrence in a subject. Note: For the purposes of this document, this is intended to include any *adverse event* whether device related or not

Serious adverse event: An *adverse event* that

- led to a death;
- led to a serious deterioration in health of a patient, user, or others;
- results in a life threatening illness or injury;
- results in a permanent impairment of a body structure or body function;
- requires in patient hospitalisation or prolongation of existing hospitalisation;
- results in medical or surgical intervention to prevent permanent impairment to body structure or a body function;
- led to foetal distress, foetal death or a congenital abnormality/birth defect.

The MEDDEV also outlines the clinical evaluation process a manufacture should follow (1 – 3 below):

1. Before a clinical evaluation is undertaken the manufacturer should define its scope, based on the essential requirements that need to be addressed from a clinical perspective, the intended use of the device and the output from the risk management process.

Consideration should be given to:

- whether there are any design features of the device or target treatment populations that require specific attention;
- whether data from equivalent devices can be used to support the safety and/or performance of the device in question;
- the data source(s) and type(s) of

data to be used in the clinical evaluation.

2. Once the scope has been defined, there are three distinct stages in performing a clinical evaluation.

Stage 1: Identification of pertinent standards and clinical data

Three sources of data are identified: literature search, clinical experience and clinical investigation.

Literature searching can be used to identify published clinical data that may assist the manufacturer to establish acceptable performance and safety of a medical device. This data may relate directly to the device in question or to equivalent devices. A report should be compiled on completion of the literature search to present the results; an example template for such a report is given in Appendix A of the MEDDEV. The literature search protocol, the literature search report and copies of relevant references become part of the clinical evidence and, in turn, the technical documentation for the medical device.

Clinical experience of the device, or equivalent devices, can generate data relating to clinical use which is outside of that of the clinical investigation. The value of clinical experience data is that it provides real world experience obtained in larger, heterogeneous and more complex populations, with a broader range of end-users than is usually the case with clinical investigations. However, the data used must be sufficient to allow for a rational and objective assessment of the information to make a conclusion about the performance and safety of the device.

Clinical investigations may be performed for all classes of devices; however, they are required for high risk devices such as implantable or class III devices unless it can be duly justified to rely on existing clinical data alone. Where a clinical investigation is carried out it is expected that documentation relating to the design, ethical and regulatory ap-

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provals, conduct, results and conclusions of the investigation needed for the clinical evaluation will be available for consideration, as appropriate; examples of such documents are elaborated on in the MEDDEV, primarily the clinical investigation plan and final report.

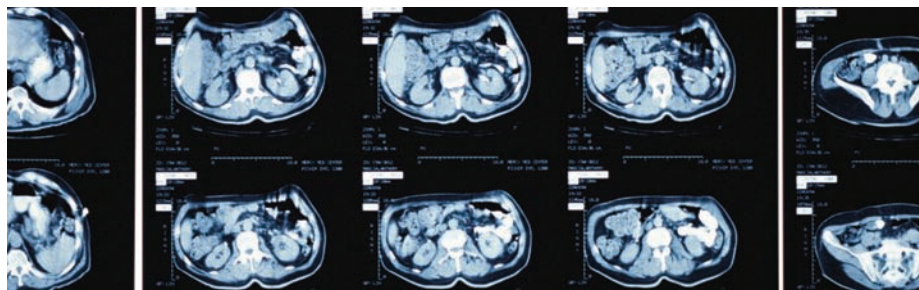
Stage 2: Appraisal of clinical data

Each piece of data is appraised to determine its suitability to address questions about the device, and its contribution to demonstrating the safety and performance of the device (including any specific claims about safety or performance). There is no single, well established method for appraising clinical data. Therefore, the evaluator should identify, in advance, the appropriate criteria to be applied for a specific circumstance. These criteria should be applied consistently. Some examples to assist with the formulation of criteria are given in Appendix C of the MEDDEV. It advises that safety and performance data should be categorised to allow for separate analysis and that the data should be weighted according to its relative contribution. An example of the method of data appraisal is given in Appendix D.

Stage 3: Analysis of the clinical data

The goal of the analysis stage is to determine if the appraised data sets available for a medical device collectively demonstrate the clinical performance and safety of the device in relation to its intended use. The MEDDEV outlines the evaluation criteria and considerations which the evaluator of the clinical data should bear in mind such as, the number of patients exposed to the device, the number and severity of *adverse events* and also that the product literature and instructions for use are consistent with the data and appropriately reflect the intended use and relevant warnings and hazards.

- At the completion of the clinical evaluation process a report should be compiled that outlines the scope and context of the evaluation; the inputs (clinical data); the appraisal and analysis stages; and conclusions about the safety and performance of the device in question. A suggested



format of the report is given in Appendix E of the MEDDEV.

The revised MEDDEV also includes a section on the role of the notified body in reviewing clinical evaluations submitted as part of the manufacturer's technical documentation /design dossiers to support their demonstration of conformity with the essential requirements. Guidance for notified bodies in reviewing clinical data is broken down into two sections based on the classification of the device and the conformity assessment procedure followed under 93/42/EEC and 90/385/EEC:

- Examination of a Design Dossier (Annex II.4; Annex 2.4) or of a Type Examination Dossier (ANNEX III; ANNEX 3)
- Evaluation as part of Quality System related procedures (Annex II.3 of 93/43/EEC)

It also states that the notified body should also have documented procedures to cover review of updates to clinical evaluation data during their scheduled surveillance activities and at the time of changes to or extensions of

EC design-examination/EC type-examination certificates. This arises from the obligation placed on the manufacturer to actively update the clinical evaluation with data obtained from post-market surveillance e.g. post-market clinical follow up and ongoing literature reviews/surveys.

Appendix F of the MEDDEV provides a checklist for use by a notified body during the assessment of clinical evaluation data, however it is stated that it should be used as a supplementary tool and should not replace the notified body report

It is also advised that notified bodies have formal, quality controlled, procedures in place relating to the assessment of clinical evaluations. The procedures should also cover review of updates to clinical evaluation data during scheduled surveillance activities and also when changes to or extension of certificates arise. MEDDEV 2.7/1 Rev.3 Clinical Evaluation: A Guide for Manufacturers and Notified Bodies can be downloaded from the Commission website:

<http://ec.europa.eu/enterprise/sectors/medical-devices/documents/guidelines/>

New Revision of Medical Devices Vigilance System Guidance Document MEDDEV 2.12/1

The European Commission has published revision 6 of the Medical Devices Vigilance System Guidance Document MEDDEV 2.12/1. This revision is effective since 20th March 2010. Revision 6 of MEDDEV 2.12/1 incorporates technical modifications to annex 3 (Report Form - Manufacturer's Incident Report) arising from the pilot online XML reporting programme that took place in 2009. There are no other changes from revision 5 of the document.

In particular, manufacturers' attention is drawn to the additional requirements within section 1 of the form (Administrative Information) where an additional question on public health threats has been added to the form together with the provision of extended options for the classification of an incident. In section 6 of the form (Medical Device Information), additional information for implantable medical devices is now required regarding the implant/explant date and the duration of implantation. A number of other layout and content changes have also been included to enhance the clarity of the form.



Ethics Committee – Parallel Review of Clinical Investigations

Under Schedule 8 of S.I. No. 252 of 1994 European Communities (Medical Devices) Regulations, 1994 the manufacturer, or his authorised representative, must provide “the opinion of the ethics committee concerned and details of the aspects covered by its opinion” as part of the application for a clinical investigation of a medical device. Previously the opinion of the ethics committee was required at the time of initial submission of the application to the IMB for review. However, ability to review such applications in parallel to the relevant Ethics Committees may facilitate the conduct of clinical research of medical devices in Ireland. Following legal advice and agreement with the Department of Health & Children, the IMB is now in a position to accept clinical investigation applications which do not have full ethics committee opinion at the time of application. However, a favourable review from both the IMB and the relevant ethics committee is required prior to the commencement of any such investigation. The full opinion of the ethics committee must be submitted to the IMB prior to the IMB granting an opinion on the application.

Additionally, any email correspondence relating to clinical investigations may now be sent to a dedicated clinical investigation email address clinical.ix@imb.ie.

Staff Update

The Irish Medicines Board is delighted to announce that **Barbara Jeroncic** has joined the Medical Devices Vigilance and Compliance section of the Human Products Safety Monitoring Department of the IMB.

Barbara takes up the position of Scientific Officer for general medical devices. Prior to joining the IMB, Barbara worked in the quality department in a pharmaceutical company.

In-vitro Diagnostic Medical Devices Information Day

The Irish Medicines Board (IMB) held an information day on in-vitro diagnostic (IVD) medical devices on Friday 12th February 2010.

The event was well attended by IVD manufacturers and various other interested stakeholders. The overall attendance for the day was approximately 60.

Feedback from attendees indicated that the presentations and case studies were well received and that the overall day was very beneficial.

The mix of presentations from the IMB and a key speaker from industry provided attendees with some important information on topics of interest in the area of IVDs. Presentations were made on the following topics:

- IVD legislation – current and future developments – *Ms. Ann O’Connor*
- Impact of international issues on future IVD developments – *Mr. Benny Ons*
- Auditing of IVD manufacturers and key issues to date – *Ms. Mairead Finucane*

- The national vigilance system for IVDs – *Dr. Judith Martin*

A case study session was held in the afternoon with practical examples relating to vigilance reporting for a range of IVDs. The case studies were presented by IMB staff and Mr. Stephen Lee, Principal Medical Device Specialist with the MHRA.

The IMB would like to thank Mr. Benny Ons (BD Biosciences Europe) and Mr. Stephen Lee (MHRA) for giving up their time to prepare and present at the information day. We would also like to thank IBEC for use of their facilities and all those who attended the event and helped make the day a great success.

If anyone would like to suggest ideas for future information days, please do so by emailing medicaldevices@imb.ie



From left to right:
Ms. Mairead Finucane (IMB),
Mr. Stephen Lee (MHRA),
Mr. Wilf Higgins (HSE/ACMD),
Dr. Joan Gilvarry (IMB) and
Dr. Judith Martin (IMB)



From left to right:
Mr. Benny Ons (BD Biosciences Europe),
Dr. Judith Martin (IMB),
Ms. Ann O’Connor (IMB)
and Mr. Eoghan O Faoláin (IMDA).



Manufacturers' Field Safety Notices and IMB Safety Notices on the IMB website

On the 1st July 2009 the IMB began publishing manufacturers' field safety notices (FSNs) on the IMB website (www.imb.ie).

All FSNs brought to the attention of the IMB since July 2009 have been placed on the IMB website, regardless of whether or not the affected device has been distributed to the Irish market. The purpose of this project is to establish a database of FSNs distributed by manufacturers which can be easily accessed by medical device users. MED-DEV 2.12/1 Rev 6 Guidelines on a Medical Devices Vigilance System requires the manufacturer or their authorised representative to advise customers of field safety corrective actions affecting their medical devices. All customers who are affected by a field safety corrective action should receive a copy of the FSN directly from the manufacturer or their authorised representative.

Following a review of the pilot phase of this project in February 2010, the IMB has decided that a summary sheet of FSNs will now be published on a monthly basis. On accessing the summary sheet, users can search for any FSN brought to the IMB's attention. The summary sheet will be published on the IMB website during the first week of the month and will list all FSNs from the previous month. This revised publication format began in March 2010. The monthly summary sheet will contain the following information:

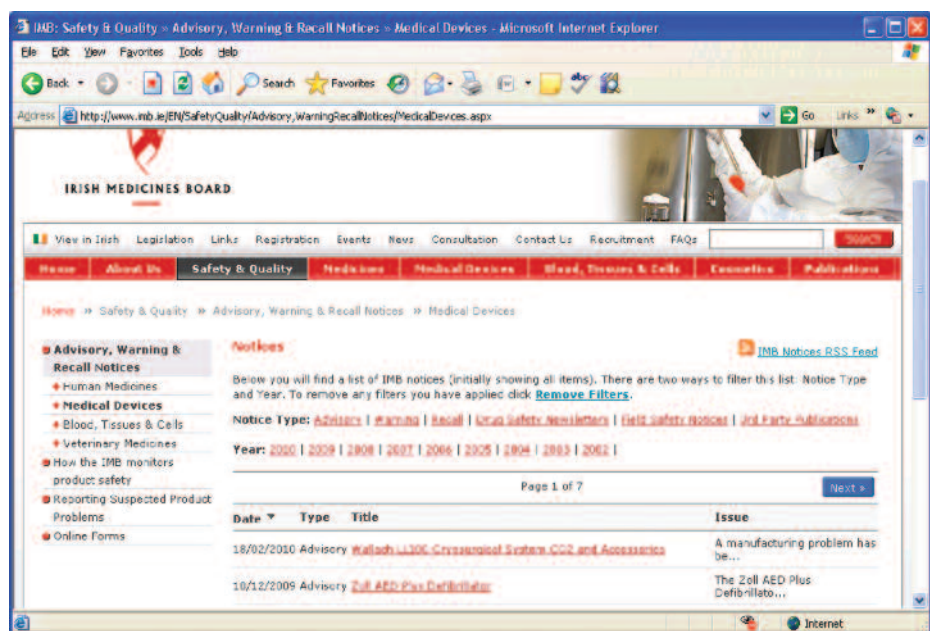
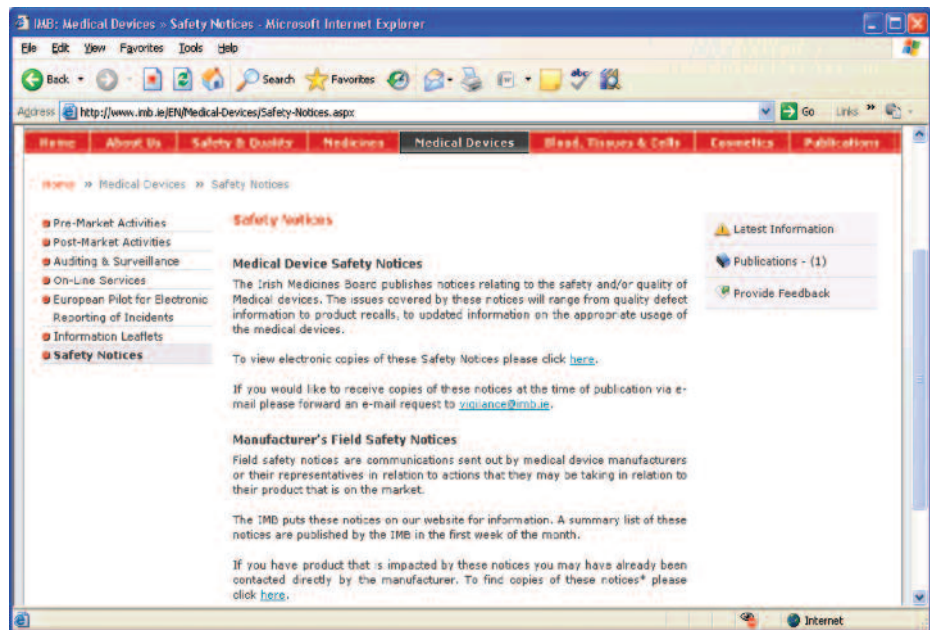
- The name of the device
- The name of the device manufacturer
- The nature of the advice given in the FSN
- A link to the FSN issued by the manufacturer

The FSN summary sheet may be accessed under 'Safety Notices' in the medical devices section of the IMB website, or under 'Field Safety Notices' in the publications section of the IMB website.

Medical device users may also access information regarding IMB safety notices for medical devices under 'Safety Notices' in the medical devices section of the website. The issues covered in these notices range from quality defect information to product recalls, to up-

dated information on the appropriate use of medical devices and are another way for users to access safety related information on medical devices. Safety

notices can also be accessed through the safety & quality section of the IMB website under 'Advisory, Warning & Recall Notices'.





Regulatory Update

Working Group on Qualification and Classification of Software

At the September meeting of the Medical Device Expert Group on Borderline and Classification it was decided to establish a small sub-working group comprised of several Competent Authorities, industry representatives and the European Commission to discuss the qualification and classification of software; both standalone and used in combination with medical devices. Ireland agreed to participate in these discussions. The group has met three times since December and is currently working on a guidance document on the classification of software. The group aims to have a first draft ready to present at the next meeting of the Medical Device Expert Group on Borderline and Classification in May.

Compliance and Enforcement Working Group (COEN)

The first meeting of the COEN group for 2010 was held in January. The work programme for COEN for 2010 was discussed. Updates were provided on specific market surveillance projects and specific cases of concern for Member States. Further discussion was held on the impact of the new approach legislation, draft guidance on the use of legal tools for market surveillance, and updates on the progress of the guidance notes for manufacturers of class I medical devices and the guidance note for manufacturers of custom made medical devices were provided.

Notified Body Operations Group (NBOG)

The first Notified Body Operations Group (NBOG) meeting of 2010 took place in February. A number of documents were finalised, with a view to presenting them for endorsement at the Competent Authority meeting in March. These documents included:

- A new guidance for Notified Bodies on auditing suppliers of medical device manufacturers.
- A new guidance for notified bodies on audit report content.
- A modified checklist for competent/

designating authorities when auditing assessments of clinical evaluations performed by notified bodies.

- A modified certificate notification form, for information exchange between Member States on product certificates suspended/withdrawn by notified bodies.

Finally, an update was provided on the ongoing peer review programme operated by NBOG where Member States are observed while conducting an audit of a notified body. The programme's objective is to harmonise the monitoring of notified bodies across the EU.

Classification & Borderline Working Group

The first Classification & Borderline Working Group meeting of 2010 took place in February. The focus of the meeting was on the revision of MEDDEV 2.4/1 Guidelines for the Classification of Medical Devices largely based on the changes arising from the revision of the Medical Devices Directives by 2007/47/EC. Consensus positions on classification/borderline products achieved by the working group are published in the Manual on Borderline and Classification which is available from the European Commission's website.

IVD Technical Group Meeting

A meeting of the IVD Technical Group (IVDTG) took place in February. Among the items discussed was the need for a revision of MEDDEV 2.14/1 rev.1 (IVD Guidance: Borderline issues – A Guide for Manufacturers and Notified Bodies). An update was provided on the revision of the IVD Directive 98/79/EC. The small group with responsibility for this revision met for the last time in December 2009 to review the feedback from Member States on the proposed revisions to the IVDD. The next steps for this project are currently being finalised. An update was also provided on the publication of the revised CTS (Commission Decision 2009/886/EC of 27 November 2009 amending Decision 2002/364/EC on common technical specifications for *in-vitro* diagnostic medical devices). It was also noted that this document con-

tains an error and a Corrigendum has been written to document the error and is available on the European Commission website. An update was also provided on the addition of vCJD to Annex II List A. The Commission advised that the technical work is complete (CTS and guidance document have been drafted) and the next steps for this project are the legal processes. The timeline for publication of the CTS and guidance document is not yet confirmed.

Clinical Investigation & Evaluation Working Group

The Clinical Investigation & Evaluation Working Group met in February. The key topic for discussion was the proposed summary template and guidance on serious adverse event reporting arising from the requirements in the revision of the MDD to 'report all serious adverse events to all Member States involved immediately'. It is proposed to use a summary table of serious adverse event reports so that Competent Authorities can monitor adverse events and seek additional information on specific events as necessary. In addition, the clinical module of the EUDAMED database to capture information on EU clinical investigations is now operational but data entry is not obligatory until 2011. This database will include a unique identification number for each EU device investigation which can be obtained from the Competent Authority where the investigation is first commenced.

Competent Authority Meeting

The 25th Meeting of Competent Authorities for Medical Devices took place in March in Madrid under the Spanish presidency. Discussions included Member States' experience with preparing for the implementation of the revised Medical Device Directive. In addition, Member States exchanged ideas from the national experience with the market surveillance provisions outlined in Regulation 765/2008. Future revisions to the medical device regulatory framework were debated including proposals for establishing a Central Management Committee for medical devices. Discussions also took place in relation to funding models for Competent Authorities for medical devices.

