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news LETTER

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EDITORIAL

Letter from the Editor

Firstly let us wish all our readers a happy and prosperous new year.

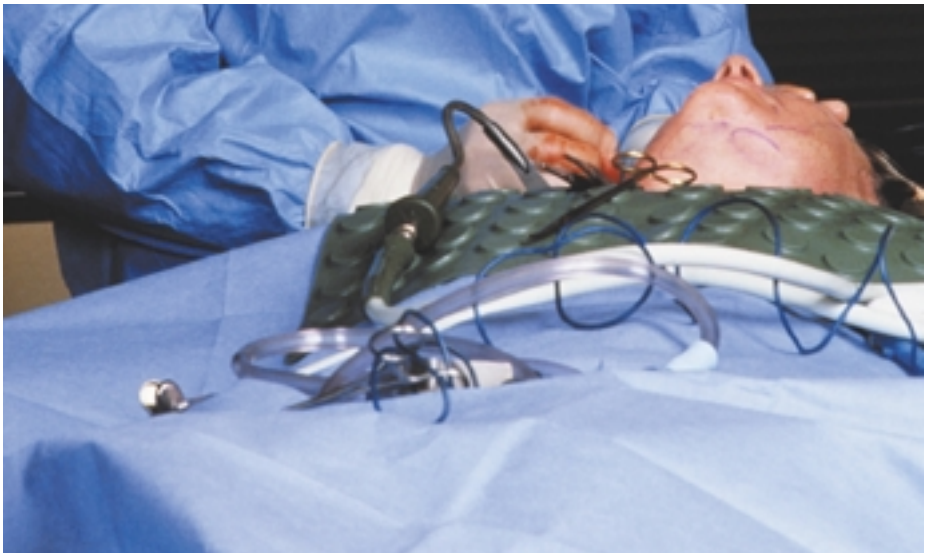
Last year was a significant one particularly in relation to the fact that the *in-vitro* diagnostics Directive 98/79/EC became mandatory on 7th December 2003.

This coming year will also be a challenging one in that we hold the presidency of the EU for the first six months of 2004. During this period, the Accession countries will become full members of the EU. Much preparation is underway to support the presidency. We recently hosted the 13th Meeting of Competent Authorities in Dublin on 12th and 13th January with the Department of Health and Children. This was a very successful meeting and allowed the European Regulators to meet and discuss issues of significance and to develop work programmes for the future.

Some of the discussions at the above meeting including the area of medical device standards. In this edition we have an article on risk management written by an industry colleague. It is important to focus on new standards and understand their practical implications.

In this edition, we are providing an update on the DATH's vigilance pilot project, which is underway in the Dublin area, and also a detailed regulatory update which includes the status in relation to in-house manufacture of *in-vitro* diagnostics by healthcare institutions.

We hope you enjoy reading this edition and as always are welcome to any suggestions or comments on the content



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The DATHS Communication System for Vigilance Issues

The Medical Devices Department of the Irish Medicines Board (IMB), over the past two years has circulated Safety Notices relating to medical devices to Irish healthcare institutions e.g. health boards and hospitals.

The aim of these circulations have been to ensure that professional users of medical devices are alerted to potential problems or risks that arise with specific devices. The process of ensuring that these notices reach the most appropriate personnel and that the recommended action is completed can be a complex, arduous task that is not always concluded satisfactorily.

A communication mechanism that ensures that Safety Notices and Manufacturer's Notices are dealt with in a prompt, transparent manner is needed. A closed loop system is required that guarantees that appropriate healthcare staff are notified, actions are taken, and completed actions are fed back to the reporting organisation to allow for closure.

The IMB has been working with the DATH's hospitals to develop a system that can cope with the varied vigilance related notices and information that requires communication including:

- Medical Device Safety Notices
- Manufacturer's Field Corrective Action Notices
- Manufacturer's Recall Notifications
- RPII Notices
- Internal Health Board / Hospital Notices / Queries
- Other Appropriate Notices

The principal focus of this model is a Hospital Vigilance Committee, a multidisciplinary committee that reviews and handles all hospital vigilance issues, that relates to medical devices. This Committee operates with the support of a Vigilance Liaison Officer and the different department heads within the hospital. Detailed descriptions of the role and responsibilities of each of these elements are outlined in the section below.

Monthly meetings of the Vigilance Committee that are organised by the Vigilance Liaison Officer provide a forum in which vigilance issues are raised, assessed, acted upon, and eventually closed out. Protocols designed and agreed by the Committee are used for the handling of extremely urgent issues or issues that arise over the weekends that cannot await the next sitting of the full committee.

The local hospital IT system has an important role in effective operation of the system both in the communication of information between Committee Members and in the posting of notices to identified staff groups on the hospital communication system.

Medical Device Information Input can include (see diagram 1 below):

- IMB Safety Notices
- MHRA Safety Notices
- FDA Communications
- Manufacturer's Field Corrective Action Notices
- Manufacturer's Recall Notifications

Medical Device Information Output can include (see diagram 2 below):

- Confirmation of receipt of the Safety Notice
- Confirmation of completion of the corrective action
- Notification of an adverse incident to the relevant groups, H&S, RPII, insurance.

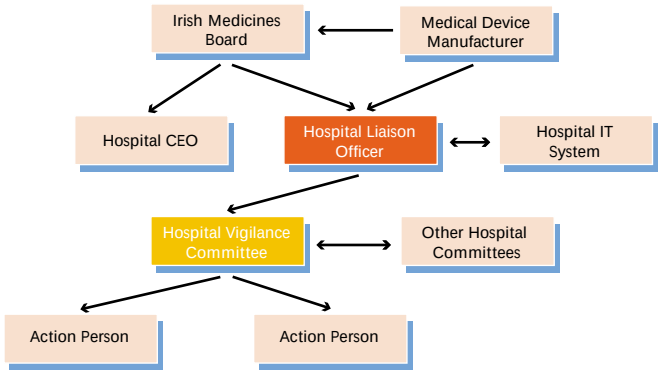
A pilot of the DATH's Vigilance system has started in four of the Dublin Academic Teaching Hospitals in October 2003. They are as follows:

- Mater Misericordiae Hospital
- Beaumont Hospital
- St. James's Hospital
- Adelaide & Meath Hospital incorporating The National Children's Hospital

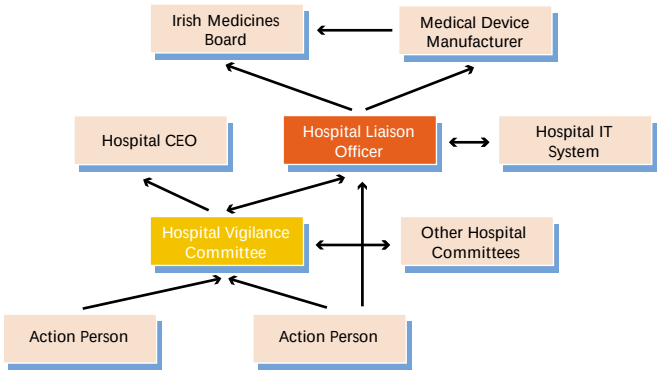
The first phase of the pilot ran between October 2003 and January 2004. The pilot will focus on testing the functional operation of the model including the processing of incoming vigilance issues notifications e.g. IMB Monthly Circulation, the processing of notifications relating to adverse incidents that may have occurred in the hospital.

Following an interim review of the feedback from the system in February 2004 and the amendment of agreed areas (if required) the pilot will continue for a further four months until June 2004 when a final review of outcomes will be conducted. To ensure the smooth running of the pilot, a training session for Vigilance Liaison Officers, Vigilance Committee Chairpersons and any other interested parties was held in October 2003. The training session provided an overview on the aim of the communication system and outline the key operation issues that will need to be implemented, including a definition of the key roles and responsibilities. Further progress updates will be provided.

In-Flow *Diagram 1*



Out-Flow *Diagram 2*



EUDAMED

As required by the In-vitro Diagnostic Medical Device Directive 98/79/EC (IVDD), a central European database (EUDAMED) has been created to capture all data relating to registration under Article 14 of the Medical Devices Directive 93/42/EEC (MDD) and Article 10 of the IVDMDD.

The aim of the EUDAMED database is to enable Competent Authorities to exchange specified regulatory data effectively and efficiently.

Pending the establishment of this centralised database, and pursuant to Article 10 of IVDD, it was obliged that Manufacturers / Authorised Representatives had to transitionally send their device notifications to the Competent Authorities of each Member State where the device was to be placed on the market.

The IMB has participated in the pilot phase of the EUDAMED project. The EU Commission has received feedback from this exercise and Phase 1 of the project is up and running and is available for Competent Authority use in relation to device registrations. Each Competent Authority is required to upload all of the device registration data in their National registers into the central European database.

Phase 2 of the project will involve the uploading of inter Competent Authority vigilance reports from each Member State's Competent Authority into EUDAMED. It is expected that this EUDAMED will continue to evolve over the coming years.

The nomenclature of choice for the EUDAMED project is the Global Medical Device Nomenclature System (GMDNS). Manufacturers are requested to implement the GMDN when registering their devices with the IMB. Further information on GMDN can be found at the GMDN website at www.gmdn.org.

Regulatory Update

Significant developments have occurred since the last regulatory update. Japan has now passed the chair of the Global Harmonisation Task Force (GHTF) to Europe. The position will be held by Europe for two years until the end of 2006. The chairman is Mr. Cornelius Brekelmans, Head of Unit with responsibility for medical devices at the DG Enterprise of the EU Commission and vice chairman is Mr. Maurice Wagner, CEO of the European trade association EUCOMED. The aim of the GHTF is to improve regulatory harmonisation where possible and appropriate at a global level.

The Medical Devices Expert Group (MDEG) approved a number of documents in its December 2003 meeting which are now published on the European Commission website. Specifically, note should be taken of the "Designating Authorities Handbook" in relation to Notified Bodies and also a new MED.DEV in relation to "*in-vitro* diagnostic medical devices: borderline issues". Agreed also was a paper in relation to "Research Use Only Products" and a paper on "Rare Blood Groups" which will be also published. It has also been agreed to review the MED.DEV on vigilance particularly in relation to global harmonisation developments.

At a meeting of Competent Authorities in relation to the reclassification of total hip, knee and shoulder joint replacements there was majority agreement amongst Member States Competent Authorities that these medical devices should be moved from class IIb to class III classification i.e. medium risk to high risk category. A meeting of the Regulatory Committee to approve the draft Directive on reclassification is expected to take place in the Spring 2004.

EUDAMED, the European databank went live on 05 January 2004 for new registration applications. With this in place it is expected that the need for IVD manufacturers to notify all Competent Authorities in Europe of IVD medical devices which they intend to place on EU markets should cease and be replaced by just one notification to the Competent Authority where the manufacturer is based. It is expected that this will be formally clarified at the next EUDAMED meeting in the Spring. The next phase of development of EUDAMED will be discussed further at this meeting.

A second successful workshop was held for the Accession countries in relation to market surveillance and vigilance issues. Most Accession countries attended and there was also a large industry presence. A third workshop is scheduled for April 2004 in Estonia prior to Accession and Ireland in its role as Presidency will play an active role.

The topic of electronic labelling was again considered by the MDEG. In principle it appears that there is an acceptance amongst stakeholders to move forward in this direction. However, the details need to be discussed for example transitional phase and the legal framework. This topic will continue to be discussed by the experts.

Initial discussions also took place in relation to the concept of in-house manufacturing and the provision of a service by healthcare institutions in relation to the IVD Directive. It was agreed that the Commission legal services would be asked for an opinion in relation to the interpretation of the Directive. Depending on the outcome it was accepted it may be necessary to form a Working Group to consider the practical implications.

Finally the MDEG accepted proposals for the Transparency Working Group in relation to transparency and confidence building in relation to medical devices. It has been agreed that a voluntary pilot phase will start in Spring 2004 in relation to manufacturers providing more information in an agreed template to the professional. Manufacturers are encouraged to participate in this pilot programme. More information on this is available from the European trade associations.

GUIDANCE NOTES

Guidance Notes Update

Guidance Note	Issue Date
Guidance Note 11: *Introduction to the* In-vitro *Diagnostic Medical Devices (IVD) Legislation*	***New Publication*** *December 2003*

Events

IMDA / FAS Quality Conference 2004
Global Regulatory Issues for the Medical Technology Sector
11th and 12th May 2004 at the Galway Bay Hotel, Salthill, Galway.

The Biomedical Division of the Institution of Engineers of Ireland presents a Seminar on *"Managing Technology in Healthcare – Meeting New Challenges"*
6th April 2004 at the IEI Headquarters, 22 Clyde Road, Dublin 4

PRESS RELEASE: PRESS RELEASE: PRESS RELEASE: 13th January 2004 PRESS RELEASE: PRESS RELEASE: PRESS RELEASE:

Competent Authorities Meeting for Medical Devices

Dublin 12th and 13th January 2004

Addressing the 13th Meeting of European Competent Authorities for Medical Devices, Minister for Health & Children, Michéal Martin said, "*technological innovation in the field of medical devices will bring major benefits to patients and is revolutionising care for patients and the disabled. At the same time these unprecedented developments are posing major challenges for regulatory authorities. Europe is working to balance the protection and safety of patients and citizens whilst encouraging innovation and access to these life-saving and life-enhancing new technologies*".

The Minister also emphasised the importance of the medical devices sector for Ireland, "*In Ireland alone we have 13 of the world's top 25 medical devices and diagnostics manufacturers. It is an extremely important industry for us in terms of employment as 9% of the country's manufacturing workforce is employed in the medical devices sector. Noteworthy also is the fact that 57% of these manufacturers have an a Research & Development function within their manufacturing sites*," he said.

The two day meeting, opened by Minister for State at the Department of Health & Children, Mr. Brian Lenihan, was hosted by the Irish Medicines Board (IMB) and the Department of Health and Children (DoH&C) in Dublin Castle and was attended by representatives of the European Commission, Member States, Accession Countries and ETFA countries.

The meeting, chaired by Ms Ann O'Connor, from the IMB and Mr Wilfrid Higgins, DoH&C, discussed in depth medical device technologies in the field of cardiovascular health and medical software (e-health), which are pivotal to two of the four key health themes under the Irish Presidency. Presentations were given on the Irish experience in regulating in-vitro diagnostics and on Ireland's newly developed electronic reporting system for registration and vigilance of medical devices which dramatically reduces administrative burdens. Specific attention was given to issues such as standardisation and the challenges posed by a range of new technologies including nanotechnology and imaging.

After in depth discussions, European Commission and Member States representatives took a number of resolutions in particular to;

- develop further policies for the evaluation and monitoring of regulation in relation to emerging technologies
- devote a specific workshop to emerging technologies such as biomedical science, nanotechnologies, tissue engineering, digital imaging/metabolic imaging and miniaturisation and
- intensify work on medical software issues including incompatibility of software products, reuse of software and software evaluation.

Finally, acknowledging the increasing workload in ensuring coherent and strict implementation of common rules throughout Europe, delegates agreed on best practice guidance for working groups and task forces of authorities and stakeholders.

Commission representatives and other participants congratulated Ireland on a highly successful meeting at the start of the Irish Presidency.

Mr. Brian Lenihan, Minister for State at the Department of Health and Children, giving his opening address to the meeting.

Ms. A.O'Connor, Medical Devices Director, IMB; Mr. M. Martin, Minister for Health and Children; Mr. W. Higgins, Chairman of the Advisory Committee for Medical Devices; Mr. C. Brekelams, Head of the Unit with responsibility for Medical Devices at the DG Enterprise of the EU Commission.

ISO 14971:2000 Risk Management for Medical Devices - A Practical Viewpoint

Ian Purdy, PhD. Director, Regulatory Affairs; Boston Scientific Europe

This article is not designed to review the detail of this standard but rather to put some perspective to the requirements and to argue the position that compliance, whilst not being an absolute requirement makes sense not only from a patient safety and regulatory standpoint but for the medical device manufacturer, it also makes sound business sense.

Firstly some key points:

- ISO 14971 (I.S. EN ISO 14971: 2000, Amd 1 2003) *Medical Devices – Application Of Risk Management To Medical Devices* comes into full effect in April of this year. At this time the transition period for EN 1441 (I.S. EN 1441:1998): *Medical Devices - Risk Analysis* expires.
- The new standard is harmonized and therefore compliance provides a presumption of conformity to the relevant Essential requirements of the Medical Device Directives. In addition the standard is quoted within the quality system standard ISO 13485: 2003 (I.S. EN ISO 13485: 2003) *Medical Devices – Quality Management Systems – Requirements For Regulatory Purposes* and is recognised by the FDA to meet the appropriate Quality Systems Regulations (QSR) requirements
- The requirements of IS EN ISO 14971: 2001 are applicable to all stages of the life cycle of a medical device but the standard does not apply to clinical judgements relating to the use of a medical device nor does it specify acceptable risk levels.

So having said all of this what does it actually mean to implement a Risk Management compliant system?

In brief, it means that decisions about the initial safety and performance of the device, the pattern of risk and the necessary risk removal or reduction procedures are thoroughly evaluated not just on an isolated basis prior to CE-marking but with an ongoing commitment to review the experience of the use of the device once in the field. In this respect the standard is a great step forward. Rather than just analyzing the risk and determining theoretical values based on likely failures and previous similar devices/techniques, real-world use needs to be assessed and analyzed and the ongoing basis for continued use of the device established.

Under the MDD it is the Manufacturer's responsibility to come to the conclusion that the evidence available supports the safety and performance of the device and that the benefits of use of the product outweigh the risks. Those risks can differ greatly according to the type of device (e.g. tongue depressor versus implantable vascular stent) and intended use (e.g. peripheral versus coronary placement) and may also vary significantly between patient groups (e.g. use in babies or diabetics). The evidence available also changes over time as user reports become available, journal articles are written and sales and complaints data is generated. Finally and very importantly in the medical device world, the role and skills of the medical practitioner are also a key influence for many devices and this consideration adds to the already complex picture of risks and benefits to be considered.

The key steps

The first stage is the identification of likely hazards; these are events, that may cause potential harm to the patient, user or environment (for example a hazard may be a wheel falling off a wheelchair). From these hazards it is the necessary to assess the risks that these pose (e.g. patient may fall out and fracture a limb). Risk is generally accepted to be a combination of the likelihood or predicted frequency of occurrence and the likely severity or seriousness of the harm that may occur (in this case the likelihood of occurrence may be classed as low but the severity of the harm may be deemed to be high). From these assessments, the manufacturer must then make a decision to either remove the risk (e.g. provide a fail-safe wheel design), reduce the risk to as low as is reasonably practical (e.g. validate the design to fail in no more than 1 in a million uses) or to appropriately inform the patient or user of the risk (e.g. through the provision of warnings, precautions etc. on labels or in the Instructions for use supplied)

So the system requires that pre-determined acceptance levels are used as a basis for assessing the overall safety and performance of the device, not only to influence the device design and manufacture but the provision of appropriate information to the patient and user (i.e. labeling and Instructions for Use). To this latter point, whilst the focus of the Medical Device Directive is rightly on the patient and end-user, the requirements of ISO 14971 also extend to considering risks to the environment and so routine or accidental interference or pollution of the environment must be considered in judging the overall risk/benefit of the device.

In performing the assessment of hazards, risks and solutions, it makes sense to address the evaluation of risk from both the bottom-up and top-down perspective. By this I refer to the engineering based analysis of potential faults/failures in the design and process that could lead to device malfunctions (often performed through Failure Modes and Effects Analysis (FMEA), Fault Tree Analysis (FTA) or similar techniques) *and* to consider how the device will actually be used (and as far as is reasonably foreseeable, misused), by whom and in what population, under which conditions.

For this to work effectively it is imperative that the people that truly understand the material, manufacture and design of the device work closely with those that best understand the actual medical practice or use of the device. In this way the real-world issues of optimizing the design for safety and performance and ergonomics are married to the construction, manufacturing and general business constraints. In considering all of these elements it is easy to see that the application of risk management can provide the manufacturer with a method to not only establish compliance to the regulations but also to make sound business decisions based on more accurately predicted and appropriately collected and analysed real-world risk.

Post-Production Information

The application of Risk management carries with it the requirement to monitor the use of the device throughout its lifetime and in this way the manufacturer is obliged to assess the ongoing acceptability of the risk/benefit profile of the use of the device. By establishing criteria for the measurement of post-production information (e.g. Sales vs complaints rates, assessment of vigilance reports made and the routine review and analysis of the published literature), a database of information can be gathered on the product. This document then provides a basis for difficult decisions that sometimes need to be taken in relation to safety concerns, reports of misuse and for the proper assessment of the need to take appropriate action. In other words, by establishing acceptable levels of risk up-front and in implementing a risk management system the company can have a strong basis for decision making on those hopefully rare occasions where safety or performance concerns arise.

Developing and applying a compliant system

Our approach in Boston Scientific was to

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gain approval from the senior management of the corporation to place Risk management at the core of our decision making and to build it into the heart of our design controls and overall quality system. This was an easy sell – risk based decision making makes sense not only for the patient, user and the regulators but also for the business. Simply put, as medical device manufacturers, if our products have questionable safety or performance we won't sell them, whether this is through having to remove them from the market or losing the confidence of our customers.

The next step within our company was to establish a cross-functional team consisting of staff from Research and Development, Quality, Regulatory and Clinical Research functions across Europe and the USA and representing each of our major divisions. Each individual was charged with representing his/her function/site/division within the team. By pulling together this varied team we were able to utilize a wide cross-section of expertise encompassing different technologies and therapeutic areas and individuals with varied skills and experience from materials specialists through to medical doctors.

Not all manufacturers have these resources at hand or available to participate in such a programme but it is important to address Risk management from this cross-functional basis in order that all aspects of risk can be thoroughly and appropriately examined. The other important issue is to utilize wherever possible, existing systems that are working well and to disrupt established, proven systems as little as possible. By having expertise in the development and quality systems processes this enable the requirements to be embedded with the system so that on ongoing compliance is robust and intrinsic to the company's operations.

Conclusions

The arrival of ISO 14971 provides a much clearer basis to establish the initial and ongoing acceptability of the risk/benefit profile of a device. A thorough cross-functional review of current systems and the involvement of individuals with a wide variety of backgrounds in the development of the systems to establish compliance are amongst the keys to success. ISO 14971 compliance provides a platform for sensible, ethical risk-based decision making, which when implemented correctly should provide a high level of assurance of both the initial and ongoing safety and performance of the device. It also happens to make sound business sense.

Frequently Asked Questions

QUESTIONS RELATING TO BORDERLINE PRODUCTS

What are Borderline Products?

In order for a product to come within the scope of the Medical Device Directives (including *in-vitro* Diagnostic Medical Devices) it must be intended by the manufacturer to be used for a medical purpose. If no medical purpose is intended by the manufacturer then the product is not considered to be a medical device.

One of the main borderline issues that arises is the determination of the borderline between the *In-vitro* Diagnostic Medical Devices Directive (IVDD) and the Medical Devices Directive (MDD). A product can only be under one or the other Directive. Thus the intended purpose for a product will be key in determining whether or not the product is an IVD or a GMD. The "intended purpose" is the use for which a device is intended according to the information supplied by the manufacturer on the labelling, in the instructions for use and / or in promotional material.

A new guidance on IVD borderline issues (IVD Guidance: Borderline Issues, A Guide for Manufacturers and Notified Bodies) has been published in January 2004. MEDDEV 2.14/1 rev.1 may be found on the medical devices section of the EU Commission website at http://europa.eu.int/comm/enterprise/medical_devices/index.htm.

In certain cases, it may not be clear if a product falls under medical devices legislation or whether it may be governed by other legislation, e.g. medicinal products legislation.

Requests for assessment of the classification may be sent to the Medical Devices Department of the IMB for clarification by using the designated classification request form. Assessment is then carried out in relation to whether the product is a medical device. The IMB's Guidance Note 15: Classification of Medical Devices provides further information on this, which can be downloaded from the IMB website.

What is "Own Brand Labelling"?

Under the different medical devices legislation (IVD, GMD, AIMD) a manufacturer is defined as the "person who is responsible for the design, manufacture, packaging and labelling of a device before it is placed on the market under his own name, regardless of whether these operations are carried out by that person himself or on his behalf by a third party".

An "Own Brand Labeller" is the person who places the product on the market under his own name and is therefore the manufacturer (as defined) for the purposes of the legislation. The "Own Brand Labeller" may not be the person who actually designed, manufactured, packaged or labelled the product but nevertheless the regulatory responsibility rests with him alone if he is responsible for placing the product on the market.

Manufacturers, including own brand labellers, should be familiar with their legislative obligations regarding use of the CE mark. The legislation imposes obligations on manufacturers and "own brand labellers" with respect to:

(a) Post production monitoring, and
(b) The reporting of adverse incidents, and any malfunction or deterioration, which might lead to an adverse incident, to the Competent Authority.

When any of the manufacturer's responsibilities are subcontracted to another party, contractual arrangements should ensure that the subcontractors meet the obligations of the legislation.

A distributor whose name appears on the packaging, labels or instructions for use is not considered to be an "Own Brand Labeller" or a manufacturer if it is clear that the product is being placed on the market under the actual manufacturer's own name /or that of the authorised representative.

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