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In this issue...

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11 Burford Road, Stratford, London E15 2ST, UK
Tel: +44 (0)1305 783020
Fax: +44 (0)1305 767379
Email: editor@globalregulatorypress.com
Editor: Victoria Clark BSc, MSc

Contents

CDRH THIRD PARTY REVIEW PROGRAM

By Rosina Robinson

What Is It?

Unlike the premarket authorisation process for new medical devices in the EU, where manufacturers/sponsors submit their technical files or design dossiers to Notified Bodies, the US Office of Device Evaluation of the Food and Drug Administration's (FDA's) Center for Devices and Radiological Health (CDRH), has until recently been the sole reviewer of all premarket applications including applications for Investigational Device Exemption (IDE), premarket notifications (510(k)s), and premarket approval applications (PMAs). Eventually, the large number of applications processed annually resulted in progressively longer review times and application backlogs.

In 1996, CDRH initiated a pilot program that authorised non-FDA third party entities to conduct selected premarket reviews. A second third party review program was added later. Both programs are voluntary and the manufacturer/sponsor of the premarket application continues to have the option to submit the premarket notification directly to the FDA, even for those devices eligible for third party review.

The following discussion looks at the Third Party Review Program from the perspective of the medical device manufacturer/sponsor of the premarket notification, and does not address the requirements for and procedures followed for the accreditation of the third party or the requirements for maintaining third party status.

Many of the references mentioned in this article include descriptions of these requirements.

Introduction

The Third Party Review Program is actually two separate programs. Both programs allow third parties authorised by the FDA to perform the preliminary review of selected premarket notifications. The first program is the Accredited Person (AP). The AP program is based on a 1996 pilot program that was later made into law by the *Food and Drug Administration Modernization Act of 1997* (FDAMA). The second program is the Conformity Assessment Body (CAB). The review of premarket notifications by CABs was developed as a single element of a comprehensive EU/US Mutual Recognition Agreement (MRA). Devices eligible for third party programs are published by CDRH on the Third Party review website[1].

Accredited Person and Conformity Assessment Body programs form Third Party Review Program

Accredited Person Program

Overview

The 1996 pilot third party program was formalised by Section 523 of the *Federal Food, Drug and Cosmetic Act*, as amended by FDAMA[2]. It was part of a program referred to as 'reinventing government' that focused on more efficient use of FDA resources for higher risk Class III devices, while also serving the needs of the medical device industry by providing more rapid reviews of premarket notifications and, therefore, more rapid clearance decisions for low-to-moderate risk, non-exempt Class I and Class II devices. At the time of its inception, the 1996 pilot program was

very limited, with only 30 Class II product types eligible for review by APs.

The main third party program in use is the AP program

When the pilot program was made permanent by the *Medical Device User Fee Modernization Act*, many of the informal restrictions for use of the program were also written into the law. The AP program is the primary third party program in current use.

Who are the APs?

APs are individuals trained and accredited by the FDA to review premarket notifications. CDRH published the first list of APs on 23 September 1998. The updated list and their respective contact information as well as a list of the devices that each AP is authorised to review is provided online at the FDA CDRH Third Party Review web page[1]. As of 5 October 2004 there were 13 APs:

APs are authorised to perform premarket notification reviews

- British Standards Institution;
- California Department of Health Services;
- Center for Measurement Standards;
- Cheiroon BV;
- CITECH;
- ENTELA, Inc;
- Intertek Testing Services;
- KEMA Quality BV;
- NIOM – Scandinavian Institute of Dental Materials;
- Regulatory Technology Services, LLC;
- TÜV America, Inc;
- TÜV Rheinland of North America, Inc;
- Underwriters Laboratories, Inc.

What are the eligible devices?

While the number of device types has expanded greatly since the time of the pilot program, not all medical devices are eligible for review in the AP program because of the restrictions that are part of the law.

Classification/inherent risk

Eligibility of a device type for review by an AP depends primarily on device classification. Class III devices are not eligible for participation in the AP program.

Eligibility also considers product risk. APs are only authorised to review low-to-moderate risk devices. Ineligible devices include the following:

- permanent implants;
- life-supporting or life sustaining devices;
- products that require clinical data to support the premarket notification.

Non-CDRH review jurisdiction

Devices outside CDRH review jurisdiction, such as devices reviewed by the Center for Biologics Evaluation and Research (CBER) or combination device/biologic or drug products for which CBER or the Center for Drug Evaluation and Research (CDER) is the lead Center are also ineligible for review by APs. For example, blood warmers were formally classified as medical devices (21 CFR §864.9205) and include three product types (product codes) within this classification. These devices are now reviewed by CBER and are, therefore, ineligible for the third party program.

Availability of device-specific guidance/ consensus standards

In the early pilot program at the beginning of the AP program, only devices for which device-specific guidance documents were available and/or for which recognised consensus standards existed were eligible for the AP program. FDA subsequently expanded the program to include any devices not expressly prohibited by the law.

Unlisted Class I devices

Unlisted Class I devices that are typically exempt from premarket notification may require premarket notification if they exceed their specified limitations on exemption. These Class I devices are eligible for third party review unless expressly prohibited by law.

Conformity Assessment Body Program

Overview

CABs were authorised by the MRA between the US and the EU that came into force on 7 December 1998[3]. The goals of the CABs are different from that of the AP program. The purpose of CABs is to facilitate trade between Europe and the US, while decreasing the manufacturer's cost of premarket compliance. Detailed information about the use of CABs and the MRA is available on the CDRH website[4].

The Medical Device Annex to the MRA includes both the exchange of quality system information (all medical devices) and premarket evaluation for selected low-to-moderate risk devices. This article describes the premarket evaluations only. Under the MRA, a European CAB can perform premarket 510(k) evaluations for a European company to determine compliance with FDA requirements (and, therefore, substantial equivalence). The same would hold true for a US CAB that can perform the premarket evaluation for a US company for compliance with European requirements.

There are two significant differences between the AP and the CAB programs: (1) European CABs may only review premarket notifications that originate in Europe and US CABs may only review premarket evaluations that originate in the US and (2) the list of eligible devices for the CAB program was originally more limited than the AP program. The critical similarity between the AP and the CAB programs is that both the APs and the European CABs perform the same type of 510(k) premarket notification review.

Who are the CABs?

CABs are third parties that have demonstrated proficiency in conducting FDA type evaluations of premarket notifications (EU CABs) and EC-type evaluations (US CABs). According to Mr Eric Rechen[5], Policy Analyst, Program Operations Staff, CDRH who is in charge of the third party programs, there are seven EU CABs:

CABs are accredited under the EC/US MRA

- AMTAC;
- British Standards Institution;
- Danish Medical Devices Certification, DGM;
- G-MED;
- SGS United Kingdom;
- TÜV Product Service;
- Underwriters Laboratories International UK.

No US CABs have yet been authorised; seven EU CABs are authorised

The list of US CABs has not yet been posted in Appendix 4 of the MRA. However, as of 13 February 2004, six US firms have been identified as moving forward to the confidence-building phase of the accreditation process:

- British Standards Institution;
- Intertek Services Corporation, Inc;
- KEMA Registered Quality, Inc;
- Orion Registrar, Inc;
- TÜV Rheinland of North America, Inc;
- Underwriters Laboratories, Inc.

While some organisations, such as the British Standards Institution and Underwriters Laboratories, Inc have both APs and CABs within them, not all locations of third parties are authorised to function in both the AP and CAB programs.

What are the eligible devices?

According to Mr Rechen, the EU CABs are authorised to conduct reviews of 97 device categories. While the number of device types eligible for review by EU CABs was originally more limited, the US expanded the list to include the same devices eligible under the AP program, as applicable according to the European Medical Device Directive (Directive 93/42/EEC). As with the AP program, the individual CAB must be authorised to conduct reviews for each specific device type.

A total of 97 device categories are currently eligible for CAB review

Why Use the Third Party Program?

Review time

The primary, if not the sole reason, for a manufacturer/sponsor to consider third party review of their premarket notification is to shorten the total review time. As will be shown below, total review time is usually shorter when a premarket notification is reviewed by third party than when it is submitted directly to the FDA. In addition, there are cases when the review time is one of the terms negotiated between the third party and the manufacturer/sponsor. Short third party review times may be subject to premium fees, however.

Program offers shorter overall review time

Product familiarity

Many of the third parties are also EU Notified Bodies that manufacturers/sponsors have already used for their CE marking process, making the third party very familiar with the device type or perhaps even the specific device. In addition, many have considerable experience with the utilisation of consensus standards to demonstrate conformity with safety and product performance requirements.

Reviewer accessibility

When FDA initiated the pilot AP program, many manufacturers/sponsors were having difficulties communicating with their FDA reviewers. Some manufacturers/sponsors believed that because the workload of the AP was not as great as that of the FDA reviewer and because the manufacturer/sponsor was paying the AP for the review, it would be easier to reach their individual reviewer.

Exemption from the FDA medical device user fee

Now that the FDA is levying a user fee for review of the premarket notification, the cost of third party review, which exempts the manufacturer/sponsor from the FDA fee, is perceived as being less burdensome. It will be interesting to see if the utilisation of third parties has increased with the advent of the medical device user fee. However, review fees levied by third parties are typically higher than the medical device user fees that are paid to the FDA.

How Do I Use the Third Party Review Program?

The use of the third party program is only slightly more complex than submission of the premarket notification directly to the FDA. Four basic steps are described below. This overview assumes that your product is both a medical device and is subject to the requirements for 510(k) premarket notification.

Step 1. Determine if your device is eligible for third party review

Identify your device on the list of eligible devices on the CDRH website[6]. This information is arranged as follows:

- the classification regulation for the device as found in the Title 21 of the US Code of Federal Regulations (by medical specialty);

- the regulation name that identifies the device and one or more product codes (three letter code) and device name;
- the regulatory class of the device (Class I or II);
- status of the device as part of an expansion pilot program (no device-specific guidance or consensus standards);
- links to relevant guidance documents and standards that apply to the particular device.

To use this list easily, you should know either the classification regulation of your device or at least the medical specialty in which it is classified. For example, if your device is a nebuliser, it is listed in the Anaesthesiology Devices section with a classification number of 868.5630. It is not designated as 'Pilot' and is, therefore, eligible for review in the third party program. Links to relevant device-specific guidance documents are provided in the last column of the table. When in doubt about the eligibility of the device for third party review, it is prudent to contact the FDA staff to verify eligibility.

Step 2. Identify third parties authorised to review premarket notifications for your device type

After you know that your device is eligible for review by an AP or CAB, it is time to select the AP or CAB to conduct the review of your premarket notification. APs are also listed on the CDRH website[7]. This page provides the contact information for each of the APs and lists the devices they are authorised to review. Using the same example of a nebuliser, we find that out of the 13 APs, 10 are authorised to review premarket notifications for nebulisers as follows:

- British Standards Institution;
- California Department of Health Services;
- Center for Measurements Standards;
- CITECH;
- ENTELA, Inc;
- KEMA Quality BV;
- Regulatory Technology Services, LLC;
- TÜV America, Inc;
- TÜV Rheinland of North America, Inc;
- Underwriters Laboratories, Inc.

Ten of the 13 APs listed are able to review 510(k)s for nebulisers

Step 3. Select the third party for review of your premarket notification

Because third parties are not all the same, talk to several about their experience with the specific product type, if there will be a delay in starting the review once the premarket notification is provided, average and range of review times, and review fees. This may be one of the considerations for selection of your third party since the FDA has not placed any limitations upon these fees. Obtain formal quotes and talk to companies who have used their services in the past. Select the third party that meets your specific needs in accordance with your company's purchasing controls. Finally, sign the contract and prepare the premarket notification.

Points to consider when choosing a third party...

Step 4. Prepare and submit the premarket notification

The premarket notification submitted to a third party must include the same information submitted to the FDA and specified in the regulations and applicable FDA guidance documents. Make it a high quality submission that is easy for the third party and FDA to review. One additional element for a premarket notification reviewed by a third party is a letter from the manufacturer/sponsor that authorises the third party to submit the

510(k)s submitted by third parties should contain additional items

510(k) to the FDA and to discuss the 510(k) with the FDA. The third party will add several other items to the submission package when they submit it to the FDA.

Third Party Review Performance Data[8]

Utilisation of third party review

According to Mr Rechen, there are currently a total of 670 types (product codes) of non-exempt Class I and II devices that are eligible for third party review and these device types account for more than 65% of all device submissions. There seems, however, to be considerable under-utilisation of third parties since third party reviews represent only 10% of the eligible 510(k)s. There also seems to be considerable disparity in the utilisation of third parties across product types. For example, third party reviews account for 29% of eligible premarket notifications submitted for radiological devices but none of the eligible orthopaedic devices.

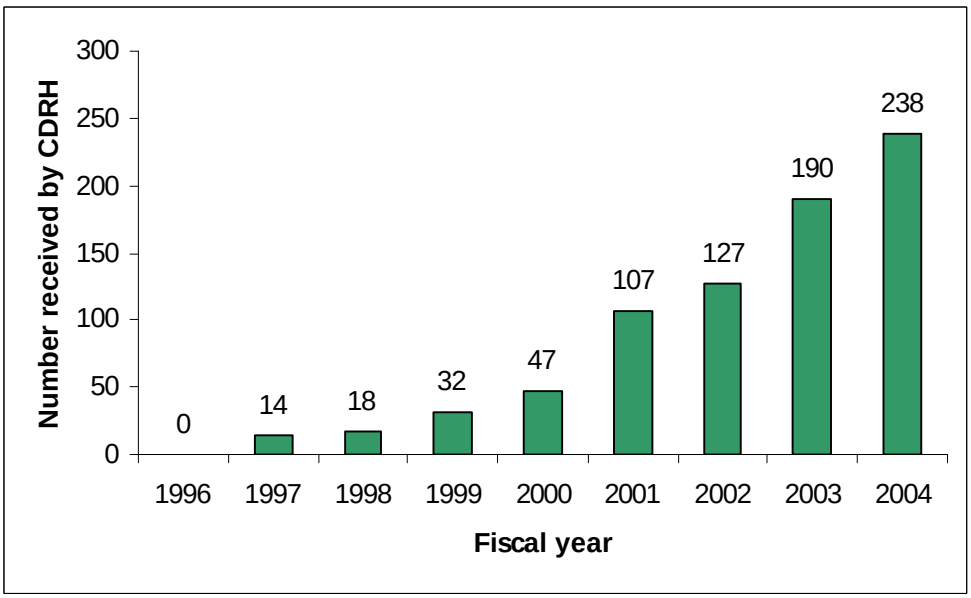
Take-up on third party reviews is very low

Figure 1 below shows the number of premarket notifications reviewed by third parties that were received by CDRH since the inception of the Third Party Review Program in 1996. As shown in Figure 1, the activity has steadily increased. The values given for fiscal year 2004 are estimates based CDRH historical data.

Review times

For fiscal year 2003, the average elapsed review time for third party reviews was 74 days (date of receipt by the third party to date of FDA final decision) while the average elapsed review time for devices reviewed by the FDA within the same product codes averaged 112 days. Excluding Special 510(k)s, for which the statutory review time is limited to 30 days, the average review time for premarket notifications for which the FDA has issued device-specific guidance documents was 72 days for third parties and 105 days for CDRH. For devices without guidance documents, third party review times averaged 83 days, while CDRH time averaged 156 days.

Figure 1. Third party reviews received by CDRH



Is Third Party Review The Right Choice?

Clearly only the manufacturer/sponsor can decide if the third party program is the right choice for the circumstances at hand. However, the third party review program may not be the best choice in the following situations:

Special 510(k)s

Special 510(k)s for device modifications have a statutory review clock of not more than 30 days. Using a third party for the review of a Special 510(k) would increase the review time because the third party would review the Special 510(k) and then send it to the FDA with their recommendations. The FDA then has 30 days to make a final determination.

Devices for which the third party has limited experience

Review times typically decrease as the third party becomes more familiar with a specific product type and the device-specific issues. It may be unwise to be one of the first of a kind that a third party has reviewed after being authorised by the FDA.

Devices whose eligibility is uncertain

Devices that are not explicitly approved for third party review or whose premarket notification may need supporting clinical data are best submitted directly to the FDA.

Manufacturers/sponsors whose devices are not ready to market

Manufacturers/sponsors whose devices are not ready to market may save money (third party review fees versus medical device user fees) by submitting their premarket notifications to the FDA during their scale up to full production.

Summary and Conclusions

The FDA Third Party Review Program (AP and CAB) offers manufacturers/sponsors a voluntary alternative to submission of selected premarket notifications directly to the FDA. Third party review can decrease total review time. Depending on the third party, the experience of the third party with the specific device type/manufacturer may provide some measure of increased assurance of review by knowledgeable reviewers. Just as with any service, however, the manufacturer/sponsor must evaluate the device to be reviewed and the qualifications of the service provider to be sure that it is the most appropriate strategy.

In certain cases, third party review may not be the best option

References

1. www.fda.gov/cdrh/thirdparty.
2. *Implementation of Third Party Programs Under the FDA Modernization Act of 1997: Final Guidance for Staff, Industry, and Third Parties*, 2 February 2001 (www.fda.gov/cdrh/thirdparty/apguide13.pdf).
3. *Guidance for Staff, Industry, and Third Parties – Third Party Programs under the Sectoral Annex on Medical Devices to the Agreement on Mutual Recognition Between the United States of America and the European Community*, 1 June 1999 (www.fda.gov/cdrh/modact/eumra.pdf).
4. www.fda.gov/cdrh/mra/.
5. Presentation by Mr Eric Rechen, Policy Analyst, Program Operations Staff, CDRH at Regulatory Affairs Professionals Society, Washington, DC, 12 October 2004.
6. *List of Devices for Third Party Review under the FDA Modernization Act of 1997*, 7 February 2002 (www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfthirdparty/current.cfm).
7. *Current List of Accredited Persons*, 5 November 2004 (www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfthirdparty/accredit.cfm).
8. Data and figures reprinted with permission of Mr Eric Rechen, Policy Analyst, Program Operations Staff, CDRH, as presented at the Regulatory Affairs Professionals Society in Washington, DC, 12 October 2004.

...continued on page 10

CLINICAL DATA IN THE EU

By Haroon Atchia

The regulations for placement of medical devices on the market in the EU are prescribed in the various European Directives but are not well defined. Concentrating on Council Directive 93/42/EEC (commonly known as the Medical Device Directive, MDD), this discussion explains the requirements, distinguishes the various options available for demonstrating clinical utility of a given medical device, and explores the role of the Competent Authority (CA) in dealing with applications for commencement of a clinical investigation for the purposes of CE marking.

Distinction Between Investigation and Data

Clinical data are always required in order to place a medical device on the market with the CE marking, irrespective of the EC product class of the device, when conformity with one or more Essential Requirements (ERs) or performances specified by the manufacturer cannot otherwise be demonstrated. Confusingly, however, the meaning of 'data' is specific and different from our day-to-day understanding.

Meaning of clinical 'data' differs from our day-to-day understanding

Clinical evaluation

The obligations for evaluating the clinical suitability of medical devices to be placed on the market with the CE mark are outlined in Article 15 of the MDD. Annex X provides further requirements on how clinical data should be obtained. Within the meaning of the MDD, clinical data constitutes either of the following:

- formal, systematic clinical investigation according to a defined protocol for establishing evidence to confirm conformity with one or more ER(s);
- critical appraisal of relevant scientific and clinical literature for establishing evidence to confirm conformity with one or more ER(s).

Any other form of clinical evaluation is not specifically prescribed but one method is now customary: comparative evaluation of the test product against a CE-marked reference product legitimately on the market.

Determination of whether clinical evaluation is necessary resides with the manufacturer (except in France). It is therefore possible that a product may undergo conformity assessment with insufficient or inadequate clinical

...continued from page 9

Further Reading

I. *Premarket Notification 510(k) Regulatory Requirements for Medical Devices*, August 1995.

II. *In Vitro Diagnostic Products: Guidance for the Preparation of 510(k) Submissions*, January 1997.

III. *Guidance for Third Parties and FDA Staff; Third Party Review of Premarket Notifications*, 28 September 2004.

IV. *Determination of Intended Use for 510(k) Devices - Guidance for Industry and CDRH Staff*, January 1998.

V. *Guidance on the Recognition and Use of Consensus Standards*, February 1998.

VI. *Guidance on the Use of Standards in Substantial Equivalence Determinations*, March 2000.

Rosina Robinson, RN, MEd, RAC is Senior Staff Consultant, Regulatory Services, Medical Device Consultants, Inc, USA and can be reached by emailing: robinson@mdci.com.

evidence and this is in fact the case for numerous medical devices. Therefore, the Notified Body should have an important role to play in discovering any product deficient in clinical evaluation but there is no stipulation for this in the MDD. Consequently, the manufacturer must determine the nature and extent of clinical data for his products, given the state-of-the-art and performances specified for the device concerned. Appropriate justification for the route selected must be documented and supported by procedures.

Clinical investigation applications for CE marking

The requirements for CE marking of medical devices are identified in the respective European Directives. The precise methods for applications to be made to each of the EU Member States (MSs) for commencement of a clinical investigation in their territories are not specified in the Directives. In most cases, the methods are not even specified in the transposition that implements the Directive in the country concerned.

Guidance on the design of clinical studies in Europe is outlined in a harmonised European Standard (EN ISO 14155-1 and -2, replacing EN 540) but this does not cover all of the elements needed for CA approval. Consequently, EU MSs have developed different measures for processing clinical investigation applications in support of the CE marking. There are a number of inherent problems with the provisions for clinical investigation in the Directives. Unlike other regulatory domains, notably the USA, there are only two conditions for products placed on the market:

- they must bear the CE marking; *or*
- be under clinical investigation or supplied for compassionate [humanitarian] use for a given patient (and cannot bear the CE marking).

Hence, there is no intermediate status such as the non-significant risk studies described by the US Code of Federal Regulations (CFR).

Pre-clinical assessment

The use of the term pre-clinical assessment should not be confused with an animal study (this is how the term is used in the USA). It should be noted that there is no recognition of the term in the MDD; in fact it is a term coined by the CA in the UK for the technical and regulatory examination of selected information required in support of an application for commencement of a clinical investigation within the meaning of Annex X to the MDD. The pre-clinical assessment application consists of the following elements:

Marketed devices must bear CE mark, be under clinical investigation or be for compassionate use

- submission of an application, supported by certain documents either specified by the CA or supplementing the application;
- examination of the design of the proposed clinical investigation;
- examination of (selected) technical aspects of the application;
- permission or objection for commencement of the proposed clinical investigation.

Depending on the complexity of a given submission, including whether the product is, for example, leading edge in technology or clinical utility or simply one that is state-of-the-art or possessing different/advanced performance, the CA is entitled to scrutinise the design of the clinical investigation. It should be noted, however, that the level of scrutiny applied by the FDA is extremely uncommon in the EU (see Table 1 overleaf).

A CA may examine the design of a clinical investigation

Table 1. Comparison between EU and US pre-clinical assessment by the respective regulatory authorities

Clinical investigation element	EU	USA
STUDY DESIGN	x	✓
- inclusion criteria	x	✓
- exclusion criteria	x	✓
- hypothesis	x	✓
- population	x	✓
- screening	x	✓
- tests	x	✓
- follow-up	x	✓
- end-points		
primary		
secondary	x	✓
TREATMENT OF DATA	x	✓
- collection	x	✓
- verification	x	✓
- analysis	x	✓
- interpretation	x	✓
OUTCOME MEASUREMENT	x	✓
- adverse events	✓	✓
- notification	✓	✓
- post-production monitoring	x	✓
DEVICE STATUS	✓	✓
- production specification	✓	✓
- non-conforming	x	✓
- labelling	x	✓

Evaluation of Clinical Data

Scientific and clinical evaluation

Clinical *evaluation* is used to demonstrate whether the performance of a medical device during specified conditions of use complies with the expectations for the device. The evaluation can also reveal whether any unanticipated or undesirable side-effects or complications occur during such use so that it may be possible to gauge whether the benefit of using the device outweighs the risk of using the device as intended or if such use poses an additional or unacceptable risk to the patient. Various elements combine to enable evaluation.

Purpose of clinical evaluation is described

Distinction between clinical investigation and evaluation

For the purposes of this discussion, *evaluation* consists of an appraisal of existing knowledge of the device or related versions, which could permit an informed decision to be made on whether to perform a clinical study or *investigation* on patients. The evaluation can therefore encompass appraisal of relevant scientific literature, review of design and production failure modes, design and production processes and review of relevant adverse incidents, thereby providing a *historical, technical perspective.* This is an important distinction, since it may well help to obviate performance of clinical investigation when overwhelming evidence of device behaviour is obtainable from other sources.

Purposes of clinical investigation

Clinical investigation is a powerful means of verifying the anticipated behaviour of a device. In certain cases, it may be possible for a prediction of device behaviour to be gauged from

non-investigational sources as illustrated in the previous section. Contrastingly, however, when the certainty of such prediction is low, confirmation of anticipated device behaviour can only be elicited from *in vivo* models, *viz* animal and human. Generally, it is considered unethical to expose a patient population to a device whose behaviour cannot be predicted with certainty or whose safety properties have not been scrutinised by some complementary means (e.g. bench verification or comparative evaluation of some description). In other words, the duty-of-care owed by the physician to his patient also extends to the manufacturer of the device, along with any others involved in bringing the product to market.

Results from a clinical investigation are required before regulatory approval can be awarded for certain devices or treatment modalities. Conditions for deciding when to perform such an investigation are clearer in the US regulatory domain than in that of the EU.

When to perform a clinical evaluation

The need to perform a clinical evaluation of a medical device should form a fundamental consideration of the design process for that device. Several factors will influence whether such evaluation should be performed; the identification of these factors is normally achievable at the design input phase of a project, although sometimes it may transpire when compliance with regulatory requirements is being determined. Generally, though, the reasons fall into one or more of the following areas:

- novel features;
- improved design;
- change of application or use;
- new option for treatment;
- medical economy;
- regulatory requirements;
- examination of a therapeutic modality whose efficacy could be influenced by operator proficiency;
- identification of institutional differences;
- improvement in quality of care.

Factors that can influence when a clinical evaluation should be performed...

Some of these reasons are self-explanatory, such as the examination of novel features or when the design or use of a device is changed. Others, however, require some clarification. Medical economy, for example, is an increasingly important constraint under which all healthcare providers now operate. Hence, equally efficacious but less costly procedures or devices are sought increasingly. As part of the goal for improved quality of care, there is a need to determine the short and long-term success rate of device procedures with the avoidance of complications. This is often related to institutional variations, especially for treatments whose efficacies can be influenced by the proficiency of the operator or unit. It is essential that such influences over performance of the device are determined so that the risk of any untoward events can be eradicated or minimised. The clinical evaluation may also reveal areas in which the instructions for use and operator training of the device require improvement or emphasis. Despite these goals, the use of clinical evaluation to establish the limits of a device cannot be condoned, though it may be used to confirm these specified limits. The factors that will trigger a clinical evaluation should form part of a uniform process under the responsibility of a nominated person or function.

Determining short and long-term success rates can be valuable

Regulatory expectations

Clinical investigation of intravascular devices is not a new concept.

Evaluations of these devices have been performed with some vigour since the late 1940s. The regulatory framework forming the basis of uniform scientific rationales for evaluation and equity, with concomitant requirements for safety and efficacy, did not arrive until some time later, with the implementation of legislation in the USA.

In the USA, the need for clinical evaluation of safety and effectiveness of devices is described in the US CFR. For example, most interventional cardiology devices are regarded as *post*-amendment Class III devices by the US FDA. Under US legislation, such devices require pre-market approval (PMA) by the FDA before they can be distributed commercially. They also require clinical investigation to determine safety and effectiveness, which is controlled by Investigational Device Exemption (IDE), again requiring FDA approval (and that of the Institutional Review Board concerned) before a clinical evaluation commences. An IDE submission is required by the FDA to assess safety and efficacy according to 21 CFR §860.7(c).

Requirements for clinical evaluation and investigation in the US...

In Europe, the regulatory requirements for clinical investigation are dictated in Article 15 of the MDD following the procedure in Annex VIII. Clinical evaluation requirements are described in Annex X to the MDD. The requirements are intended to regulate every step from first consideration of the need for evaluation and justification of the study to the publication of the results. The Annex consists of two main sections, entitled General provisions and Clinical investigations, and sub-sections covering Objectives, Ethical considerations and Methods.

Article 15 of the MDD stipulates requirements for clinical investigation

Devices highlighted as candidates for consideration of clinical evaluation are typically ones and that fall within Classes III, IIb and IIa. Taking account of any relevant harmonised standards, the adequacy of the clinical data can be based upon various factors, such as results of clinical investigation, results of risk analysis, design calculations, inspection and technical tests. The regulatory requirements do not indicate under what circumstances a clinical evaluation should be performed or what features to test, since individual situations will dictate these considerations.

Use of harmonised European standards

A system for constructing and managing a clinical investigation is outlined in the harmonised EN ISO 14155. This is similar to standard practices contained in equivalent international standards. The scope of the standard does not seek to specify or elaborate on ethical constraints or identification criteria for deciding when to perform clinical investigation, deferring instead to the requirements of Article 15.

Options for clinical investigation

The requirement in Article 15 and ER 14 of Annex I is for clinical investigation to fulfil the requirements of Annex X. If an investigation has been conducted in compliance with EN ISO 14155, then compliance with ER 14 is *presumed*. This is not to be construed as a universal requirement for clinical investigation, of course. Yet it is important to understand that, in order to fulfil the safety principles of the MDD, the clinical behaviour of a given device must be known before it can be released for general consumption.

Clearly, a manufacturer must ensure that he has discharged his duty-of-care (e.g. to the patient), not least of which to avoid any inadvertent

negligence. Hence, if clinical investigation is not merited, what are the options? With this in mind, it would be prudent to recognise that informed knowledge or prediction of expected device behaviour can be elicited from other key sources:

- comparative evaluation with other sources;
- known behaviour of related versions;
- design verification or calculations;
- behaviour in suitable animal models;
- literature review.

In any case, before the performance of a clinical investigation is decided upon, these other options must be accommodated. It should be only as a last resort that the need for clinical investigation becomes inescapable; the corollary being that a given design should ideally be launched on the market with an impeccable anticipated behaviour.

Evaluation of published literature and historical performance (scientific and clinical literature review)

Depending on the nature of the device, the intended use and performance, it may be possible to gauge the risk to patients by performing an evaluation of published literature or historical performance. These approaches must still satisfy the ERs and so the review of such information must enable a comprehensive appraisal of actual failure modes, incidence and severity of outcome with expected performance.

Analysis of adverse incidents (complaints) reported for the device in question (and, where applicable, the device family or related families) should attempt to convey a perspective (i.e. incidence of types of failure, origins and significance). Caution, however, is advised in this since such analyses are required to be used as a trigger for any corrective action in order to minimise or eradicate the risk of a particular failure (as required by section 3.1 of Annex II), so any corrective action that is instigated may yet necessitate an *investigation* for modified devices. Historical controls are useful when the study end-points are objectively measured; the disease is predictable and consistent.

A major drawback with literature review is that of *equivalence*. Since variations in technique, application, patient population, investigation structure, and factors monitored, assessment of outcome and interpretation undoubtedly exist between studies conducted by different centres, the significance of the conclusions must be rigorously appraised. Wherever possible, statistical analysis should be applied to determine significance. If this reveals unreliability in the quality of the data or concern over the risk of the device, then the commencement of a uniform clinical investigation must be considered very strongly. Literature controls are usually poor since it is almost impossible to have all relevant information and they fail to contain the rigours of establishing clear parameters in defining the group (i.e. inclusion and exclusion criteria are frequently poorly specified). This approach can be useful, however, in generating rather than testing a hypothesis.

Statistical analysis should be used wherever possible

Laboratory or bench testing of devices and quality systems audits play very important roles in helping to reduce the risk of a product to the patient. Nevertheless, for any device that poses a degree of risk to the patient, the effectiveness of the device must be assessed and evaluated against the risks that the device presents. This points to the need for conducting clinical

Effectiveness should be evaluated against risks posed to a patient

studies for such a device. Even for devices that do not pose a risk to patients, it could be argued that there is an ethical duty to assess the effectiveness of any new device in comparison with other options for treatment or other devices for the same condition, before the device is introduced to the market. Slavish adherence to clinical studies, on the other hand, might result in very slow application of new technologies.

Introduction of new technologies must not be hampered by slavish adherence to clinical studies

One of the most difficult considerations is how substantial a modification to a device must be before a further clinical study is required. Manufacturers of certain, complex devices constantly introduce new, improved versions, some of which differ only slightly from their predecessors. Whether the modification alters the form, fit, function and efficacy of the device will need to be identified, since if this is the case, a clinical study may be advocated. If this not the case, some modifications will not need clinical study.

If not properly defined, clinical studies may be deficient in a number of ways. Common deficiencies include:

Common deficiences in clinical studies are listed

- lack of a clearly stated hypothesis;
- poor study design;
- inadequate specification for patient inclusion;
- inclusion criteria;
- exclusion criteria;
- inadequate end-points;
- inadequate assessment and interpretation criteria.

Use and abuse

There is increasing concern about the general level of diligence within our industry when it comes to clinical investigation. Often, manufacturers are too hasty in deciding whether or not to proceed with an investigation, with poorly conceived design objectives and marketing desires being the predominant causes. In many cases, manufacturers submit applications for commencement of clinical investigation without having exhausted non-clinical verifications, clearly in breach of their duty-of-care.

There is also increasing evidence of manufacturers seeking routes to avoid pursuing a systematic, approved investigation, using the foil of Annex VIII and custom-products to circumvent the requirements of the MDD. In any case, a number of manufacturers fail to recognise that a device whose conformity is declared under Annex VIII must still meet the ERs, so it is illegal not to have the background work completed even before engaging in a debate about the ethics of clinical investigation.

In principle, therefore, a device to be the subject of a clinical investigation must be identical with or very close to its expected final, *post*-production level of safety behaviour when the investigation commences.

Guidance on clinical data

Clinical evaluation guidance has been developed by the Co-ordination of Notified Bodies. Recommendation NB-MED/2.7/Rec 1 contains the elements specified in Table 2 (opposite).

The guidance contained in NB-MED Rec 3 (Evaluation of clinical data) has been supplemented by MEDDEV 2.7.1, *Guidelines on medical devices - Evaluation of clinical data: A guide for manufacturers and Notified Bodies* (April 2003). MEDDEV 2.7.1 (see Table 3, opposite) presents guidance to manufacturers on the review and analysis of clinical data, and guidance to Notified Bodies on the review of a clinical data evaluation submitted by the manufacturer. The scope of the

guidelines is restricted to Directives 90/385/EEC and 93/42/EEC. Although no *secondary* purpose is identified, an additional one is stated: to provide assistance to manufacturers on expectations (presumably on the evaluation of clinical data by the Notified Body).

The *primary* purpose of the guidelines re-iterates certain obligations on the manufacturer:

- demonstration of achievement of intended purpose (cf. safety);
- demonstration of achievement of claims (cf. safety);
- demonstration of achievement of intended purpose (cf. performance);
- demonstration of achievement of claims (cf. performance);
- expectation that such demonstration will be based on clinical data.

Table 2. Content of NB-MED/2.7/Rec 1: Guidance on clinicals

Section	Title	Coverage
I	Definition	Clinical investigation Safety Performance Clinical evidence
II	Need to perform clinical investigation	General points on demonstration of clinical evidence and when clinical investigation is needed

Table 3. Content of MEDDEV 2.7.1

Section	Title
1.	Introduction and purpose
2.	Background
3.	Explanation of terms
3.1	Clinical data
3.2	Evaluation of clinical data
4.	Clinical data to be provided by the manufacturer
4.1	Manufacturer's statement on the clinical data used to affix the CE marking
4.2	Identification of aspects of safety and performance to be addressed through clinical data
4.3	Literature route
4.3.1	Requirements
4.3.1 (i)	Methodology
4.3.1 (ii)	Critical evaluation of the literature
4.3.2	Conclusions for analysis of literature review
4.4	Clinical investigation route
4.4.1	Need for clinical investigation(s)
4.4.2	Conduct of clinical investigations
4.4.3	Requirements
4.4.3 (i)	Identification of relevant documents
4.4.3 (ii)	Information to be checked
4.4.3 (iii)	Final report
4.4.4	Independent analysis
4.4.5	Conclusions from analysis of clinical investigation data
5.	The role of the Notified Body
5.1	Examination of a design dossier (Annex II.4) or of a type examination dossier (Annex III)
5.1.1	Decision-making
5.1.2	The report of the Notified Body
5.2	Evaluation as part of quality system related procedures (Annex II.3)
5.2.1	Review of the procedures
5.2.2	Review of samples
6.	Notified Body specific procedures and expertise
7.	References

The relevance of clinical data to Conformity Assessment against the ERs is re-stated. It is important to note that the guidelines recommend that clinical data **must** contain:

- published data on market experience (actual device);
- un-published data on market experience (actual device);
- published data on market experience (reference device);
- un-published data on market experience (reference device);

or consist of prospective clinical investigations (actual device) **or**:

- promulgated clinical investigation (reference device);
- other promulgated studies (reference device).

Clinical data must demonstrate a positive benefit to risk ratio

In order to fulfil the expectations for evaluation of clinical data, the manufacturer must produce a report concluding that the benefits (intended) outweigh the risks *and side-effects* of the device. Further, manufacturers intending to apply the guidelines must define various actions in order to justify the approach to be taken:

- decide whether clinical data are necessary for *every* device to demonstrate compliance with the ERs (i.e. regardless of whether the device is implanted or belongs to EC Product Class III etc) and the claims made for the device;
- take account of the type of data needed;
- take account of risk (management) assessment.

The options available for clinical evaluation are:

- compilation of scientific and clinical literature (the literature must be relevant and current with a clinical evaluation as necessary); *or*
- (systematic) clinical investigation (results of all clinical investigations); *or*
- combination of scientific and clinical literature examination and clinical investigation.

Whatever option is followed, market experience about the device must also be included in the clinical evaluation report. Experience indicates that application of the guidelines for compilation of scientific and clinical literature examination is difficult.

In addition to provision of guidance to the manufacturer, MEDDEV 2.7.1 also contains expectations for the Notified Body (see Table 4 opposite).

Experience from conformity assessment, however, indicates that few Notified Bodies operate appropriate procedures to fulfil the guidelines.

The Notified Body Recommendations cite their definitions on clinical investigation, safety and performance from EN ISO 14155. Safety is also mentioned in connection with ER I, Annex I to the MDD.

The term clinical evidence is used synonymously with clinical data (Annex 10 to the MDD) but is taken to mean:

- conclusion by a qualified expert that clinical data on a medical device allow compliance of the device with the ERs when the device is used under the conditions and purposes specified by the manufacturer;
- conclusion by a qualified expert that the benefits of using the medical device outweigh the undesirable side-effects when the device is used under normal conditions.

The guidance does not define what constitutes a qualified (clinical) expert

Table 4. Recommendations for Notified Bodies intending to apply MEDDEV 2.7.1

Implementation of policies for assessment of clinical data

Implementation of procedures for assessment of clinical data

Ensuring procedures include measures for:

- availability of suitable resources, especially relevant knowledge;
- competence needed for evaluation of clinical data;
- assessment of scientific and clinical literature examination;
- assessment of clinical investigation results;
- evaluation and risk management strategy;
- understanding device technology;
- understanding medical procedure concerned;
- use of external experts, including medical professionals;
- use of examiners with clinical investigation training and conduct;
- review opinion of any experts used.

nor how these conclusions can be substantiated by the experts.

Section II (Need to perform clinical investigation) is confusing. This section indicates the need to perform a clinical investigation results from the fact that:

- clinical evidence must be obtained for all medical devices;
- clinical investigation may be needed if the safety and performance of the medical device cannot be demonstrated adequately in other ways.

The demonstration of clinical evidence is permitted through assessment of:

- pertinent literature;
- relevant data;
- results of clinical investigation.

Demonstration means the conclusion by a qualified expert that the medical device complies with the specified performance and has an acceptable risk to benefit ratio. Actually, the demonstration of clinical evidence should have been entitled along the lines of 'demonstration of acceptable clinical suitability' encompassing the performance, safety and compliance concerns.

The guidance postulates that since it may not be possible to demonstrate clinical evidence (cited as 'safety and performance' in this part of the guidance) under the following circumstances, clinical investigation is expected to be likely for:

- a novel device of unknown components, features or mode of action;
- significant modification of an existing (approved) device that could affect clinical safety and performance;
- new indications for use of an existing (approved) device;
- a device consisting of novel materials;
- a device consisting of existing materials contacting the body in a new mode of exposure with a lack of convincing clinical experience;
- a device consisting of existing materials contacting the body for prolonged duration of contact.

MEDDEV 2.7.1 states clinical investigation is likely to be needed for...

Relevant scientific literature

The word *relevant* is not defined in the MDD. The manufacturer will have to decide the due weight to give the relevant scientific literature and the critical evaluation of its compilation,

together with limitations in the quality, accuracy or paucity of the literature. This is not so easy if there is no clear understanding of what some very important words may mean.

Where the literature is several years old and is culled from various sources, it must be established whether the techniques used and the source from which the literature was derived remain relevant given any advancement of science generally, and particularly with regard to the intended purpose of the specific device.

Relevancy of 'old' literature must be determined in light of scientific advancements

The problem for a manufacturer choosing to compile all relevant scientific literature when the decision to market the particular device has already been made is that he may not be inclined to find fault when carrying out a so-called critical evaluation. An independent critical evaluation by an outside organisation may remove the appearance of bias if presented in court.

Where the currently available scientific literature is very recent, there remains the question of what emphasis should be placed upon certain elements and techniques. It is also important to decide whether the interpretation accredited to the literature is capable of a contrary view. If so, it could be used as persuasive evidence in court to establish that the adverse effects do not constitute acceptable risks or that there has not been conformity with Annex I concerning the characteristics and performance of the device under normal use.

The scientific literature should address the relevant sections of Annex I. This should confirm that the adverse effects constitute acceptable risks and that there is conformity with the ERs concerning the characteristics and performance of the device under normal conditions. It may also highlight any omissions.

Literature must meet the needs described in Annex I to the MDD

Reliance on clinical literature

Probably the most prolifically used method of gathering clinical data, the use of scientific and clinical literature in support of placement of a medical device on the market, has become meretricious. Critical appraisal of scientific and clinical literature is typically in the form of a clinical literature review. Common deficiencies in clinical literature review are:

- an inadequately defined hypothesis;
- an inability to correlate literature with the ERs adequately;
- an inability to correlate literature with the precise device or device type adequately;
- that clinical studies reported in scientific and clinical journals rarely satisfy the principles of EN ISO 14155.

In electing to use clinical literature review, a manufacturer must ensure the following if conformity with one or more ER(s) is to be satisfied:

- reference articles must be relevant to the specified property of the device under evaluation;
- the information in the articles cited must be of sufficient detail to permit determination of achievement of the Safety Principles contained in ER 2;
- any issues concerning the intended use of the device that would be identifiable through clinical investigation should be equally identifiable from the reference articles cited;
- there must be adequate treatise of the articles cited to enable comprehensive evaluation of the behaviour (safety and performance) of the device design parameter under study.

Follow-up of patient prognosis can prove to be problematical since the information in any clinical study reported in the literature tends not to be according to EN ISO 14155 (further, such studies ought to be conducted under Annex X or are invalid for the purposes of clinical investigation in support of Article 15).

Limitations of clinical literature review are most glaring for devices that are 'non generic' since it may be impossible to obtain adequate detail on the performance of the product because its features are novel or the clinical application for which it is intended was previously unaccepted or untried. It is against this background that the true utility of scientific and clinical literature evaluation must be considered.

In practice, scientific and clinical literature reviews compiled by manufacturers are poor. Typically, the selection of reference articles is partial and rarely withstands scrutiny of the clinical hypothesis under study. Further, the relevance and application of such compilations is often fraught with weaknesses induced by the paucity of clinical studies conducted outside formal controls. Often, the nature of follow-up is biased clinically and does not account for device performance.

In most clinical studies, there is a considerable lack of (detailed) characterisation of accessory devices used. Article 15 of the MDD is ripe for abuse. By permitting manufacturers the option of not performing clinical investigations before placing a medical device on the market if scientific and clinical literature can support the presumption of conformity, many manufacturers see this as an invitation for doing less than is acceptable.

When examining clinical data produced in line with Article 15, it places a great deal of responsibility on the EC design-examiner. Therefore, the clinical data must be scrutinised with the following objectives in mind:

- study hypotheses must correlate with ERs as applicable;
- if clinical investigation is conducted, this should at least follow the principles and structure of EN ISO 14155 (certain CAs require EN ISO 14155 to be followed, regardless of the obligations of Article 5.1 of the MDD);
- if the scientific and clinical literature review has been compiled according to Annex X to the MDD, this must be of equal quality and scientific merit to *substitute* for an Annex X-devised clinical investigation;
- where devices are long-term duration or permanently implanted, then both clinical investigation and scientific and clinical literature review must deal with this scientifically;
- evidence of Informed Consent and Local Research Ethics Committee/ Institutional Review Board approval should be expected in the Product Design Dossier (PDD);
- where clinical investigation has been conducted, evidence of CA approval should be expected in the PDD;
- where clinical investigation has been conducted, the clinical investigation protocol and corresponding report are expected in the PDD.

Factors to be borne in mind by EC design examiners...

Simple letters of testimonial from physicians, whether sponsored by the applicant manufacturer or not, are unacceptable. The design of the scientific and clinical literature review must be described and justified. There must be judicious yet balanced selection of articles in order to ensure an equitable perspective on the test product. Any scientific and clinical literature must also deal with relevant constructive knowledge.

A testimonial letter from a physician is not adequate

Examination of Clinical Data during Conformity Assessment

In keeping with most leading regulatory domains throughout the world, conformity assessment may be divided into two activities:

- verification of conformity with quality system requirements, normally through a site audit;
- examination of technical evidence of design conformity with product or technology specific requirements, normally through off-site assessment of a formal submission.

Thus, it is uncommon for clinical data to be scrutinised during a quality management system audit, especially as Notified Bodies only very rarely assign specialists with sufficient product-based clinical and statistical knowledge to be able to judge clinical data. Hence, a conformity assessment audit of clinical data is typically confined to confirmation of coverage of procedures for clinical data and audit of records demonstrating compliance with the procedures.

Notified Bodies rarely examine clinical data during QMS audits

Problems drawn to the attention of the UK CA prompted a strengthening of duties required of the Notified Body; thus, audits conducted by UK-designated Notified Bodies must include verification that any clinical investigation permitted by the CA has been followed faithfully.

Stricter requirements apply to UK-designated Notified Bodies

The Medical Devices Expert Group (MDEG) has identified the proper implementation of provisions on clinical data as one of the critical areas for improvement. The following are cited as particular problems:

- unavailability of clinical data (all EC product classes);
- insufficient verification of clinical data by Notified Bodies;
- irrelevance of clinical data related to the device in question (i.e. clinical data do not relate to device characteristics and performances);
- interpretation (confusion in wording of the MDD).

Consequently, the MDEG founded a Clinical Evaluation Task Force to consider the improvements in clinical data for medical devices already, or to be, placed on the market with the CE marking. The MDEG has committed to the production of guidance on clinical investigation of implantable medical devices and also endorsed the NB-MED Recommendation about clinical data.

The proposal to endorse the NB-MED Recommendation on clinical evaluation is meretricious – a rethink of the precise duties of Notified Bodies and CAs is instead argued for:

- determination of need for clinical investigation;
- improvements in criteria whereby clinical investigation be considered unnecessary;
- design of the clinical investigation;
- formal training of EC design examiners and other personnel expected to examine clinical data.

The lack of central CA repositories for information and monitoring investigations is considered to be one of the most serious issues facing Notified Bodies during conformity assessment, notably during EC design examination. The Notified Body is already in an inauspicious situation by the time it conducts a design examination. For example, the purview of clinical investigation (Article 15) does not permit Notified Body involvement

from application for commencement of a clinical investigation, nor awareness of the decision by the respective CA, never mind the fact that consent may have been awarded injudiciously [examples of this are known among the CAs, ranging from poorly-designed clinical investigation protocols, inadequate sample (patient populations), inadequate clinical monitoring (including unsatisfactory or unscientific end-points) and paucity of follow-up, to poorly-defined hypotheses, analysis and interpretation of data]. By the time the Notified Body becomes involved through conformity assessment, it is in an invidious position: for how can the subordinate Notified Body fault consent given by a CA? It is extremely difficult to contemplate how guidance from the Clinical Evaluation Task Force will overcome these problems. One way of avoiding them would be to ensure Notified Bodies become integrated in the demands of Article 15 and to ensure the CAs act uniformly according to a pan-European procedure. It must be pointed out that reliance on developing standards to help in the formulation of clinical investigation design are poor substitutes for mandatory controls, consensus at CA level, and contradictory to Article 5.1 of the MDD. Further, there is considerable indication that (aside from certain exceptions) CA scrutiny of applications for commencement of Annex X clinical investigations remains useful.

Recommendation NB-MED/2.7/Rec 3 *Evaluation of clinical data* has been prepared by the Co-ordination of Notified Bodies to provide guidance to EC design examination and other technical assessors on evaluation of clinical data. Obligations for Notified Bodies are described in section 5.1. The basis is that the Notified Body (the EC design examiner under Annex II) should possess sufficient proficiency. The design examiner must be able to evaluate whether the clinical data in the PDD:

- describe the intended characteristics related to clinical aspects;
- describe the intended performances related to clinical aspects;
- verify the intended characteristics related to clinical aspects;
- contain an adequate risk analysis and undesirable side-effects are estimated;
- contain documented justification of acceptable risks when weighed against the intended benefits.

The EC design examiner is obliged by section 5.1.1 c1 to:

Obligations placed on EC design examiners by section 5.1.1 c1...

- ensure that clinical performance of the device is listed;
- ensure that clinical characterisation of the device is listed;
- ensure that expected benefits of the device are listed;
- ensure that expected benefits of the device are characterised;
- demonstrate use of the clinical data to evaluate the list of hazards identified;
- determine that the hazard aetiology has been adequately estimated;
- confirm adequacy of hazard aetiology has been evaluated by ALARP (as low as reasonably practicable).

The EC design examination report should be expanded to cover the following elements (section 5.1.2 of the Recommendation):

An EC design examination report should contain...

- name of manufacturer;
- device details;
- basis of evaluation (e.g. MDD, Annex II, section 4);
- list of documents submitted;
- description of device;
- assessment of clinical safety and performance;
- conclusion.

[It should be noted that any (single) risk/benefit ratio requires a negative conclusion to be drawn.] This section of the Recommendation contains a note on the conclusion (Note 5), which states that:

'In some cases, the combination of conditions specified in order to characterise different risk/benefit ratios as acceptable may be contradictory or impracticable, and so leads to a negative conclusion.'

No advice is given in Recommendation on how clinical data should be evaluated

The Recommendation does not actually provide any specific guidance on how to evaluate clinical data.

Demonstration of Safety and Performance

Commonly ill considered or even remaining unrecognised by manufacturers and Notified Bodies alike, in order to fulfil the requirements for placing a medical device on the market, the safety and limits of performance of a medical device must be demonstrated. These expectations extend over the course of the service and shelf-life of the device.

A device's safety and limits of performance must be demonstrated

Since there is also an obligation to ensure the complications of a particular device are commensurate with the risks associated with its use when weighed against the corresponding benefits, the manufacturer is obliged to have evidence for all claims promulgated.

Summary

In summary, clinical data are required for all EC product classes, although the nature of the clinical data may vary according to the class. All clinical data must be relevant and concerns exist about the level of scrutiny. Devices for clinical investigation must also comply with Annex VIII and permission is required before commencing any clinical investigation. The practical options for clinical evaluation are:

- clinical investigation (or trial);
- scientific and clinical literature review; *or*
- a comparison evaluation.

It should be noted that the options provided by the MDD do not include a comparison evaluation in that it is not specifically permitted by the MDD, but is common in practice.

The requirement for clinical evaluation is to be found in Annex I General requirements 1, point 6 and point 3, and Section II Requirements regarding design and construction, point 14. The requirement for a clinical evaluation arises:

- wherever there is an undesirable side-effect associated with the use of the device; *and/or*
- as the means of establishing conformity with Annex I as regards the characteristics and performance of the device when used under normal conditions.

The MDD provides for a clinical evaluation to be carried out by either of the following:

- a compilation of the relevant scientific literature currently available on the intended purpose of the device and the techniques employed as well as, if appropriate, a written report containing a critical evaluation of its compilation; *or*
- the results of all the clinical investigations made, including those carried out in conformity with Section 2 of Annex X.

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Haroon Atchia is CEO and Technical Director at the international medical device consultancy Quality First International Limited, London, UK. He has many years of hands-on experience in preparing regulatory submissions, ranging from Product Design Dossiers, technical documentation, 510(k)s, IDE submissions and clinical evaluation protocols. Haroon is also a specialist EC design examiner, a technical assessor for a number of Notified Bodies, and a CMDCAS auditor.

MOVING TOWARDS AN IT-BASED RISK MANAGEMENT SYSTEM

By Terry Knapp

Overview

The systematic manner, driven by regulatory agency oversight, in which medical devices, pharmaceuticals and biologicals are developed and commercially deployed, has served the citizens of the US and the rest of the world quite well for many years. This is not to say that the process is without flaw. On the contrary, as the pace of innovation steadily increases, and as the potential for more and varied therapeutic interventions in the form of devices, pharmaceuticals and biologicals accrue to the armamentarium of treating physicians, the potential risks compound along with potential benefits.

Limitations of traditional risk management methods and tools are now being recognised

Historically, the prescribing physician assessed all factors of a patient's health and prescribed the pharmaceutical product or applied the device suitable for that patient. Moreover, the prescribing physician was likely to oversee the care of a given patient for years on end. Now, such circumstances are often no longer the case.

The mobility of both patients and physicians, managed care, Preferred Provider Organisations, integrated healthcare delivery organisations and all manner of fluidity in the delivery system erodes one-on-one doctor-patient relationships. Increasingly, availability of pharmaceuticals (though not yet implantable devices) via the Internet and other sources, coupled with the overwhelming torrent of web-based health information, has led to a rash of self-diagnosis and self-medication. Compounding and exacerbating the trend is increasingly aggressive direct-to-consumer (DTC) advertising by many of the pharmaceutical giants and even medical device manufacturers.

Additional requirements were introduced by the SMDA

Amidst the most obvious manifestations of the increasing consumerisation of medicine, regulatory agencies are acknowledging the limitations of the traditional risk management methods and tools in the commercial deployment of medical devices and pharmaceuticals.

For medical devices, formal classification and associated development and deployment regulations did not come under US federal control until 1976, when the Center for Devices and Radiological Health (CDRH) was created as a division of the Food & Drug Administration (FDA) pursuant to the *Medical Device Act* of that same year. (Certain US states, such as California, had medical device regulations in place prior to federal pre-emption.) Since then, numerous medical device related problems have emerged as major foci of litigation, to the detriment of doctors, patients and manufacturers.

Tragic medical device brouhahas that include failed heart valves and temporomandibular joint prostheses drove the creation of the *Safe Medical Devices Act of 1990* (SMDA) that called for registry and tracking of recipients of certain types of implantable devices to establish systematic post-market surveillance and adverse event reporting. The MedWatch system, a quasi-voluntary reporting of device-related incidents by the medical

profession, was put in place by the FDA. This was mirrored by the vigilance requirements of the EU. Shortly after this, the breast implant 'crisis' of 1992–1995 illuminated once again the many shortcomings in risk management for medical devices. What was a 20-year-old woman who had breast implants by a 60-year-old surgeon to do when she had an implant problem 10 or 20 years later? Who was the manufacturer? Where was the surgeon? In too many instances, neither answer was known – to the detriment of the patient *and* the manufacturer.

As recently as 2002, a European manufacturer of orthopaedic prostheses settled a class action lawsuit after 31,000 hip implants failed in patients due to a manufacturing quality control error. The cost for settlement was US$1.2 billion. Where were the early warning data that could have prevented enormous human suffering, loss of corporate reputation and financial disaster?

Increasingly, regulatory agencies are seeking ways in which to fulfil their mission of protecting healthcare consumers by meaningful risk reduction measures in the deployment of medical products over which the agencies maintain jurisdiction. On 3 March 2003, the FDA issued three Concept Papers from the Centers for Drug Evaluation and Research and Biologics Evaluation and Research addressing pre-market risk assessment, risk management programmes and good pharmacovigilance programmes. These Concept Papers serve as harbingers of the direction intended by the FDA regarding these matters, and their principles apply as much to medical devices as to pharmaceuticals.

Much of the remainder of this discussion will focus on the FDA Concept Paper entitled *Risk Management Programs*. Firstly, let us examine the stakeholders in the product risk management equation, and the risk management tools that have traditionally been employed by the industry. Then, in the context of the Concept Paper, project solutions made affordable and efficient by modern information technology (IT).

Stakeholders – Those At Risk

Manufacturers, investigators, prescribers (doctors), patients and regulatory agencies: these are the key stakeholders in the development and commercialisation of pharmaceuticals, biologicals and implantable medical devices. Each bears responsibilities and each also bears risk. Table 1 (overleaf) details these responsibilities and risks.

Main stakeholders in the risk management equation are...

The stakes are high for each participant listed. Are current risk management tools and approaches up to the job? Even a cursory examination of the evidence yields a resounding 'no'. Why? Because there are so many gaps in data acquisition and reporting due to lack of connectivity among stakeholders, lack of incentives, lack of established reporting channels and lack of awareness. Most attempts to systematise reporting are based on paper documents, paper trails and afterthought and most often these systems do not work with any consistency. In a 1992/93 report, ECRI, a non-profit health services research agency, documented a 72% attrition rate in less than 24 months for device registry and tracking of patients with devices subject to the SMDA regulations. The hip implant failures referred to earlier and other instances of harm to patients are *prima facie* evidence of the failure of the current product risk management paradigm.

Current risk management tools are often paper based and lacking in consistency

Table 1. Medical products – stakeholder responsibilities and risks

Stakeholder	Responsibility	Risk
Manufacturer	• develop products according to the *Quality System Regulations*, ISO 13485 quality system requirements, and cGLP (current Good Laboratory Practice), cGMP (current Good Manufacturing Practice), and cGCP (current Good Clinical Practice) regulations • understand potential hazards posed by a product and analyse the risk • create a direct relationship with those who are subject to the product risk	• financial (liability) • regulatory (approval and continued marketing) • reputation (brand) • lack of easy mechanism to connect with all other stakeholders (especially patients)
Doctor	• comply with guidelines for investigators • assess the product in relation to individual patient indications and contraindications, and prescribe accordingly • monitor patient for adverse events and therapeutic efficacy • recognise adverse events • report adverse events	• financial (liability, ability to practice) • reputation
Patient	• compliance with instructions for use (presuming that the patient is informed and provides consent) • inform responsible parties of potential adverse events (if a mechanism for such communication exists)	• injury • death • financial loss • no connectivity with regulatory agency, manufacturer or (sometimes) doctor
Regulatory agency (e.g. FDA)	• govern/oversee product development and commercialisation, including messaging (labelling), to minimise risks to patients and ensure efficacy for approved indications	• political • funding (congressional oversight) • no control over physician practices and off-label uses • no control over patient compliance • no enforcement of MedWatch or vigilance for doctor or patient reporting

Current Risk Management Approaches

Until now, the FDA approach to product risk management over time has been a patchwork effort coupled with an inability to enforce. An example is the MedWatch system for reporting adverse events associated with medical devices, especially devices implanted in patients, such as heart valves and breast implants. The SMDA requires the manufacturer to maintain a registry of patients and to track patients who have such devices. Registration should be easy, similar to creating registration for those who buy toasters at appliance stores. However, the registration of recipients of medical devices is far from automatic. The surgeon or operating room nurse may or may not complete the registration. The patient is often not party to the registration, eliminating the

potential for subsequent tracking. Assume, however, that the patient's device and the patient are registered in a database (now with the consent of the patient pursuant to the *Health Insurance Portability and Accountability Act of 1996* (HIPAA) privacy rules). Is there assurance that the patient can be tracked? From the patient's perspective, is there assured continuing access to the surgeon who implanted the device? Often there is, at least for some period of time. But surgeons move, as do patients. Is there connectivity between patient and manufacturer? Seldom are such connections systematically established for patients having a given manufacturer's products. How, then, are adverse events reported in a statistically meaningful manner? How are patient satisfaction levels determined? How are patients notified in case of a product warning or recall?

MedWatch was established as a means for physician reporting of device-related adverse events. For the doctor, MedWatch reporting is voluntary, not mandatory. This necessarily biases any collected data that might reflect incidence or outcome. The patient may report device-related adverse events directly to the FDA, *if* the patient recognises an adverse event for what it is, *and* knows the particulars of the product, *and* is cognisant of the reporting mechanism – a highly uncertain set of circumstances. Usually patients bring complaints to the treating physician, if the physician is available. The doctor then determines if there is a product-related problem. If so, the doctor may or may not report the problem to the FDA via MedWatch. Also, the doctor may or may not report it to the manufacturer. If the FDA builds a file of sufficient specific adverse event data in this manner, it could then alert the manufacturer that a problem exists with a particular product. Obviously, the system is haphazard and disconnected, a fact that is not lost on litigating attorneys.

Prospective New Initiatives

The FDA recognises that patients are the most important stakeholders. On 3 March 2003, the Agency issued three Concept Papers on the topic of risk management for pharmaceuticals and biologicals for public comment. These white papers outline the FDA's proposed approaches and potential requirements of industry for product risk assessment, risk management programmes, and assessment of the programmes in action. The forward-thinking, far-reaching concepts, if enacted appropriately, have the potential to reduce risk for all stakeholders. The concepts are every bit as applicable to medical devices as to pharmaceuticals and biologicals.

Principles of FDA's risk management Concept Papers apply equally to medical devices

The balance of this discussion will address specific elements of the FDA Concept Paper entitled *Risk Management Programs*, with comments directed at the manner in which modern IT-based solutions can assist manufacturers, doctors, pharmacists and patients to derive maximum benefit coupled with lowest risk in the use of pharmaceuticals and biologicals. These IT-based services may be directly extrapolated to the risk management of medical device development and deployment.

Risk Management During Clinical Research

Firstly, the FDA correctly describes 'risk management' as 'the overall and continuing process of minimizing risks throughout a product's lifecycle to optimize its benefit/risk balance'.

FDA's definition of risk management...

Any prudent person believes that a risk management programme for any medical product begins before the product is subjected to the first clinical trial. That first risk management step, Hazard Assessment and Risk Analysis (HARA), entails the creation of a compendium of the potential hazards (elements or circumstances associated with the use of a product that if encountered will injure or harm the user) and the analysis of probability (risk) that such injury or harm will occur. This academic exercise establishes a referenceable baseline for clinical testing and then commercialisation of the product. Safety and efficacy data gathered over the lifecycle of the product allow continuous refinement of the HARA profile. The risk analysis also serves as the guiding reference for product development under design controls, as specified in the FDA's *Quality System Regulations* (QSR) and in ISO 13485 requirements.

Hazard assessment and risk analysis are the first stages in the risk management program

Once the initial risk analysis exercise has been performed and documented, and bench research and product development under design controls have been completed to the point deemed adequate for the clinical testing phase, clinical trials begin. Regulation, Institutional Review Board (IRB) and Ethics Committee oversight govern the conduct of the clinical research phase of product development.

Clinical research is controlled by regulation, the IRB and the Ethics Committee

The key risk management components during clinical research include protocol design by the sponsor (manufacturer), then review and approval (in the US) by the FDA and IRB. The IRB or the Ethics Committee is responsible for review and approval of the clinical protocol and the Informed Consent Document (ICD), a critical risk management tool for patient protection.

During the course of the trial, the sponsor and/or the sponsor's representative (usually a Contract Research Organisation), the IRB/Ethics Committee and, periodically, the FDA monitor adherence to protocol, and gather data regarding unanticipated adverse events. However, the informed consent process, the most significant risk management tool for individual patient protection, remains significantly flawed.

Once the ICD is approved by the IRB, there is little assurance that the research subjects have received all of the information contained in the ICD, that the subject indeed understood the information, or that the subject's questions and concerns were captured and addressed. These shortcomings have caused ethicists to question the validity of the current informed consent paradigm.

Recent IT developments have created answers to these concerns in the form of electronically assisted clinical research informed consent (CRIC). A multimedia, interactive CRIC 'module' delivers all information approved by the IRB or Ethics Committee for the ICD. An available IT-based educate-and-consent system creates an end-to-end informed consent process that significantly enhances the patient-investigator relationship while saving time and reducing risk. The web-based process, which is hardware platform independent, assures the following elements of the consenting process:

- every session is compliant with 21 CFR Part 50 and the Declaration of Helsinki informed consent regulations and with HIPAA and EU Privacy Directive security and privacy requirements;

- all approved information is delivered uniformly to every patient, every time;
- patient understanding of all relevant concepts (risks, benefits, alternatives, study parameters) is both gauged and documented;
- patient questions and concerns are captured, saved and reported to the investigator/physician;
- data pertinent to the study are captured, saved and reported in the course of the informed consent session (e.g. quality of life data, attitudes, pre-existing conditions or any information specified by the sponsor or the investigator that must be obtained from the patient);
- all patient interactions with the system are recorded and archived, as is the entire multimedia session and patient responses;
- patient, investigator and witness signatures may be captured digitally in accordance with pertinent regulations;
- session reports containing patient questions, responses to embedded surveys and grasp of subject matter are immediately sent to the investigating physician to facilitate final face-to-face interaction with the patient;
- summary reports (pooled data) are always available to the IRB for continuous improvement in generating patient understanding;
- summary reports of pooled data are always available to the sponsor to monitor rates of accrual at disparate sites and other indices of site performance;
- the ICD may be created in multiple languages for multi-national trials or trials incorporating diverse patient populations;
- changes in the CRIC module to accommodate study modifications or supplemental information (e.g. as new adverse events arise) are quick and accompanied by instantaneous update across the system;
- the CRIC risk management tool also establishes automatic *registration* of the patient on a private and secure, permission-driven communications platform for future tracking, surveys, outcomes determinations etc.

Electronically assisted CRIC has several advantages over traditional methods

The attributes of IT-driven CRIC may also serve as precursors to strategies for risk management as a product is prepared for commercial introduction – and to the specific proposals of the FDA in its *Risk Management Programs* Concept Paper.

Risk Management During a Product's Commercial Lifecycle

The basic risk management tool that the FDA has always required of pharmaceuticals, medical devices and biologicals is product labelling in the form of the professional package insert (PI). That tool, while essential, has been increasingly marginalised as the industry has invested ever more heavily in DTC advertising for prescription-only pharmaceuticals and medical devices. Short advertising slots of 30- to 60-seconds do not provide a balanced risk/benefit discussion, nor can they put the product in proper perspective for all conditions inherent in mass audiences. The result is a population of patients who may demand a specific product, leaving the doctor to reactively deny the product (if contraindicated) rather than proactively prescribe the product (if indicated). This creates the potential for increased risk to patients, increased product liability and increased physician liability. Yet, no one

Increased DTC advertising may affect the risk to patients, product liability and physician liability

can deny the economic power of the 'pull' that DTC advertising exerts.

The FDA is clearly seeking to establish a balance in the risk/benefit equation as it relates to the flow of information about products.

An IT-based approach contains the potential to enable targeted information flow to the considerable benefit of all stakeholders, especially for the manufacturer, as the information has the potential to supplement DTC advertising in a responsible manner.

In many cases, the PI provides adequate risk management

The FDA concedes that while every pharmaceutical product, device and biological carries risk to some degree, for many products the PI is sufficient risk management. The risk management classification proposed by the Agency is as follows:

FDA's four proposed classification levels...

- **Level 1**: package insert only;
- **Level 2**: Level 1 plus education outreach to professionals and consumers;
- **Level 3**: Level 2 plus systems that guide the circumstances for practitioners and/or patients to prescribe, dispense or receive a product;
- **Level 4**: access to product requires adherence to specific (risk management) programme elements from Levels 2 and/or 3.

The FDA describes the types of tools and approaches to meet these proposed levels of risk management. One can easily envisage an IT approach that addresses each of these areas with specific solutions that enhance patient safety, yet creates important customer relationship management for the manufacturer who adopts these methods. The FDA has used an example to illustrate these tools or methods. Let us adopt the FDA example for the purposes of this discussion.

EXAMPLE: Because of potential harm and associated risk, no patient with Condition A should use Product B.

This example leads to the following FDA-stipulated objectives to achieve the goal, and the associated tools described by the FDA to meet the objectives:

Objective 1: Ensure that physicians are fully knowledgeable about withholding Product B from patients with Condition A.

Generic tools (FDA):

- educate physicians with product labelling, detailing continuing medical education (CME) or other methods;
- have physicians self-attest or be tested/certified that they possess appropriate knowledge;
- require documentation that Condition A is not present prior to prescribing and dispensing;
- limit prescribing only to registered practitioners who meet certain requirements including being skilled in recognising, treating and monitoring Condition A.

IT approach to address Objective 1:

An IT platform with education and verification tools more than meets this Objective. The steps are simple, economical and auditable. They reduce the risk for the manufacturer, the prescriber and (most importantly) the patient. Firstly, the manufacturer creates a Prescriber Education Module (PEM) detailing the information about the product and the contraindications for use in patients with Condition A. The multimedia, interactive module, hosted on the manufacturer's servers and data centre educates the physician, verifies physician understanding, signals

physician compliance via signature, provides for CME logging, and creates auditable 'certification' that the prescriber is qualified according to criteria stipulated by the manufacturer. The manufacturer may then limit product access to only qualified prescribers and share the information with qualified dispensing pharmacists (if applicable). Moreover, the 'survey' element of patient education closes the loop that requires documentation that Condition A is not present before a prescription is issued to a specific patient. All information delivery, exchange, documentation and reporting is private, secure, electronic and web-based.

Objective 2: Create patients who are fully knowledgeable that Condition A is contraindicated with Product B and are able to help their prescriber know if they have Condition A.

Generic tools (FDA):

- educate patients and provide self-assessment materials about Condition A and its contraindications with Product B;
- provide prescribers with a checklist that actively solicits patient history or symptoms consistent with Condition A.

IT approach to address Objective 2:
The previously discussed IT-based CRIC attributes are directly transferable to Product Informed Consent (PIC), with the following immediate benefits:

- patients are educated, with verified understanding of the specific benefits and risks of the product;
- built-in customised surveys or checklists gather information that the prescriber needs to ascertain patient status relative to a specific contraindication (e.g. Condition A);
- patients may pose questions and concerns directly to the prescribing doctor, even when the education session occurs at home;
- patient acknowledgement and/or consent to product use can be captured in the form of a digital signature;
- all sessions are logged and archived;
- the web-based tools are private and secure;
- enrolment in a registry (if so stipulated by the manufacturer) is automatic and establishes the requisite connectivity for subsequent tracking (if so stipulated by the manufacturer);
- the report of patient knowledge, verification of status relative to Condition A, and online validated prescription (if criteria are met) for Product B is available online and at any time to doctors and/or licensed pharmacists.

Digital signatures can be used to confirm patient education and consent to product use

Online availability of information means it can be easily accessed by doctors/pharmacists whenever necessary

Objective 3: Pharmacists or hospitals must be able to confirm that a patient with a Product B prescription does not have Condition A.

Generic tools (FDA):

- provide education materials and training of pharmacists or hospital personnel to ask patients if they have Condition A;
- have the pharmacist or nurse check for documentation from the prescribing physician that Condition A is absent in a given patient;
- have the pharmacist or nurse check pharmacy or hospital records for evidence that Condition A is likely to be present.

IT approach to address Objective 3:
The solutions to this Objective have already been described. Firstly, pharmacists or doctors who intend to dispense Product B should avail themselves of the PEM described in the approach to address Objective 1. Secondly, the patient education, data acquisition, response and consent elements of the PIC module and the online attestation of the prescriber that the patient is free of Condition A, plus the online prescription, coupled with pharmacist's (or doctor's or nurse's) access to the information online with documentation of the dispensation of Product B, creates a seamless, electronically assisted process that serves as a product risk management system (PRMS) for any given product.

Furthermore, the IT-based PRMS creates the easy addition of a tracking function, because authorised and authenticated access to reporting (as stipulated by the manufacturer and/or FDA) is always available via the Internet to doctor, pharmacist, nurse and patient. This solves mobility problems and creates a permission-based connectivity whereby the manufacturer can proactively seek outcome data or customer (doctor, patient, pharmacist, nurse) satisfaction indices.

A tracking function can be easily added to an IT-based PRMS

Summary

An IT-based PRMS extends the interventions and tools now being used in FDA and other regulatory agencies' required risk management programmes. An IT-based PRMS can provide:

- generalised education and outreach to health professionals and consumers/patients, with documentation of understanding and acquisition of critical data impacting use decisions;
- systematised guidance for the circumstances of individual prescribing, dispensing and/or product use (such as patient informed consent, certification programmes for practitioners, and records documenting that safety measures have been satisfied);
- restricted access capabilities designed to enforce individual compliance with programme elements (such as prescribing only by 'certified' physicians, dispensing only by 'certified' pharmacists, and dispensing only to patients with documented safe use conditions).

In addition, the electronic infrastructure of an IT-based PRMS creates economy and certainty unavailable in paper-based counterpart systems, as well as long-term tracking opportunities with full privacy and security that easily satisfied HIPAA and EU Privacy Directive requirements.

Product support and product risk management, along with relationship management between manufacturers and the health professionals who prescribe and dispense products and the patients who use a product in treatment, need not be disparate exercises. Information tools embodied in an IT-based PRMS create efficient, auditable means for the manufacturer to reduce costs, reduce liability risk, and improve the marketing of valuable medical products.

Dr Terry Knapp is a pioneer in the use of IT-based informed consent for privacy and management of personalised healthcare information, and has designed and conducted clinical trials in the US and Europe. Dr Knapp, a Stanford trained surgeon, invented, developed and deployed the first global transponder-based implantable device registry, tracking, post-market surveillance and adverse event reporting informatics system, creating a risk-management-based IT solution to medical device tracking regulations. Dr Knapp currently serves as President and CEO of OrthoNetx, Inc., a device company that is also developing IT-based product risk management support systems.

POSITIONING MEDICAL DEVICES WHEN REIMBURSEMENT IS NOT AN OPTION (2)

By Nancy L Reaven

The Multi-tiered Approach

There is a structure and process to deploying a reimbursement strategy. Firstly, manufacturers should investigate the coverage, coding and payment issues that will provide opportunities or create challenges to their technologies. These issues should be investigated early, well before product launch, so that there is time to deal proactively with identified challenges. If there are identified risks to favourable coverage, coding and payment, the appropriate steps to address these challenges should be outlined and employed. These steps might include applying for new billing or procedure codes, developing alliances with specialty societies to educate decision makers about the benefits of the technologies and initiating studies that will address the areas of concern that may otherwise lead to disadvantageous reimbursement policies.

At the same time, manufacturers should investigate the ways that their technologies are likely to impact existing clinical processes and try to anticipate the resulting impact on provider processes and economics. By thinking about and conducting health economics research into these issues early, manufacturers are in a better position to:

- develop marketing messages that can impact perception about technologies well before they are launched into the market;
- incorporate economic variables into clinical trials, which when collected and analysed can have a profound impact on coverage and reimbursement policies;
- condition the market by publishing articles addressing the clinical and economic deficiencies associated with conventional approaches; *and*
- address the specific concerns of their customers before these concerns become a barrier to product adoption and sales.

Manufacturers can develop data and presentation tools to illuminate the financial impact of their technologies under realistic assumptions of coverage, coding and payment policies. By illustrating that technologies can provide clinical and economic value even under problematic or non-existent reimbursement, manufacturers can reassure their customers that technologies are worth buying and using. Various approaches and tools can be used to get this point across, including white papers, academic publications, budget-impact software models and case studies.

Examples of methods used to reassure customers that technologies are worth buying and using

However, the quality of the approach to demonstrate technology value is crucial to the success of this strategy. Poor study design, poor data or a focus on irrelevant issues can cause this approach to fail.

A quality approach is the key to success

Defining the Perspective

Before embarking on a value study, it is crucial to identify which perspectives need to be addressed and to target the outcomes that are meaningful to each constituency. As a general rule, if influencing coverage and reimbursement policy is the primary

goal then the perspective of an insurer, either Medicare, Medicaid or private insurance should be explicitly taken into account in study design. Insurers are interested in whether a new procedure/ technology contributes to improvements in clinical care or saves healthcare costs or, ideally, does both. By structuring a study to measure these elements, the resulting analysis is likely to have an impact.

Hospitals, on the other hand, are primarily interested in the impact of procedures/technologies on hospital operations, and are less interested in more widely drawn studies that might examine total healthcare resource utilisation and costs. Therefore, studies that focus on hospital operations, length of stay, service intensity, cost and market appeal will be viewed with more interest by hospitals.

Studies should be carefully targeted to address the needs of the primary decision-maker

Physicians are primarily interested in clinical improvements that are combined with time savings, practice efficiencies and the ability to reach more patients. Studies and data that address these issues are therefore the most appealing to physicians.

Finally, employers are interested in keeping employees healthy and in the state of their funded health benefit programmes. Thus, reductions in medical expenditures, sick days and injuries as well as increasing employee productivity are meaningful to employers.

From an employer's point of view, the main issues are...

The definition of 'outcomes' is a key component of the 'value' equation. For most new technologies, clinical equivalence to the accepted 'gold-standard' approach is the minimum acceptable standard. Most hospitals and insurers will not adopt a new technology if the clinical outcome is not at least as good as the conventional standard, even if the technology is less expensive or conveys other economic benefits. On the other hand, technologies that provide a significant clinical improvement, especially for very common or very expensive procedures or diseases, can sometimes get favourable coverage and reimbursement decisions with few challenges. For example, CMS made an unprecedented move to issue coverage decisions for drug-eluting coronary stents even before final FDA clearance due to the perceived revolutionary nature of the technology. Most new technologies, however, are neither inferior nor are they revolutionary innovations. Rather, they represent incremental improvements to current approaches; they are less invasive, faster, less equipment intensive, facilitate access to smaller vessels or tortuous anatomy, have higher specificity/sensitivity etc. Some technologies improve the quality of life, but may have no economic benefits at all, or may increase costs. In order to determine which questions need to be answered by research into the value proposition, the relevant outcomes should be matched to the perspective of the customer or decision-maker.

The Definition of Value and Possible Metrics

In addition to being relevant to the primary perspective of the audience and focused on outcomes of interest to them, a technology can contribute to economic outcomes in different ways. The metrics used to measure value can include some or all of the following:

- clinical outcomes;
- hospital admissions;
- hospital length of stay;
- per procedure direct costs;
- facility efficiency (e.g. patient through-put);

- procedure-related complications/ medical errors;
- change in the use of supplies, drugs, equipment and laboratory tests;
- procedure time;
- number of physician visits and/or number of specialty referrals;
- number of sick days;
- workers compensation and/or disability claims;
- Quality-Adjusted Life Years;
- cost-effectiveness;
- marketing appeal;
- reduction in legal liability.

As manufacturers consider studies and analyses to develop a 'value' equation, the metrics used should be carefully selected to ensure that they are relevant and meaningful to the ultimate customer. A study using Quality-Adjusted Life Years as the primary variable being measured may be interesting to a hospital, but a study using hospital admissions and length of stay as the primary variables may be much more compelling.

Conclusion

An analysis of the reimbursement landscape will identify the opportunities and challenges in the fundamentals of reimbursement: insurance coverage, coding and payment. Once these opportunities and challenges are known, technology manufacturers should launch simultaneous strategies designed to change the reimbursement decision that is contributing to the problem, if such change is possible, while building a 'value' story that is strong on data and evidence, is targeted to the right audience, is accommodating of their perspective and focuses on outcomes and measurements that are meaningful to them.

Identify opportunities and challenges in insurance coverage, coding and payment

Nancy L Reaven is President of Strategic Health Resources, a consulting and information technology firm providing support to medical technology, pharmaceutical and biotechnology companies in the areas of reimbursement positioning, health economics and 'value analysis' of medical technology.

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Denmark's Authorisation Scheme for Human Tissues & Cells

European Directive 2004/23/EC, which sets standards for the quality and safety of the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, is due to be transposed into Danish legislation by 7 April 2006. Centres responsible for the management of human tissues and cells for subsequent use in humans must now apply to the Danish Medicines Agency for authorisation of these activities[1].

Reference

1. Danish Medicines Agency website, 17 January 2005.

MDD Revisions

A draft revision of the Medical Device Directive (MDD, 93/42/EEC), dated 1 October 2004, has been prepared by the European Commission. This text is still very much a 'work in progress' and may yet be amended before it is submitted to the European Parliament and the Council as a proposed Directive, which is scheduled to take place in the spring of 2005. Proposed changes of note include:

- addition of a clear definition of the term 'clinical data' and clarification of the role of, and need for, clinical evaluations and post-marketing follow-up;
- introduction of a database for clinical investigations that will be accessible by the Competent Authorities to enable them to effectively share information about clinical investigations;
- amendments to the section concerning the classification of borderline products, including deletion of the text stating that personal protective equipment is not covered by the MDD;
- addition of a list of information that will not be treated as confidential (e.g. information on the registration of persons responsible for placing devices on the market, Competent Authority vigilance reports, and data relating to certificates issued, modified, supplemented, suspended, withdrawn or refused);
- inclusion of a mechanism to permit electronic labelling of medical devices;
- clearer requirements for Notified Bodies to sample technical documentation across the range of CE marked devices during quality assurance conformity assessments;
- amendment of the definition of 'central circulatory system' to include 'aorta descendens to the bifurcatio aortae'.

A copy of the draft revision document can be downloaded from the Internet at www.qualityfirstint.com/info_center/links.htm.

Devices Utilising Animal Tissues

A correction[1] to Directive 2003/32/EC concerning medical devices utilising tissues of animal origin[2] has been published in the *Official Journal of the European Union*. The corrigendum affects the first paragraph of Article 5(4) of the Directive and replaces '…the tissues or the derivatives intended to be incorporated in the medical device…' with '…the tissues or the derivatives intended to be utilised in the medical device…'.

References

1. *Official Journal of the European Union*, 2005, **L6**, 10 (8 January 2005).
2. *Official Journal of the European Union*, 2003, **L105**, 18 (26 April 2003).

Electromagnetic Compatibility Directive

A revised Directive on electromagnetic compatibility (EMC) was published in the Official Journal on 31 December 2004[1]. The Directive simplifies the regulatory procedures covering EMC and reduces the costs for manufacturers, yet increases the information and documentation on products available for use by the inspection authorities.

Directive 2004/108/EC removes two cumbersome conformity assessment procedures that required the mandatory involvement of an independent inspection and verification body, thereby reducing costs for manufacturers. The onus is now on manufacturers to establish the conformity of their products and for correctly affixing the CE mark.

The revised Directive repeals Directive 89/336/EEC of 3 May 1989[2] and will come into force in the Member States within the next three years.

References

1. *Official Journal of the European Union*, 2004, **L390**, 24 (31 December 2004).
2. *Official Journal of the European Communities*, 1989, **L139**, 19 (23 May 1989), as amended.

Data Protection

A new set of standard contractual clauses that can be used by businesses to ensure adequate protection for personal data when they are transferred from the EU to non-EU countries has been approved by the European Commission[1]. Standard contractual clauses provide companies with a simple method of complying with the requirements of the EU Data Protection Directive of 1995[2] and this is the third set of clauses to be made available since the Directive came into effect in 1998.

The new clauses, particularly those concerning litigation, allocation of responsibilities or auditing requirements, are considered to be more business-friendly whilst still offering a similar level of data protection. However, in an effort to prevent abuses, data protection authorities have been given more powers to intervene and impose sanctions where necessary.

Data transfer to Argentina, Canada, Guernsey, the Isle of Man, Switzerland, and US companies that adhere to the 'Safe Harbor' Privacy Principles do not require use of contractual clauses as the Commission recognises that the systems in place in these countries offers adequate data protection.

References

1. *European Commission Press Release*, IP/05/12, 7 January 2005.
2. Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data. *Official Journal of the European Communities*, 1995, **L281**, 31 (23 November 1995).

Mammography Equipment in France

A Decision[1] has been published concerning the prohibition of the marketing, application and use of certain medical devices intended for the production and interpretation of analogue mammography prints. Only devices that fulfil the requirements specified in the Decision may be marketed and used in France.

Reference

1. *Décision du 26 novembre 2004 portant interdiction de la mise sur le marché, de la mise en service, de l'utilisation de certains dispositifs médicaux destinés à la réalisation et à l'interprétation de clichés de mammographie analogique*. *Journal Officiel de la République Française*, No 299, 24 December 2004.

In Vitro Diagnostics: New French Regulations

A total of six new Regulations affecting *in vitro* diagnostic medical devices (IVDs) in France have been issued. These cover:

- the IVDs that are in List A and List B, as mentioned in Article R.5221-6 of the Public Health Code[1];
- conditions for the application of the Essential Requirements for IVDs, as defined in R.5221-15 and -16 of the Public Health Code[2];
- the procedures that must be in place to prove conformity of an IVD with the Essential Requirements[3];
- the procedure for applying for authorisation to conduct evaluations of IVDs for compliance with the Essential Requirements, and the content of the application dossier[4];
- obligations that must be met by organisations that perform evaluations of IVDs for compliance with the Essential Requirements[5];
- the form and dimensions of the CE mark being placed on an IVD, its packaging and instructions for use before it is placed on the market[6].

References

1. *Arrêté du 9 novembre 2004 fixant les listes de dispositifs médicaux de diagnostic in vitro mentionnées à l'article R. 5221-6 du code de la santé publique*. *Journal Officiel de la République Française*, No 280, 2 December 2004.
2. *Arrêté du 9 novembre 2004 précisant les conditions de mise en oeuvre des exigences essentielles de santé et de sécurité applicables aux dispositifs médicaux de diagnostic in vitro et définies aux articles R. 5221-15 et R. 5221-16 du code de la santé publique*. *Journal Officiel de la République Française*, No 280, 2 December 2004.
3. *Arrêté du 9 novembre 2004 précisant les modalités d'application des procédures définies aux articles R. 5221-23 à R. 5221-28 du code de la santé publique et relatives à l'évaluation de la conformité des dispositifs médicaux de diagnostic in vitro aux exigences essentielles de santé et de sécurité*. *Journal Officiel de la République Française*, No 280, 2 December 2004.
4. *Arrêté du 9 novembre 2004 fixant le contenu du dossier de demande d'habilitation prévue à l'article R. 5211-54 du code de la santé publique pour la mise en oeuvre des procédures d'évaluation de conformité des dispositifs médicaux de diagnostic in vitro aux exigences essentielles de santé et de sécurité*. *Journal Officiel de la République Française*, No 280, 2 December 2004.
5. *Arrêté du 9 novembre 2004 fixant les conditions d'application de l'article R. 5211-56 du code de la santé publique relatif aux obligations des organismes habilités à mettre en oeuvre les procédures d'évaluation des dispositifs médicaux de diagnostic in vitro*. *Journal Officiel de la République Française*, No 280, 2 December 2004.
6. *Arrêté du 9 novembre 2004 précisant la forme et les dimensions du marquage CE devant être apposé sur les dispositifs médicaux de diagnostic in vitro avant leur mise sur le marché ainsi que sur leurs emballages commerciaux et leurs notices d'utilisation*. *Journal Officiel de la République Française*, No 280, 2 December 2004.

Germany's Second DRG Amendment Law Compromise

At the end of November 2004, the arbitration committee between the upper house of the German parliament (the *Bundesrat*) and the lower house (the *Bundestag*) finally issued a decision that the DRG [diagnosis related group] reforms should include a new innovation clause for local coverage of new technologies[1]. This move was welcomed by BVMed, the German medical technology association, and Germany's reimbursement system will now be adapted to reflect the challenges arising from demographic development and medical advancement through medical technology. The draft of the *2nd DRG Amendment Law* had been approved by the German Federal Cabinet in August 2004[2].

References

1. *BVMed Press Release*, 2004, No 22, 1 December 2004.
2. *Journal of Medical Device Regulation*, 2004, **1**(1), 51.

Irish Guidance on Adverse Incident Reporting for IVDs

The Irish Medicines Board (IMB) has issued guidance to manufacturers and users on the adverse incident reporting requirements that apply specifically to *in vitro* diagnostics (IVDs)[1]. The document covers, *inter alia*, what to report, how to report it and the role of manufacturers, distributors, users and the IMB in adverse incident reporting.

Reference

1. IMB Guidance Note 18: *Guidance Note on Adverse Incident Reporting for In-vitro Diagnostic Medical Devices*, Revision 0, 17 December 2004.

Devices Containing Tissue of Animal Origin in Portugal

In Portugal, manufacturers of medical devices that fall within the scope of Directive 2003/32/EC have an additional six months in which to have their EC design-examination certificates or EC type-examination certificates re-evaluated in accordance with the requirements of this Directive[1]. Directive 2003/32/EC was transposed in to Portuguese law by Decree Law No 129 of 1 June 2004.

Directive 2003/32/EC[2] sets out detailed specifications relating to risks of transmitting transmissible spongiform encephalopathies under normal conditions of use to patients or others via medical devices manufactured using animal tissue that is rendered non-viable, or non-viable products derived from animal tissue. Article 7 of the Directive describes the transition periods for implementation and gives the date of 30 September 2004 as the date by which all applicable medical devices with EC design-examination certificates or EC type-examination certificates that were issued before 1 April 2004 should have had them re-evaluated. However, delays by many Member States in transposing the Directive and designating suitable Notified Bodies caused the European Commission to request some flexibility from Member States with respect to this deadline.

INFARMED, the Competent Authority for medical devices in Portugal, has provided applicable manufacturers whose re-evaluation process has not been completed with an additional six months in which to comply. However, to be able to take advantage of this extension, manufacturers must submit a request to INFARMED to keep their product on the market. Details of what this request should contain are specified in the Circular.

References

1. *INFARMED Circular*, No 128/CA, 26 November 2004.
2. Commission Directive 2003/32/EC of 23 April 2003 introducing detailed specifications as regards the requirements laid down in Council Directive 93/42/EEC with respect to medical devices manufactured utilising tissues of animal origin. *Official Journal of the European Union*, 2003, **L105**, 18 (26 April 2003).

Payments to Slovak Republic's SÚKL

Since 1 January 2005, any payments submitted to the State Institute for Drug Control in the Slovak Republic (SÚKL) should be made to their new bank accounts. For domestic payments, the bank account number is 7000133673/8180. For payments from foreign countries, the IBAN is SK3481800000007000133673 and the SWIFT (BIC) is NBSBSKBX.

Swiss Information on Use of High Energy Lasers

Recommendations and requirements concerning the correct application of high-energy lasers in medicine and cosmetics have been issued by SwissMedic[1]. This information takes into account the new regulations on the use of high-energy lasers that came into force on 1 September 2004[2] and supersedes the recommendations provided by the former *Fachstelle Medizinprodukte* of the *Budesamtes für Gesundheit*, dated 29 September 1997[3].

References

1. *Anwendung von hochenergetischen Lasern in Medizin und Kosmetik*, SwissMedic, December 2004.
2. *Journal of Medical Device Regulation*, 2004, **1**(1), 53.
3. *Risiken der Laserbehandlung in Medizin und Kosmetik*. *BAG Bulletin*, No 38, 29 September 1997.

Guidance on Medical Weighing Machines Issued in Switzerland

SwissMedic has released a document that provides guidance on how to determine which regulations apply to a particular medical weighing machine[1]. On 1 May 2004, the Swiss transposition[2] of Directive 90/384/EEC on non-automatic weighing instruments[3] came into force; however, many weighing machines can also be considered to be medical devices, falling under the requirements of the *Medizinprodukteverordnung*[4] (which transposed Directive 93/42/EEC). This guidance document lists a number of possible uses of weighing machines and then states which regulation(s) apply in each case.

References

1. *Inverkehrbringung von medizinischen Personenwaagen*, SwissMedic, 4 November 2004.
2. SR 941.213, 16 April 2004.
3. Council Directive of 20 June 1990 on the harmonisation of the laws of the Member States relating to non-automatic weighing instruments. *Official Journal of the European Communities*, 1990, **L189**, 1 (20 July 1990), as amended.
4. SR 812.213, 17 October 2001.

Medical Device Alerts Issued by UK MHRA

The UK Medicines and Healthcare products Regulatory Agency (MHRA) has issued three general Medical Device Alerts:

MDA/2005/005 - Wheelchairs used on vehicle mounted passenger lifts (13 January 2005)

This Alert draws attention to the need for adequate policies and procedures to be in place to ensure that wheelchair users entering or leaving a vehicle using a passenger lift do so in accordance with the manufacturer's instructions for use and the principles specified in the Medical Devices Agency's Device Bulletin DB2003(03) - *Guidance on the use of wheelchair and vehicle mounted passenger lifts*. All staff, wheelchair users and others should receive adequate training, and the effectiveness of this training should be reviewed on a regular basis.

MDA/2005/002 - Wheelchairs, seating and accessories (4 January 2005)

Failure to adhere to the manufacturer's instructions for use, or inappropriate or inadequate maintenance, have been identified as the causes of several incidents resulting in the death or serious injury of wheelchair users. The MHRA has called for all personnel involved in the provision, prescription, repair, maintenance and use of wheelchairs, seating and accessories to ensure that:

- the most recent copies of the instructions for use and maintenance information are readily available;
- a copy of the instructions for use is passed on to users each time a device is issued;
- maintenance is always performed in accordance with the manufacturer's instructions and the principles described in the Medical Devices Agency's Device Bulletin DB2000(02) - *Medical Devices and Equipment Management: Repair and Maintenance Provision*;
- reporting procedures are in place if a problem arises, including any problems arising from inadequacies in the manufacturer's instructions.

MDA/2005/001 - Reporting Adverse Incidents and Disseminating Medical Device Alerts (4 January 2005)
This document describes what is meant by 'adverse incident' and outlines the procedures for reporting them. It also provides a summary of the dissemination process for Medical Device Alerts and of the roles played by a Safety Alert Broadcast System Liaison Officer and Medical Device Liaison Officer. Printable incident report forms and electronic forms for on-line reporting are available on the MHRA website (www.mhra.gov.uk).

UK Healthcare Industries Task Force

The Healthcare Industries Task Force (HITF) was established by the UK government and the medical device industry in order to bring innovative medical devices and procedures to the market to benefit patients and the National Health Service (NHS) and stimulate investment in the UK economy. In November 2004, HITF published its first report[1] that outlined an ambitious work programme to achieve these aims, including:

- modernising the Device Evaluation Service and transferring its management to the NHS Purchasing and Supply Agency with effect from 1 April 2005;
- creating an Innovation Centre to stimulate and promote innovation in the NHS;
- establishing pilot Healthcare Technology Co-operatives at academic centres of excellence to pioneer specialist treatments and techniques;
- increasing research and development capacity for medical devices through UK Clinical Research Collaboration;
- improving the training and education received by NHS staff on the use of medical devices;
- ensuring that the UK's influence on European and international regulatory matters is maximised;
- setting up a focused export strategy for the UK healthcare sector;
- ensuring procurement is done in a more informed and efficient manner;
- providing patients and the general public with better information on the value of healthcare products in everyday life;
- implementing a new data collection system to gain a clearer picture of the healthcare industry and its performance.

Reference

1. *Better health through partnership: A programme for action*, HITF final report, November 2004.

Reclassification of Two Embolisation Devices

The following two embolisation devices have been reclassified from Class III (premarket approval) to Class II (special controls) and have had their names and identifications revised[1]:

- vascular embolisation devices (previously arterial embolisation devices), which are intended to control haemorrhaging due to aneurysms, certain types of tumours and arteriovenous malformations;
- neurovascular embolisation devices (previously artificial embolisation devices), which are intended to permanently occlude blood flow to cerebral aneurysms and cerebral arteriovenous malformations.

A proposed rule to change the names, revise the identifications and reclassify these devices was issued in February 2004. As no adverse comments were received, the rule was finalised and came into force on 28 January 2005.

A document entitled *Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Vascular and Neurovascular Embolization Devices* has been designated as the special control for these devices[2] as the Food & Drug Administration considers that it will, along with general controls, provide a reasonable assurance of the safety and effectiveness of these devices.

References

1. *Federal Register*, 2004, **69**(249), 77898 (29 December 2004).
2. *Federal Register*, 2004, **69**(249), 78038 (29 December 2004).

External Penile Rigidity Devices: Classification

The Food & Drug Administration (FDA) is classifying external penile rigidity devices intended to create or maintain sufficient penile rigidity for sexual intercourse into Class II (special controls) and is exempting them from the premarket notification requirements. No comments were received on the proposed rule of 17 March 2004 so a final rule[1] was issued in December 2004, which became effective on 27 January 2005. Manufacturers of these devices will need to demonstrate that the devices meet the recommendations of the *Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: External Penile Rigidity Devices*[2] or in some other way provide equivalent assurances of safety and effectiveness.

References

1. *Federal Register*, 2004, **69**(248), 77621 (28 December 2004).
2. *Federal Register*, 2004, **69**(248), 77757 (28 December 2004).

Assisted Reproduction Laser Systems: Classification

Assisted reproduction laser systems have been classified into Class II (special controls) following issuance of a final rule[1] that became effective on 27 January 2005. In determining this classification, the Food & Drug Administration (FDA) identified four possible risks to health associated with use of the device:

- damage to the embryo;
- ineffective treatment;
- hazards associated with electrical equipment; *and*
- electromagnetic interference and electrostatic discharge hazards.

The special controls guidance document[2] entitled *Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Assisted Reproduction Laser Systems* describes measures that, if followed by manufacturers and combined with the general controls, will generally address the risks associated with these laser systems and lead to a timely review and clearance of the premarket notification.

The assisted reproduction laser system is defined as 'a device that images, targets, and controls the power and pulse duration of a laser beam used to ablate a small tangential hole in, or to thin, the zona pellucida of an embryo for assisted hatching or other assisted reproduction procedures'.

References

1. *Federal Register*, 2004, **69**(248), 77623 (28 December 2004).
2. *Federal Register*, 2004, **69**(248), 77756 (28 December 2004).

Clinical Chemistry and Clinical Toxicology Devices: Classification

A final rule classifying newborn screening test systems for amino acids, free carnitine and acylcarnitines using tandem mass spectrometry into Class II (special controls) came into force on 27 December 2004[1]. The special control that will apply to these devices is a guidance document entitled *Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Newborn Screening Test Systems for Amino Acids, Free Carnitine, and Acylcarnitines Using Tandem Mass Spectrometry*[2].

A newborn screening test system for amino acids, free carnitine and acylcarnitines using tandem mass spectrometry is defined as 'a device that consists of stable isotope internal standards, control materials, extraction solutions, flow solvents, instrumentation, software packages, and other reagents and materials. The device is intended for the measurement and evaluation of amino acids, free carnitine, and acylcarnitine concentrations from newborn whole blood filter paper samples. The quantitative analysis of amino acids, free carnitine, and acylcarnitines and their relationship with each other provides analyte concentration profiles that may aid in screening newborns for one or more inborn errors of amino acid, free carnitine, and acylcarnitine metabolism'.

The Food & Drug Administration does not believe that these screening test systems pose any direct risk to human health. However, the Agency has identified that a failure of the test to perform as indicated or an error in the interpretation of the results could lead to an indirect risk of improper medical management of patients with inborn metabolic errors. It is considered that the designated special controls guidance document, along with general controls, will address these indirect risks in order to provide a reasonable assurance of the safety and effectiveness of the device.

References

1. *Federal Register*, 2004, **69**(226), 68254 (24 November 2004).
2. *Federal Register*, 2004, **69**(226), 68383 (24 November 2004).

General Hospital and Personal Use Devices: Classification

On 10 January 2005, a final rule[1] took effect classifying implantable radiofrequency transponder systems for patient identification and health information into Class II (special controls). The final rule also exempted these devices from premarket notification requirements.

The Food & Drug Administration (FDA) identified a number of potential health risks associated with the use of these devices, namely:

- adverse tissue reaction;
- migration and/or failure of the implanted transponder;
- compromised information security;
- failure of an inserter and/or an electronic scanner;
- electromagnetic interference, electrical hazards and/or magnetic resonance imaging incompatibility;
- needle stick injuries.

The special controls guidance document[2] entitled *Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Implantable Radiofrequency Transponder System for Patient Identification and Health Information* is intended to help minimise the risks identified above by identifying suitable performance and safety testing, and appropriate labelling.

References

1. *Federal Register*, 2004, **69**(237), 71702 (10 December 2004).
2. *Federal Register*, 2004, **69**(237), 71821 (10 December 2004).

Withdrawn Proposed Rules

With effect from 26 November 2004, the Food & Drug Administration has withdrawn[1] a number of old and outdated proposed rules, proposed actions and advanced notices of proposed rulemakings. This action has been taken to reduce the Agency's regulatory backlog and to allow it to focus its efforts on current public health issues. The withdrawals that are relevant to the medical device industry are:

- Color Additives; Proposed Use of Abbreviations for Labeling Foods, Drugs, Cosmetics, and Medical Devices (*Federal Register*, 1985, **50**, 23815);
- Medical Devices; Classification of Sponges for Internal Use (*Federal Register*, 1978, **43**, 55697);
- Medical Devices; Classification of Powered Myoelectric Biofeedback Equipment (*Federal Register*, 1979, **44**, 50464);
- Porcine Burn Dressing (*Federal Register*, 1982, **47**, 2828);
- Neurological Devices, Proposed Rule to Reclassify the Electroconvulsive Therapy Device Intended for Use in Treating Severe Depression (*Federal Register*, 1990, **55**, 36578);
- Hematology and Pathology Devices; Premarket Approval of the Automated Blood Cell Separator Intended for Routine Collection of Blood and Blood Components (*Federal Register*, 1988, **53**, 5108);
- Current Good Manufacturing Practice for Blood and Blood Components; Proficiency Testing Requirements (*Federal Register*, 1989, **54**, 24296);
- Cardiovascular Devices; Effective Date of Requirement for PMA of Nonroller-Type Cardiopulmonary Bypass Blood Pump (*Federal Register*, 1993, **58**, 36290);
- Metric Labeling; Quantity of Contents Labeling Requirements for Foods, Human and Animal Drugs, Animal Foods, Cosmetics, and Medical Devices (*Federal Register*, 1993, **58**, 67444);

- Dental Devices; Effective Date of Requirement for Premarket Approval of Over-the-Counter (OTC) Denture Cushions or Pads and OTC Denture Repair Kits (*Federal Register*, 1995, **60**, 35713);
- Dental Devices; Effective Date of Requirement for Premarket Approval of Partially Fabricated Denture Kits (*Federal Register*, 1995, **60**, 61232).

Reference

1. *Federal Register*, 2004, **69**(227), 68831 (26 November 2004).

HDEs, Special Controls & Environmental Assessment Exclusions

A proposed rule[1] to add two further categorical exclusions to the regulation on environmental impact considerations has been issued by the Food & Drug Administration (FDA). The proposed exclusions are for humanitarian device exemptions (HDEs) and the establishment of special controls as the FDA believes that neither of these actions, either individually or cumulatively, have a significant impact on the environment and therefore do not require an environmental assessment or an environmental impact statement. The special controls exclusion will only apply if the action will not result in an increase in the existing levels of use of the device or changes in the intended use of the device or its substitutes. The period for submitting comments on this proposed rule expired on 27 December 2004.

Reference

1. *Federal Register*, 2004, **69**(226), 68280 (24 November 2004).

Reclassification of Iontophoresis Devices

Interested parties have been given the opportunity to comment[1] on the Food & Drug Administration's (FDA's) intent to initiate proceedings to reclassify those iontophoresis devices currently in Class III (premarket approval) into Class II (special controls). Once the FDA has reviewed any comments, it will decide whether to proceed with the reclassification and also whether a panel meeting will be necessary before any action is taken.

The FDA did propose an amendment to the physical medicine devices regulations back in August 2000 to remove the Class III iontophoresis device identification but this proposed rule was withdrawn on 4 November 2004[2] following the substantial comments the Agency received on the subject.

Iontophoresis devices are intended to use a direct current to introduce ions of soluble salts or other drugs into the body and induce sweating for diagnostic or other uses. If the device is intended for use in the diagnosis of cystic fibrosis or another intended use, and the labelling of the drug intended for use with the device bears adequate directions for the device's use with that drug, then the device is classified into Class II (special controls). An iontophoresis device that is intended for any other purpose is classified as Class III (premarket approval).

References

1. *Federal Register*, 2004, **69**(213), 64313 (4 November 2004).
2. *Federal Register*, 2004, **69**(213), 64266 (4 November 2004).

Reprocessed Single-Use Devices

The Food & Drug Administration (FDA) has determined that many reprocessed medical devices originally intended for single-use only (SUDs) may no longer be commercially distributed in the USA[1]. Under the *Medical Device User Fee and Modernization Act of 2002,* reprocessors of certain types of previously cleared reprocessed SUDs were required to submit additional cleaning, sterility and functionality validation data to the FDA so that the Agency could determine if these devices should continue to be legally marketed.

The FDA completed its review on 2 November 2004 and of the 44 supplemental validation submissions (SVSs) received, 11 were considered to be Not Substantially Equivalent or were withdrawn by the reprocessor after submission and therefore can no longer be legally marketed. A total of 19 SVSs were found to be Substantially Equivalent and may continue to be marketed, 12 SVSs were deemed to be Substantially Equivalent for some models, and two are still awaiting a final decision.

Follow-up inspections will be performed by the Agency to ensure that the companies affected by this review comply with the determinations. Enforcement action will be initiated if necessary.

Reference

1. *FDA Talk Paper - FDA Completes Review of Reprocessed Single Use Devices*, T04-48, 2 November 2004.

MDTCA/MDUFMA Summaries Available

A document summarising the changes made by the *Medical Devices Technical Corrections Act* (MDTCA) to the *Medical Device User Fee and Modernization Act of 2002* (MDUFMA) was issued by the Food & Drug Administration in November 2004. The document provides a detailed explanation of the changes made to MDUFMA in three main areas:

- provisions for third-party inspections;
- expansion of the provision for electronic labelling;
- postponement of the effective date of new section 502(u) of the *Federal Food, Drug & Cosmetic Act* until 26 October 2005, 18 months later than the original effective date.

A copy of this summary can be found at www.fda.gov/cdrh/mdufma/mdtcasummary.html.

In addition, the Agency has issued a MDUFMA summary document (dated November 2004), which includes the changes made by the MDTCA. A copy of this can be downloaded from www.fda.gov/cdrh/mdufma/mdufmasummary.html.

Guidance Documents - Final

Guidance for Industry - Cybersecurity for Networked Medical Devices Containing Off-the-Shelf (OTS) Software
Issued: 14 January 2005

Clarification is provided on how current regulations, including the *Quality System Regulation*, apply to cybersecurity maintenance activities. These maintenance activities should typically be performed throughout the lifetime of a networked medical device incorporating OTS software to ensure an adequate degree of protection against cybersecurity threats (e.g. viruses and worms).

Guidance for Industry and FDA Staff - Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems
Issued: 13 January 2005

This document serves two main purposes. Firstly, it provides the medical device industry with guidance on how to develop and apply non-clinical test protocols, test methods, test reports, and develop labelling to support the safety and effectiveness of intravascular stents and their associated delivery systems. Secondly, it provides guidance to FDA staff on how to review non-clinical test protocols, test methods, data, reports, and labelling submitted by sponsors in support of the safety and effectiveness of intravascular stents and their associated delivery systems. It supersedes the information provided on stent and delivery system testing provided in the draft document entitled *Carotid Stent - Suggestions for Content of Submissions to the Food and Drug Administration in Support of Investigational Devices Exemption (IDE) Applications*, which was issued in October 1996.

Guidance for Industry and FDA Staff - Clinical Data Presentations for Orthopedic Device Applications
Issued: 2 December 2004

This guidance document recommends general clinical data presentation formats for premarket notifications (510(k)s), investigational device exemption (IDE) annual progress reports, premarket approval applications (PMAs), and annual and post-approval study reports for orthopaedic implant devices. Its purpose it to help ensure consistency and understanding between the Food & Drug Administration and sponsors when discussing and presenting clinical data. The scope of the document does not extend to the presentation of preclinical data, nor does it describe all the elements required for 510(k)s, IDEs or PMAs.

Guidance for Industry and FDA Staff - Use of Symbols on Labels and in Labeling of In Vitro Diagnostic Devices Intended for Professional Use
Issued: 30 November 2004

Guidance is provided on the use of 25 selected graphical symbols from ISO 15223 and EN 980 that may be used in place of text to convey some of the information required by the Food & Drug Administration's (FDA's) labelling requirements for *in vitro* diagnostics (IVDs) intended for use by healthcare professionals only. The only significant amendment from the draft guidance issued in October 2003 is deletion of the statement in section III where the FDA had proposed to exercise enforcement discretion if a company used the symbol for 'manufacturer' to satisfy §610.64 as it no longer believes this symbol is applicable to §610.64.

Guidance for Industry and FDA Staff - Resolution of Disputes Concerning Payment or Refund of Medical Device User Fees Under MDUFMA [*Medical Device User Fee and Modernization Act of 2002*]
Issued: 17 November 2004

This document sets out the Food & Drug Administration's (FDA's) recommendations concerning the most timely and effective way to resolve disputes concerning FDA actions that affect the payment or refund of a user fee assessed under MDUFMA. The guidance covers the following topics:

- internal review through the supervisory chain under 21 CFR §10.75;
- recommended procedures for resolving disputes that affect payment or refund of medical device user fees in the form of questions and answers;
- sources of additional information.

Guidance for Industry and FDA Staff - Frequently Asked Questions (FAQs) on the Status of Reprocessed Single Use Devices (SUDs) that Receive a Not Substantially Equivalent (NSE) Letter
Issued: 8 November 2004

This document provides answers to the following commonly asked questions about reprocessed SUDs and NSE letters:

- What is an NSE letter and what does it mean if it pertains to a reprocessed SUD?
- Will the Food & Drug Administration (FDA) require reprocessors to recall a distributed device that is the subject of an NSE letter or a letter acknowledging withdrawal?
- Should a customer continue to use in-stock, reprocessed SUDs once the reprocessor can no longer distribute as a result of an NSE letter or a letter acknowledging withdrawal?
- Is there an FDA website that lists information about which reprocessed SUDs are no longer eligible for commercial distribution?
- What other information can I learn from the FDA's website about the status of reprocessed SUDs that were subject to supplemental data requirements?
- If I have additional questions, who can I contact?

Guidance for Industry and FDA Staff - Clinical Trial Considerations: Vertebral Augmentation Devices to Treat Spinal Insufficiency Fractures
Issued: 24 October 2004

The purpose of this guidance is to provide information relating to clinical studies that the Food & Drug Administration may recommend in support of premarket notification submissions for devices used in spinal vertebral body augmentation for the purpose of treating insufficiency fractures of the spinal vertebral body due to minor trauma, osteoporosis or other lytic conditions. Topics covered include clinical indications, surgical procedures, the clinical investigational plan and study monitoring.

Goods that are not Medical Devices in Australia

In accordance with subsection 41BD(3) of the *Therapeutic Goods Act 1989*, the following therapeutic goods are declared not to be medical devices:

'Topical applications intended to remove or neutralise chemical, biological or radiological agents used in chemical, biological or radiological warfare'[1].

Reference

1. *Therapeutic Goods (Articles that are not Medical Devices) Order No 2 of 2004*, 22 December 2004.

Tamper-Evident Packaging

A draft Therapeutic Goods Order (TGO) concerning tamper-evident packaging has been prepared and is expected to be gazetted in Australia in early 2005[1]. TGO 71 will adopt the document entitled *Code of Practice for the Tamper-Evident Packaging (TEP) of Therapeutic Goods* (Edition 1, June 2003) as a standard for therapeutic goods in Australia.

Reference

1. Therapeutic Goods Administration website, 15 December 2004.

Diagnostic Goods of Human Origin

The Australian Therapeutic Goods Administration (TGA) has decided not to proceed with its proposed revision of Therapeutic Goods Order (TGO) No 34 *Standard for Diagnostic Goods of Human Origin* to include *ex vivo* diagnostics[1]. The revision is no longer considered necessary as the introduction of new legislative requirements for *in vitro* diagnostics (IVDs), and human tissues and cellular therapies (which will include *ex vivo* products) is expected on 1 July 2005. Appropriate controls for *ex vivo* reagents will then be addressed through the new regulatory frameworks for human tissues and cellular therapies.

TGO 34 will continue to be the applicable standard for IVDs of human origin until the end of the transition period for introduction of the new IVD regulatory framework. Under the new framework, all IVDs will be required to comply with the Essential Principles for quality, safety and performance. The TGA is proposing that the European standard EN 13641: 2002, *Elimination or reduction of risk of infection related to in vitro diagnostic reagents*, be adopted as a standard that may be used to demonstrate compliance with the Essential Principles for viral safety of IVD reagents and that it will consequently supersede TGO 34. Any comments on the proposed adoption of this standard should be directed to Mrs Robyn Wood, Medical Device Assessment Section, Office of Devices, Blood & Tissues, TGA, PO Box 100 (MDP 100), WODEN ACT 2606, Australia (email: robyn.wood@health.gov.au).

Reference

1. Letter to stakeholders entitled *Revised Therapeutic Goods Order for Diagnostic Goods of Human Origin,* October 2004.

Australia's Prostheses Reimbursement Scheme

Reforms to the prostheses reimbursement scheme for privately insured patients were introduced into the Australian Parliament on 1 December 2004 by the Minister for Health and Ageing[1]. According to the Medical Industry Association of Australia,

the *National Health Amendment (Prostheses) Bill 2004* was cautiously welcomed by the device industry but concerns were raised over the fact that patients could face new 'out-of-pocket' costs for some procedures currently covered by private health insurance.

Reference

1. *Media Release - Cautious support of prostheses reforms*, Medical Industry Association of Australia, 1 December 2004.

Australian Classification Guidelines Published

A guidance document concerning the classification of medical devices was posted on the Australian Therapeutic Goods Administration website on 17 January 2005[1]. The document forms part of a series that is intended to improve general understanding of the regulatory system governing medical devices in Australia. This specific document provides guidance on the classification rules for medical devices and relates to the following sections of the medical device legislation:

- Section 41BD of the *Therapeutic Goods Act 1989*;
- Regulation 3.2 of the *Therapeutic Goods (Medical Devices) Regulations 2002*;
- Schedule 2 of the *Therapeutic Goods (Medical Devices) Regulations 2002*; *and*
- the Dictionary in the *Therapeutic Goods (Medical Devices) Regulations 2002*.

Reference

1. *Australian medical devices guidelines: 25. Classification of medical devices*, January 2005.

Draft TGA Fact Sheets

Two new draft medical device fact sheets were posted on the Australian Therapeutic Goods Administration (TGA) website on 5 November 2004 to provide the opportunity for comment by interested parties. The fact sheets cover:

- suspension and cancellation of medical devices; *and*
- offences, enforcement and the illegal supply of medical devices.

The three Fact Sheets that were issued in September 2004 have also been updated: *Class I Medical Devices*; *Manufacturers of Class I Medical Devices*; and *Using GMDN [Global Medical Device Nomenclature] Codes*.

Private Label Devices: Draft Canadian Guidance

Interested parties had until the end of January 2005 to submit comments on a draft guidance document that clarifies how private label manufacturers can meet their medical device licensing regulatory obligations[1]. The draft guidance applies to new and amended medical device licence applications submitted by private label manufacturers of Class II, III and IV medical devices.

'Private label manufacturer' is the name given to businesses that sell medical devices under their own name or trademark whilst having limited or no control over the *activities* covered by the definition of 'manufacturer' in the *Medical Devices Regulations*. However, private label manufacturers still fall within the definition of 'manufacturer' because they sell medical devices under their own name and the activities described in the definition are performed on their behalf. Therefore,

private label manufacturers and their devices are still subject to the requirements of the *Medical Devices Regulations*.

Reference

1. *Draft Guidance for Industry - Private Label Medical Devices*, 7 December 2004.

SBD and ND Documents for Devices Marketed in Canada

In a Notice dated 3 November 2004, the Health Products and Food Branch clarified its intention with respect to the production of Summary Basis of Decision (SBD) and Notice of Decision (ND) documents for certain medical devices placed on the market in Canada[1]. The devices covered by the scope of this action are new Class IV medical devices that relate to any one of the following:

- priority review applications;
- *in vitro* diagnostics for donor screening;
- cardiovascular devices with a novel technology (e.g. endovascular stenting systems);
- new indications for use for cardiovascular and neurological devices.

Other devices are expected to be phased in to the scope of this action over time.

SBD documents will summarise the scientific and regulatory reasons for Health Canada's decision to grant a marketing authorisation for a medical device. They will be prepared and published for all relevant device licence applications issued after 1 January 2005, and it is Health Canada's intention to publish SBDs within four months of authorisation for sale. Health Canada is also proposing to allow sponsors a two-week comment period prior to publication of each SBD to verify the accuracy of the data and identification of any proprietary material included.

The Notice also contains a proposal to publish ND documents at the time of issuance of a medical device licence to provide a brief summary of the authorisation received and general information about the product. The scope of application would be the same as that for SBDs.

Reference

1. *Health Products and Food Branch Proposals for Summary Basis of Decision (SBD) and Notice of Decision (ND) Documents: Devices*, 04-121869-138, 3 November 2004.

Health Canada's Safety Advice on Electrically Operated Beds

Hospitals, nursing homes and long-term care centres have been provided with safety information on beds with electric foot switches[1]. Health Canada has recommended that all relevant facilities should:

- immediately assess the need for electric foot switches and evaluate any design features that could minimise the risk (e.g. optical sensors that detect the presence of an object under the mattress deck);
- discuss any safety features with the bed's manufacturer;
- follow the manufacturer's instructions if a decision is made to deactivate the electric foot switch;
- leave the bed in its lowest position when a patient is left unattended;

- immobilise or lock the bed's height adjustment when cleaning;
- lock all electrical functions when moving a bed that has a battery;
- not purchase electrically operated beds unless safeguards have been built in to prevent accidental activation.

Similar action has also been taken in France and the UK[2].

References

1. Letter to Hospital Chief of Medical Staff, Nursing homes and Long term care centres, Health Canada, 12 January 2005.
2. *Journal of Medical Device Regulation*, 2004, **1**(1), 56.

Antimicrobial Agents Used on Devices in Canada

The *Standard for the Fabrication, Control and Distribution of Antimicrobial Agents for Use on Environmental Surfaces and Certain Medical Devices* (Guide-0049) has been updated and reissued. The document dated 1 December 2004 supersedes the July 2002 version and contains amendments associated with regulatory changes pertaining to these products. A copy of the new standard can be viewed on the Internet at www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate.

Chinese Device News

On 1 November 2004, the State Food & Drug Administration's (SFDA's) Department of Medical Devices released the 2005 edition of the *Classification Catalogue for Medical Devices* for public comment.

On 7 January 2005, the SFDA posted a notice on its website to say that the fourth, fifth and sixth issues of *National Medical Device Quality Announcement 2004* had been issued. At the same time, it announced the availability of related product quality sampling results.

Hong Kong's Medical Device Administrative Control System

The initial phase of the implementation of Hong Kong's new Medical Device Administrative Control System (MDACS) was launched on 26 November 2004. This phase allows for the voluntary listing of Class IV medical devices by manufacturers and importers with the Department of Health.

The listing of Class II and III medical devices, the listing of importers and local manufacturers, and the introduction of an adverse incident reporting system will follow in subsequent phases.

An *Application Form for Listing Class IV Medical Devices* (MD-C4) and an *Essential Principles Conformity Checklist* (MD-CCL) can be downloaded from the Internet at www.info.gov.hk/dh/useful/meddev/mdacs.htm. Additionally, two guidance documents have been issued:

- *Overview of the Medical Device Administrative Control System* (GN-01), which summarises the role of the MDACS, describes the role of a Local Responsible Person within the system and includes information on how to apply for a listing;
- *Guidance Notes for Listing Class IV Medical Devices* (GN-02), which provides detailed information on preparing an application submission for inclusion of a Class IV medical device into the MDACS's List of Medical Devices.

Background

A risk-based framework for regulating the supply of medical devices in Hong Kong was first proposed in July 2003 in a Consultation Document entitled *Regulation of Medical Devices*. This document stated that an administrative control system should be established whilst legislation is being enacted 'to facilitate the transition to the long-term statutory control'. Following a period of public consultation, the government decided in early 2004 to implement the proposed MDACS by phases, under the auspices of the Medical Device Control Office of the Department of Health.

It is hoped that the introduction of medical device listing and monitoring of adverse incidents will help to raise the public's awareness of the use of safe medical devices and 'enable the traders to familiarise themselves with the future mandatory requirements' and 'provide an opportunity to collect more information and feedback from the industry as a reference to fine tune the long-term regulatory framework'.

Free Trade Agreements

A Free Trade Agreement between the USA and Australia entered into force on 1 January 2005 meaning that more than 99% of US manufactured goods exported to Australia immediately became duty free. The Agreement opens markets and streamlines mutual access between the two countries in the areas of intellectual property, services, government procurement, e-commerce and investment, with the potential to increase trade by billions of dollars.

It was announced in December 2004 that New Zealand, Australia and the Association of South East Asian Nations (ASEAN) are to start negotiations towards a Free Trade Agreement. According to New Zealand Prime Minister Helen Clark, an agreement would be 'a significant trade breakthrough and an opportunity to build closer links with our ASEAN neighbours'.

Kazakhstan Joins IEC

In November 2004, Kazakhstan progressed from being a participant in the International Electrotechnical Commission's (IEC's) Affiliate Country Programme to the position of Associate Member. This brings IEC's total membership to 63 countries.

As an Associate Member, Kazakhstan may now participate in all IEC technical meetings and other meetings held within the framework of the annual general meeting. It will also have access rights and be able to comment on all IEC technical documents. Additionally, it may submit a request to become a participating member on a maximum of four technical committees and/or sub-committees with the right to vote on technical work emanating from these chosen committees.

EC/US MRA - Electromagnetic Compatibility

A new EC Conformity Assessment Body concerned with electromagnetic compatibility has been designated under the Mutual Recognition Agreement (MRA) between the EC and the USA[1]. DARE Consultancy BV from the Netherlands has been added to the list of Conformity Assessment Bodies under the column 'EC access to the US market' in Section V of the Sectoral Annex on Electromagnetic Compatibility.

Reference

1. *Official Journal of the European Union*, 2004, **L371**, 50 (18 December 2004).

Japan Publishes Draft Requirements for IVDs

Towards the end of 2004, the Japanese Ministry of Health, Labour and Welfare (MHLW) issued an English version of the draft regulation concerning marketing authorisation requirements for *in vitro* diagnostics (IVDs)[1]. A marketing authorisation application plus supporting documentation must be submitted to the MHLW for approval. The precise documentation required varies by product category but may include overseas usage statistics, technical specifications, stability data, performance data, a risk analysis, details of the manufacturing process and clinical trial information. Once the application has been reviewed, approval is granted based on one of the following four categories:

- new product (where the IVD is designed to detect or measure a new item);
- approval criteria (where the IVD meets established approval criteria);
- non-approval criteria (where the IVD does not meet any established approval criteria);
- non-conformity (where the IVD does not meet the relevant criteria for its category).

Reference

1. *Pacific Bridge Inc Asian Medical Newsletter*, **4**(9), December 2004.

Low Risk Medical Devices in Japan - Third Party Certification

When the new *Pharmaceutical Affairs Law* is fully implemented in April 2005, all low risk or controlled medical devices will have to undergo evaluation by a third party to ensure compliance with current regulatory and quality control standards prior to marketing[1].

The Ministry of Health, Labour and Welfare (MHLW) is in the process of establishing a third party accreditation process, which will be based on standards developed by the International Standards Organisation (ISO) and the International Electrotechnical Commission (IEC). Once accredited, the MHLW will provide third parties with guidance on issues such as operational standards, their responsibilities and confidentiality requirements.

Reference

1. *Pacific Bridge Inc Asian Medical Newsletter*, **4**(9), December 2004.

Japan's Rules for Marketing Authorisation Holders

After 1 April 2005, firms will either have to be, or have, a licensed marketing authorisation holder in Japan in order to be able to sell their medical devices on the Japanese market[1]. The Ministry of Health, Labour and Welfare has published a draft guidance document concerning the requirement for a marketing authorisation holder to be located in Japan, which is consistent with the new *Pharmaceutical Affairs Law* reform regulatory guidelines.

Reference

1. www.rozynski-associates.com, December 2004.

Thailand's Medical Device Bill

Thailand's *Bill of Medical Device* is still under consideration by the Juridicial Council and it may be a further two months before a decision is reached[1]. This statement

was issued by Ms Yuvadee P, Director of the Medical Device Control Division of the Food & Drug Administration to THAIMED, the Thai Medical Device Suppliers Association.

Reference

1. *THAIMED Focus*, Issue 16, December 2004.

Thai FDA's One Stop Service Centre

On 17 November 2004, the Thai Food & Drug Administration (FDA) opened a One Stop Service Centre on the ground floor of its offices, next to the Siam Commercial Bank[1]. Manufacturers and/or distributors must now submit all applications for healthcare products, including medical devices and pharmaceuticals, to this Centre.

Reference

1. *THAIMED Focus*, Issue 16, December 2004.

Quality System Documentation in Thailand

An amendment to extend the scope of Ministerial Announcement No 6 on Free Sale Certificates (FSCs) is still being drafted[1]. At present, only Class III devices require quality system documentation to be attached to an application for an FSC. The Thai Food & Drug Administration is now preparing a list of other medical devices for which such documentation will be required, and this new list will include products from Classes I, IIa and IIb. Progress of this amendment is being monitored closely by THAIMED, the Thai Medical Device Suppliers Association, to ensure that any new rules and conditions are acceptable to both the Agency and the industry.

Reference

1. *THAIMED Focus*, Issue 16, December 2004.

Other News from the Thai FDA

Other news items (as of December 2004) from the Thai Food & Drug Administration (FDA) affecting the medical device industry are as follows[1]:

- guidelines on the Good Manufacturing Practice procedures to be adopted by manufacturers and regulators under the proposed initial voluntary scheme were expected to be finalised by the end of 2004;
- guidelines on the submission of applications for medical device advertising have been finalised and are awaiting signature by the Secretary General of the Thai FDA;
- the FDA is considering whether or not to allow refurbished or reused medical devices to be imported into Thailand;
- amendment of Ministerial Announcement No 18 on HIV tests is under consideration to extend the scope to include devices used in blood donor screening, organ transplant screening and test kits for the monitoring of treatment and other relevant procedures;
- industry has called for a review of the current regulations concerning the importation of radiation equipment into Thailand but this matter is still pending at the Office of Atomic Peace as the Working Group required to consider and amend the regulations has not yet been established due to personnel changes within the Agency.

Reference

1. *THAIMED Focus*, Issue 16, December 2004.

Packaging & Packaging Waste

On 17th November 2004, the European Parliament voted to adopt a legislative resolution relating to packaging and packaging waste in the 10 new Member States[1]. This resolution was based on a report that recommends amendments that would replace the single date of 31 December 2012[2] proposed by the Commission for achieving recycling and recovery targets for packaging and packaging waste with individual dates for each of the 10 Member States reflecting their views on how quickly they can meet the targets.

References

1. *The Week in Europe*, PE 349.778, November 2004.
2. *Journal of Medical Device Regulation*, **1**(1), 73.

Electrical & Electronic Equipment

A legislative proposal establishing maximum concentration values for certain hazardous substances in electrical and electronic equipment has been formally adopted by the European Commission[1]. The adoption of COM(2004) 606 took place on 23 September 2004[2] and was transmitted to the Council of the European Union on the same day. As no action was taken by the Council, the measures were formally adopted by the Commission and published in the Official Journal on 30 December 2004.

References

1. *Official Journal of the European Union*, 2004, **C323**, 4 (30 December 2004).
2. *Journal of Medical Device Regulation*, 2004, **1**(1), 73.

Batteries and Accumulators

The Environment Council was able to reach a swift agreement at a meeting held on 20 December 2004 on a proposed new Directive concerning the collection and recycling of all waste batteries and accumulators to prevent their incineration and disposal[1]. The Council agreed collection targets for these products of 25% and 45% of the average annual sales over the past three years to be achieved in four years and eight years, respectively, after transposition of the Directive.

The Council also introduced a partial ban on portable cadmium batteries and deleted the 80% collection target for these batteries proposed in the original Commission Proposal. The ban will not apply to portable cadmium batteries used for emergency and alarm systems, medical equipment or cordless power tools although the exemption for cordless power tools may be reviewed four years after the date for transposing the Directive into national laws. Portable cadmium batteries not covered by this ban will be collected through collection schemes to be set up under this Directive or, if incorporated in appliances, under the Directive on Waste Electrical and Electronic Equipment[2]. These batteries are also covered by the general collection targets for all portable batteries.

References

1. *European Commission Press Release*, IP/04/1517, 20 December 2004.
2. Directive 2002/96/EC of the European Parliament and of the Council of 27 January 2003 on waste electrical and electronic equipment (WEEE). *Official Journal of the European Union*, 2003, **L37**, 24 (13 February 2003).

ISO/TR 14969: 2004

The Technical Report that provides guidance on the application of the requirements for quality management systems contained in ISO 13485: 2003 was issued towards the end of 2004[1]. The purpose of this document is to promote a better understanding of the requirements of ISO 13485 and to illustrate some of the various methods and approaches available for meeting them. It does not include requirements to be used as the basis of regulatory inspection or certification assessment activities and it does not add or modify the requirements of ISO 13485.

Reference

1. ISO/TR 14969: 2004, *Medical devices - Quality management systems - Guidance on the application of ISO 13485: 2003*.

ISO 14155 on Clinical Investigations

All clinical trials conducted in Europe should now follow the procedures specified in ISO 14155, *Clinical Investigation of Medical Devices for Human Subjects* instead of EN 540, *Clinical Investigation of Medical Devices for Humans*. ISO 14155 helps to standardise the procedures for clinical investigations by clarifying the division of responsibilities between investigators and sponsors and by providing additional guidance on document and data control, patient tracking and informed consent procedures.

Whilst the device industry views ISO 14155 as an improvement on EN 540, there is a general view that further refinements are still required. Areas of concern include the lack of consensus on how Ethics Committees should be constituted and who should be able to audit investigators.

Nanotechnology Standardisation Recommendations Issued

The American National Standards Institute's Nanotechnology Standards Panel (ANSI-NSP) has released a series of recommendations that can be used as the basic framework for developing standards in the field of nanotechnology[1]. The ANSI-NSP acts as the cross-sector co-ordinating body for standards in the area of nanotechnology and provides the forum within which stakeholders can work together to promote, accelerate and co-ordinate the timely development of useful voluntary consensus standards.

As a result of the Panel's first meeting in September 2004, a set of priority recommendations were developed for those areas of nanotechnology that are considered to require the most urgent standardisation. The recommendations identify four broad standardisation topics to be most urgent in a 12-month-or-less timeframe:

- general terminology for nanoscience and technology, including definition of the term 'nano';
- systematic terminology for materials composition and features, including composition, morphology and size;
- toxicity effects, environmental impact and risk assessment;
- metrology, methods of analysis and standards test methods, including particle size and shape, and particle number and distribution.

The Panel also identified manufacturing and processing as well as modelling and

simulation as items of lower urgency and agreed upon standardisation timeframes of three to five years in these areas.

Reference

1. *ANSI-NSP Releases Priority Recommendations Related to Nanotechnology Standardization Needs*, 17 November 2004.

Digital Imaging & Communications in Medicine

A total of 25 new features have been incorporated into the 2004 update of the Digital Imaging and Communications in Medicine (DICOM) standard released by the National Electrical Manufacturers Association (NEMA)[1]. Areas covered by these enhancements include, *inter alia*:

- web access to new media that can be used to transport DICOM information;
- functionality for some of the newer specialities that use DICOM (e.g. dentistry, ophthalmology);
- features to capture the specific information needed to do reporting in areas such as vascular and intravascular ultrasound or breast imaging;
- the conformance statement definition, which has been enhanced to increase a user's understanding of a product's DICOM functionality and better describe a product's ability to inter-operate with another product that supports DICOM features.

The DICOM standard is a 16-part set of rules that creates a single language for exchanging digital images and related information (e.g. patient name, reason for the procedure and the instrument used). The standard is used, or will soon be used, by almost all medical imaging professionals as it enables users to acquire, display, store, retrieve, move or print medical images between instruments, computers and hospitals.

Copies of the 2004 standard can be purchased by part or as an entire set from the NEMA website (www.nema.org/stds/ps3set.cfm).

Reference

1. *NEMA Press Release*, 20 December 2004.

Meeting Report: Is Technology Convergence the Future of Medical Devices?

'Advances in molecular medicine, biotechnology, nanotechnology, and information science will stimulate convergence of the device, pharma and biotech world'. This was the view presented by Dr Bill van Antwerp of Medtronic Minimed at an IIR conference on Drug-Device & Biologic Combination Products held in London, UK in December 2004.

These days, most medical devices are implantable electrical devices designed to alleviate problems associated with diseases rather than actually providing a cure for the disease itself. New, innovative technological combinations such as biologics delivered using a medical device, however, offer significant potential to make treatments safer, more effective, more convenient or more comfortable for patients.

But is the international regulatory environment keeping pace with these advances in technology?

European Regulatory Developments

In Europe, there are moves towards greater regulation of borderline products through amendments to the scope of the medicinal product legislation (Directive 2004/27/EC)[1], which are due to take effect on 30 October 2005, and implementation of the human tissue products Directive (2004/23/EC)[2] on 7 April 2006. There is also a new proposed regulation covering human tissue engineered products, which are to be defined as '[a]ny autologous or allogeneic product which: contains, consists of, or results in engineered human cells or tissues; and has properties (or is presented as so having) for the regeneration, repair or replacement of a human tissue or human cells, where the new tissue or the new cells, in whole or in part, are structurally and functionally analogous to the tissue or the cells that are being regenerated, repaired or replaced.' However, as the regulations tighten, the borderline issues also change, potentially causing more confusion to companies trying to navigate their way around this regulatory minefield.

Changes in the USA

The USA has about 14 years of regulated combination product history, dating back to the *Safe Medical Devices Act of 1990*. Over the years it became evident that there was a need to make someone in the Food & Drug Administration (FDA) directly accountable for combination product/borderline issues so, in 2002, the Office of Combination Products (OCP) was established. The OCP is responsible for ensuring prompt designations and review assignments, timely and effective premarket reviews, and consistent and appropriate postmarket regulation.

In May 2004, the FDA proposed a rule[3] to define Primary Mode of Action (PMOA), a term with no current legal definition in the US, in an effort to simplify the designation process for sponsors. Under the proposal, PMOA would be defined as 'the single mode of action (e.g. drug, device, biological product) of a combination product that provides the most important therapeutic action of the combination product'.

If it is not possible for the FDA or the sponsor to determine which mode of action of a combination product provides the most important therapeutic action, the FDA would usually assign the product to the Center that regulates other similar combination products.

If there are no other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole, the FDA would assign the product to the Center with the most expertise to evaluate the component of the combination that presents the most significant safety and effectiveness concerns.

Speaking at the IIR conference in London via a telephone link, Mark Kramer, Director of the OCP, stated that he hopes that this proposed rule will be finalised during the first half of 2005.

When questioned about the draft guidance document concerning the application of Good Manufacturing Practice to combination products[4], Mr Kramer anticipated that it would be finalised very soon. According to Mr Kramer, the majority of the comments received during the consultation process supported the concept of the guidance and agreed with the major elements, and the suggested alterations and/or clarifications were fairly minor.

Mr Kramer also made reference to a noticeable trend in the US for sponsors to submit multiple marketing applications for combinations products, despite the increase in fees associated with doing so. One of the major reasons for this is likely to be exclusivity. Exclusivity rights only appear in the laws governing drugs (medicinal products) so if a drug/device combination is approved under a premarket approval application, exclusivity rights will not apply. However, if the drug component is approved separately using a New Drug Application then exclusivity rights will apply.

The Way Forward

It is vital that device companies recognise the skill set that will be required to compete in the 21st century, said Dr van Antwerp. This will include molecular biology, cell biology, mechanical design and chemistry to name but a few areas.

The convergence of biology, chemistry, information technology and nanotechnology is the way forward for device development yet establishing a successful interface between these disciplines will be one of the greatest challenges for companies to overcome. The key to success will lie in the interfacial disciplines such as biochemistry, biophysics and biomedical engineering.

The medical device industry must embrace all types of future technologies to ensure that it continues to develop better, smarter, more effective devices.

References

1. Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use. *Official Journal of the European Union*, 2004, **L136**, 34 (30 April 2004).
2. Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. *Official Journal of the European Union*, 2004, **L102**, 48 (7 April 2004).
3. *Federal Register*, 2004, **69**(89), 25527 (7 May 2004).
4. *Draft Guidance for Industry and FDA: Current Good Manufacturing Practice for Combination Products*, September 2004.

Victoria Clark

Elemental Essentials: Harmonised Standards

The situation in Europe prior to the efforts to unify practices in specified market sectors made it impossible to ensure mutual recognition of requirements for medical devices between one Member State and another. The efforts to produce European Standards were therefore conceived as a fundamental means of fostering such recognition of expectations, so that the goals of freedom of movement could be achieved, but not at the cost of safety. As a by-product of this exercise, a consolidation of costs can be arrived at, once the need for multiple, national approvals clearances and registrations become extinct. Since standards in themselves do not necessarily relate to safety, manufacturers still need to relate to the Essential Requirements.

What is a Harmonised European Standard?

Harmonised standards are European standards that are adopted by European standards organisations, prepared in accordance with the General Guidelines agreed between the European Commission and the European standards organisations, and follow a mandate issued by the Commission after consultation with Member States.

A harmonised standard must match the Essential Requirements of the relevant Directive, however it does not necessarily cover all Essential Requirements and thus obliges the manufacturer to use other relevant technical specifications in order to meet all the Essential Requirements of the Directive.

Although European standards are considered as harmonised before publication of the references in the *Official Journal of the European Union*, it is this publication that gives presumption of conformity to the Essential Requirements of the Directive in question.

How are Standards Prepared?

European Standards are prepared as a collaborative effort by representatives from the EU Member States. These representatives are usually nominated by the relevant standards organisations in the Member States. The representatives form part of each national delegation that negotiates at the European forum. Examples include the European Committee for Electrotechnical Standardisation (CENELEC) or the Committee for European Standardisation (CEN).

The actual instruction of work to begin on a European Standard is given by the European Commission through a mandate. After formal, defined stages for drafting, review and internal approval, a draft version of the standard is issued for formal vote and subsequently public comment before being passed. At this point the draft becomes ratified, whereupon it is listed in the *Official Journal of the European Union* and certain Gazettes, thereby acquiring the status of a harmonised standard.

What are the Advantages and Disadvantages of Standards?

The main advantages of standards are that they provide a uniform starting point for achieving a certain set of agreed conditions and also that they can help to demonstrate compliance with certain statutory or regulatory demands, most notably the requirements of the European Directives. The main disadvantages of standards are that they do not always cover all products or versions for a product type and often they do not even appear to relate to all key issues relevant to the product. There are some significant problems with using a European Standard as the means of demonstrating presumed conformity with the Medical Devices Directive, either for one or all Essential Requirements, for example.

Standards can also be useful because they allow the technical detail or depth needed for a particular device or device type to be maintained elsewhere from the Directive concerned. This means that the process of

legislation has less to consider and is therefore potentially accelerated. Also, it tends to be easier to amend an existing standard compared to legislation.

Additional, acute problems are evident when one considers that existing and new standards actually reflect accepted elements and practices. They therefore are not proscriptive, thereby offering nothing new for the future (this is usually the case).

Presumption of Compliance – What Does it Mean in Practice?

The European Commission has declared that compliance with one or more elements of a European Directive, including those for medical devices, is presumed if a relevant harmonised European standard (EN) is used as the means of achieving a given set of conditions. Also, it is important to point out that manufacturers using a harmonised EN for compliance testing for use in certain conformity routes, notably Annex II or IV, need not have the tests conducted by the Notified Body or other officially appointed third party. The responsibility for correct testing still resides with the manufacturer, so test reports etc would still need to be maintained. The testing, if not performed by a Notified Body for example, would still need to meet the expected standards and codes of practice.

When deciding whether or not to use European standards as a means of achieving compliance, remember that:

- not all European standards will be harmonised;
- it is unlikely that the opportunity will emerge for more than one harmonised European standard to be available for the same area (i.e. there will be no other choice for presumption of compliance);
- in the absence of a harmonised European standard, alternative measures can be elected.

On The Move...

Michael Leavitt, the outgoing Environmental Protection Agency administrator and former governor of Utah, was confirmed by the US senate on 26 January as the new US Secretary of Health and Human Services. He replaces Tommy G Thompson who announced in December 2004 his intention to resign.

On 14 November 2004, **Dr Edward Otto** took over the position of Director of the Office of Cellular, Tissue and Gene Therapies within the US Food & Drug Administration's Center for Biologic Evaluation and Research. Dr Otto, who has extensive experience in gene therapy product research and development, took over from Dr Joyce Frey-Vasconcells who had been Acting Office Director for several months.

Towards the end of 2004, **Prof. Dr. Pakdee Phothisiri** was appointed as the new Secretary General of Thailand's Food & Drug Administration.

ADVAMED, the Advanced Medical Technology Association, has promoted **Megan Ivory** to the position of Executive Vice President for Government Affairs. One of the top priorities for Ms Ivory will be to secure legislation that will add predictability and stability to the medical device user fee programme and allow for the programme's continuation. The Association has also announced the appointment of **Nancy Travis**, former deputy director of the US State Department's Office of Economic Policy, as Associate Vice President of the Global Strategy and Analysis department.

Health Canada has appointed **Dr Peter Cooney** as its new Chief Dental Officer. Dr Cooney will head the newly formed Office of the Chief Dental Officer and will report to the Assistant Deputy Minister of the First Nations and Inuit Health Branch.

Josef von Rickenbach, Chairman and CEO of PAREXEL International Corporation, has been elected as Chairman of the Association of Clinical Research Organizations (ACRO) for 2005. **Dr Candace Kendle**, Chairman and CEO of Kendle, has been elected as Treasurer. The ACRO represents the clinical outsourcing industry to regulators, biopharmaceutical customers and policy makers internationally.

Dr Andreas Koehler has been elected as the new chairman of the German National Association of Statutory Health Insurance Physicians (*Kassenärztliche Bundesvereinigung,* KBV). The elected vice chairman was **Ulrich Weigeldt**, head of the Association of General Practitioners.

New Approach Regulations - Part 2

Elements of New Approach Directives

The European New Approach Directives are all strikingly similar in structure and consist of:

- Recitals;
- Articles; *and*
- Annexes (Conformity Assessment Procedures).

The standard elements of each Directive are:

- harmonisation through Essential Requirements only;
- only products compliant with the Essential Requirements may be placed on the market and put into service;
- conformity to corresponding Essential Requirements is presumed if harmonised standards transposed as national standards are applied;
- voluntary application of standards and other technical specifications;
- variety of Conformity Assessment Procedures available for selection by manufacturers.

Table 1 (below) describes in more detail the sections that make up a New Approach Directive.

Adoption of Directives into Member State law

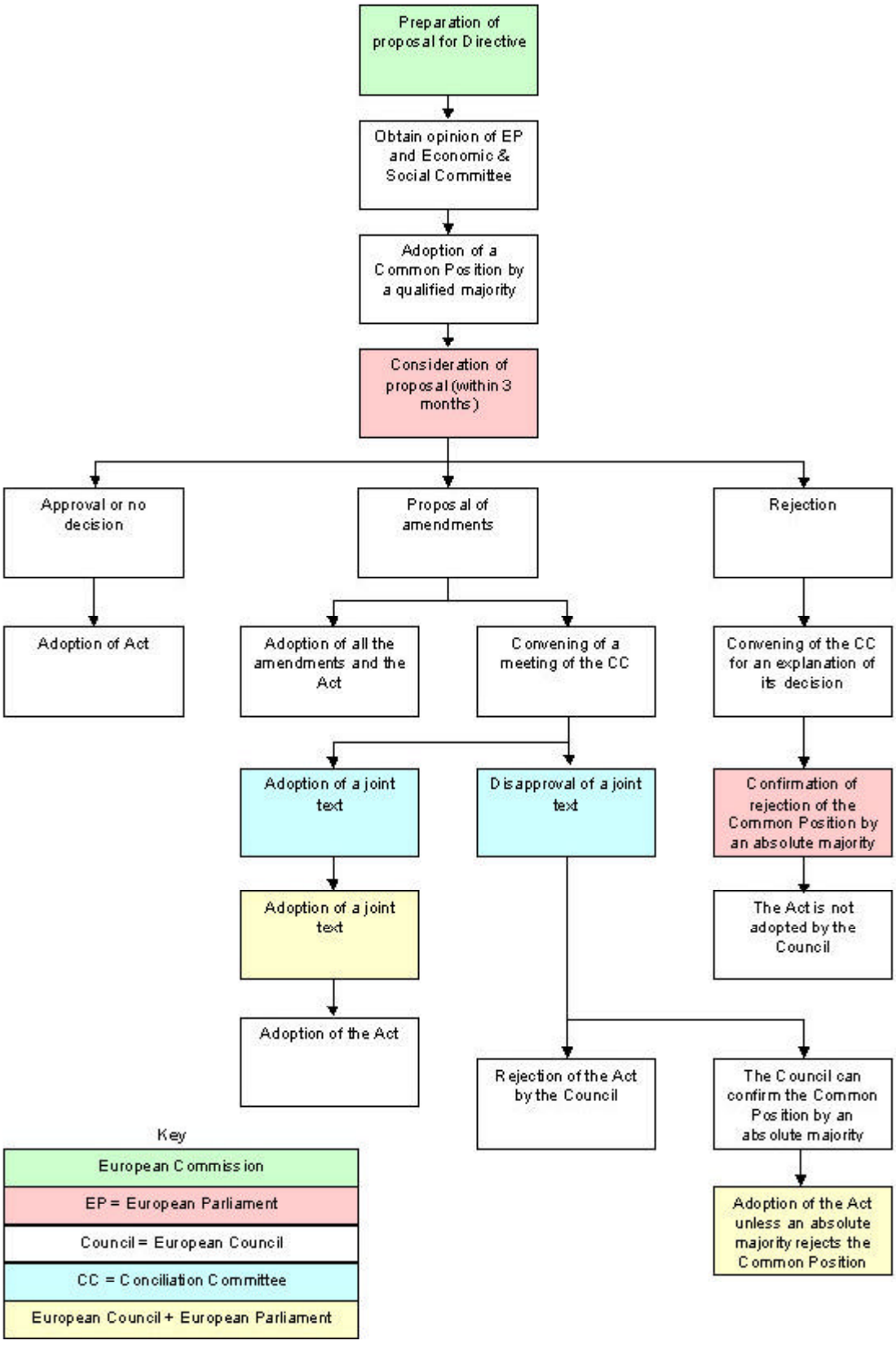
New Approach Directives are adopted by the Commission according to Article 251 of the EC Treaty (the Treaty of Rome). The process for this adoption is shown in Figure 1 on page 67.

Table 1. Elements of New Approach Directives

Element	Content	Notes
Scope	Defines range of products covered by the Directive or nature of hazards the Directive is intended to avert.	Several Directives may apply to the same product.
'Placing on the Market' and 'Putting into Service'	Measures necessary to ensure products are placed on the market only if they do not endanger safety and health of persons and other public interests covered by the Directive.	
	Measures necessary for market surveillance.	
	Member States are permitted to adopt additional national provisions to ensure such protection.	Measures must not require modification or influence conditions for placing a product on the market.
Essential Requirements	Essential Requirements include all that is necessary to achieve the objective of the Directive.	Products can only be placed on the market if they comply with the Essential Requirements.
Free movement	Member States must presume that products bearing a CE mark comply with the applicable Directives.	Member States may not prohibit, restrict or impede placement on the market or putting into service of correctly CE marked products.

	Member States may prohibit, restrict or impede free movement of a correctly CE marked product because of a hazard not covered by the applicable Directive.	
Presumption of conformity	Conformity is presumed for products complying with national standards transposing harmonised standards.	Where a manufacturer has not applied or has only applied such a standard partially, the measures taken and their adequacy must be documented in order to comply with the Essential Requirements.
	The Commission must consider if the national measure is justified and inform all Member States who must in turn take appropriate action in view of their general obligation to enforce Community legislation.	
Safeguard clause	Measures to prohibit or restrict the placing of products bearing the CE mark on the market are needed if products might compromise safety and health, as covered by applicable Directives.	Member States must inform the Commission when they take this measure.
Conformity Assessment	Manufacturers must subject a product to a Conformity Assessment Procedure in order to affix the CE mark.	
Notified Bodies	Third Party Conformity Assessment is conducted by Notified Bodies.	Notified Bodies are designated by the Member States.
CE marking	Products complying with the Directive must bear the CE mark.	CE marked products comply with Essential Requirements of applicable Directives and are subject to Conformity Assessment Procedures specified in the Directives.
	Member States must take appropriate measures for protecting the CE mark.	
Co-ordination of implementation	Member States who consider that a harmonised standard does not completely meet the Essential Requirements of a Directive must inform the Commission.	
Transposition and translational provisions	Member States must transpose the Directive into national legislation.	Member States must also inform the Commission of measures taken.
	Member States must allow products on the market at the date of application of the Directive in question until the end of the period of transition.	Member States must also permit such products to be put into service beyond that date.

Figure 1. Process for adoption of Directives by the EU



Country Overview: China

Regulatory Authorities

The State Food and Drug Administration (SFDA), formerly called the State Drug Administration, is responsible for the regulation, registration and inspection of medical devices. The SFDA's main roles with respect to medical devices are to:

- draft laws and regulations on the administration of medical devices and supervise their enforcement;
- control the registration and regulation of medical devices;
- draft relevant national standards, draw up and revise professional standards of medical devices and manufacturing practices, and supervise their implementation;
- ensure the quality of medical devices and medicinal products in manufacturing plants, distribution facilities and medical institutions;
- produce a regular national quality bulletin on medical devices and medicinal products;
- investigate and take legal action against any production and sales of counterfeit and/or inferior quality medicinal products and medical devices;
- regulate radioactive pharmaceuticals, narcotics, psychotropics and other controlled medicinal products and medical devices in accordance with the law.

Address: State Food and Drug Administration
A38, Beilishi Road, Beijing 100810
People's Republic of China

Fax: +86 010 68310909

Email: inquires@sda.gov.cn

In addition, there is a General Administration of Quality Supervision, Inspection and Quarantine (AQSIQ) that is responsible for the safety registration, certification and inspection of certain medical equipment.

Legal Framework

Regulations for the Supervision and Administration of Medical Devices (1 April 2000)
These Regulations form the basis of China's medical device regulatory system. They have been amended several times, most significantly by Order No 16 below.

Order No 16 - Provisions for Medical Device Registration (9 August 2004)
This Order contains provisions for medical device registration, including medical device registration tests, clinical trials, registration application and approval, re-registration, legal liabilities and supplementary provisions.

Order No 15 - Provisions for Medical Device Distributing Enterprise License (9 August 2004)
These newly amended Provisions comprise seven chapters: General Provisions; Requirements for Application of Medical Device Distributing Enterprise License; Procedure for Application of Medical Device Distributing Enterprise License; Modify and Renew of Medical Device Distributing Enterprise License; Supervision and Inspection; Legal Liabilities; and Supplementary Provisions.

Order No 12 - Provisions for the Supervision of Medical Device Manufacturing (20 July 2004)
These Provisions comprise seven chapters: General Provisions; Application and Approval of Medical Device Manufacturing Enterprise Establishment; License Management of Medical Device Manufacturing; Management of Entrusted Medical Device Manufacturing; Supervision and Inspection; Legal Liabilities; and Supplementary Provisions.

Order No 10 - Provisions for the Instructions, Labels and Package of Medical Devices (8 July 2004)
This sets out clear rules for the format, content and management of the instructions for use, labelling and packaging of medical devices.

Approval Processes

Product registration

A non-domestic company wishing to place a medical device on the market in China must submit the following information to the SFDA:

- registration form, which can be downloaded from www.cmdi.gov.cn;
- legal production qualification (e.g. registration with the US FDA);
- a manufacturing authorisation document from the country of origin;
- a business licence for the Chinese agent registering the device;
- a declaration of compliance with all applicable quality standards;
- an operation manual for the device;
- a type testing report issued by an SFDA-recognised medical devices quality test agency;
- clinical trial report (only required for certain types of devices);
- a letter stating that the product is of the same quality as those sold in the country of origin;
- a letter providing details of the local agent who will be responsible for sales and after-sales customer service in China plus a letter from the agent confirming this position;
- a declaration that the data provided in the registration dossier is accurate.

Two original copies of the application must be submitted in both Chinese and English. The Agency will then send this information to the Medical Device Evaluation Center (MDEC) for review. MDEC will send its findings back to the SFDA and, if everything is in order, the SFDA will issue an import product licence.

Renewals

Product licences must be renewed every four years. In the past, renewal applications have often been treated in the same was as new product registrations, requiring technical evaluations and leading to a very time consuming process.

In August 2004, the SFDA indicated that re-registration would become automatic for devices that had not undergone any significant changes. However, manufacturers should still be aware that applications for re-registration must be submitted to the SFDA six months before the date of expiry of the current licence.

Amendments

For changes or additions to the manufacturing location, a new product registration application must be submitted. However, an amendment to the product registration may be submitted for basic changes (e.g. for manufacturer's name or a product line extension).

Clinical trials

All clinical trials for medical devices must follow Good Clinical Practices and the clinical centre or hospital chosen for the trial must be on the SFDA approved list. The *Medical Device Clinical Trial Regulation*, which became effective in April 2004, provides detailed requirements for clinical protocols, clinical hospitals and clinical reports.

Labelling Requirements

The labelling of medical devices imported into China must be in Chinese, must be affixed before the devices pass through customs, and include:

- the registration certificate number;
- product features; *and*
- the scope of use of the product.

There is also a requirement for consumers to be informed of any related symptoms (side-effects) as well as all other necessary warnings and precautions.

Order No 10 contains a number of prohibitions against absolute expressions of efficacy, such as 'most effective treatment', 'full recovery guaranteed' and 'immediate effect'.

Other prohibitions include language that provides guarantees, such as 'money back if not effective', 'most advanced' and 'the best'.

Also, the labelling, packaging and instructions for use for a medical device must not:

- specify a cure rate or efficacy rate, or make comparisons with the safety and efficacy data of a competitor's product;
- make use of the name or image of any company or individual for the purpose of approval or recommendation;
- contain expressions that could make people feel that they have contracted a certain condition, or which misleads people into feeling that they would contract a certain condition or their condition could get worse by not using this medical device.

The Instructions for Use must be reviewed and approved by the SFDA during the registration process. Once it has been approved, no changes may be made without prior SFDA approval.

Inhalt

Drittparteien-Prüfsystem des CDRH

In der EU besteht das Verfahren für die Marktzulassung von neuen Medizinprodukten darin, dass die Hersteller/Kostenträger ihre technischen Daten oder Design Dossiers an die Benannten Stellen senden. Im Gegensatz dazu war das US Office of Device Evaluation of the Food and Drug Administration's (FDA's) Center for Devices and Radiological Health (CDRH) bis vor kurzem die einzige Prüfstelle für alle Anträge auf Marktzulassung einschließlich der Anträge auf Investigational Device Exemption, auf Premarket Notification und auf Premarket Approval. Die große Anzahl an Anträgen, die jährlich bearbeitet wurden, führte schließlich zu zunehmend längeren Prüfzeiträumen und Antragsstaus. 1996 startete das CDRH ein Pilotprogramm, das es Dritten (nicht die FDA) erlaubte, ausgewählte Anträge auf Marktzulassung zu prüfen. Ein zweites Prüfverfahren für Drittparteien wurde später eingeführt. Die Nutzung dieser Verfahren ist freiwillig und der Hersteller/Kostenträger des Antrags auf Marktplatzierung hat nach wie vor die Möglichkeit, die Premarket Notification direkt bei der FDA einzureichen, selbst jene Produkte, die von Dritten geprüft werden könnten.

In diesem Artikel untersucht **Rosina Robinson** das Drittparteien-Prüfsystem aus der Perspektive eines Herstellers/Kostenträgers der Premarket Notification ohne in die Anforderungen und die Folgeabläufe für die Akkreditierung der Drittpartei oder die Anforderungen für die Auftrechterhaltung des Status als Drittpartei einzutauchen. Viele der in diesem Artikel genannten Literaturhinweise schließen jedoch Beschreibungen dieser Anforderungen ein.

Hin zu einem IT-basierten Risikomanagement-System

Angesichts der ganz offensichtlichen Anzeichen für den steigenden Medikamentenkonsum sind sich Rechtsinstitutionen auch der Grenzen der traditionellen Risikomanagement-Methoden und -Werkzeuge beim kommerziellen Einsatz von Medizinprodukten und Pharmazeutika bewusst. In diesem Artikel spricht **Terry Knapp** spezifische Elemente des Concept Paper der FDA mit dem Titel *Risk Management Program* an, und kommentiert die Art und Weise, in der IT-basierte Lösungen Herstellern, Ärzten, Apothekern und Patienten dabei helfen können, den größten Nutzen bei gleichzeitig geringst möglichem Risiko im Einsatz von Pharmazeutika, Bio- und Medizinprodukten zu erzielen.

Klinische Daten in der EU

Die Vorschriften für die Platzierung von Medizinprodukten auf dem Markt der Europäischen Union sind in den verschiedenen EC-Direktiven festgehalten jedoch nicht sehr präzise formuliert. **Haroon Atchia** erklärt an Hand der Council Directive 93/42/EEC (am besten bekannt als Medical Device Directive, MDD) die Anforderungen, unterscheidet zwischen den verschiedenen Möglichkeiten, den klinischen Nutzen eines bestimmten Medizinprodukts aufzuzeigen, und erläutert die Rolle der zuständigen Behörden bei der Bearbeitung von Antragsstellungen für den Beginn von klinischen Tests im Hinblick auf eine CE-Zertifizierung.

Medizinprodukte positionieren wenn Kostenerstattung nicht möglich ist (2)

Die Aussichten einer Technologie auf 'Kostenerstattung' beziehen sich auf drei zusammenhängende Prozesse: die Aussichten auf Versicherungsdeckung, die Rechnungs- und Ablaufcodes, die ihr zugeteilt werden und die eigentliche Auszahlung, wenn es überhaupt dazu kommt, die erfolgt, wenn die Technologie benutzt wird. In den meisten Fällen ist die Benutzung der Technologie, und nicht die Technologie selbst, Gegenstand der Kostenerstattung. In der Folge kann somit der Preis für die Technologie ein großes Hindernis für die Produktakzeptanz darstellen, es sei denn, es werden zusätzliche Gelder in den Prozess der Kostenerstattung einbezogen oder der Käufer ist davon überzeugt, dass die Technologie klinische und wirtschaftliche Vorteile hat, die unabhängig von einer Kostenerstattung gelten. Um Medizinprodukte erfolgreich platzieren zu können, müssen Hersteller den 'Wert' der Technologie auf eine Art und Weise benennen können, die die Käufer und Benutzer verstehen.

Im ersten Teil dieses Artikels, der in der Novemberausgabe veröffentlicht wurde, zeigte **Nancy L Reaven** einige Gründe und Beispiele dafür, dass es in den USA keine Kostenerstattung für Medizintechnologien gibt und erörterte Strategien, um daraus sich ergebende Hindernisse bei der Produktakzeptanz zu überwinden. Der zweite und letzte Teil des Artikels konzentriert sich auf die finanziellen Anreize und Perspektiven, die für Technologiekäufer relevant sind, und schlägt verschiedene Herangehensweisen an die relevanten 'Wert'analysen vor.

Europa Update

- Zulassung von menschlichem Gewebe und Zellen in Dänemark
- Änderungen in der MDD
- Produkte, die tierisches Gewebe verwenden
- Richtlinie zur elektromagnetischen Kompatibilität
- Datenschutz
- Mammografie-Geräte in Frankreich
- In vitro-Diagnostika: neue Vorschriften in Frankreich
- Kompromiss bei der zweiten Änderung des DRG in Deutschland
- Anleitung zur Anzeige von unerwünschten Zwischenfällen in Irland
- Produkte, die tierisches Gewebe enthalten, in Portugal
- Zahlungen an das slowakische SUKL
- Informationen zur Benutzung von Hochleistungs-Lasern in der Schweiz
- Leitfaden zu medizinischen Personenwaagen in der Schweiz
- Medizinproduktwarnungen des britischen MHRA
- Arbeitsgruppe der britischen Gesundheitsindustrie

US Update

- Neuklassifizierung von zwei Embolisierungsprodukten
- Äußerlich angewandte Erektionshilfsmittel: Klassifizierung
- Lasersysteme für Assistierte Reproduktion: Klassifizierung
- Produkte für klinische Chemie und für klinische Toxikologie: Klassifizierung
- Produkte für die Nutzung in Krankenhäusern und für den persönlichen Gebrauch: Klassifizierung
- Widerruf von Gesetzesanträgen
- HDEs, spezielle Kontrollen und Befreiung von Umweltverträglichkeitsprüfungen
- Neuklassifizierung von Iontophorese-Produkten
- Wiederaufbereitete Einweg-Produkte
- MDTCA/MDUFMA-Zusammenfassungen erhältlich
- Zusammenfassungen endgültiger FDA Leitfäden erhältlich

Internationales Update

- Güter, die in Australien keine Medizinprodukte sind
- Geprüfte Verpackungen
- Diagnoseprodukte mit menschlichem Gewebe
- Kostenerstattung für Prothesen in Australien
- Klassifizierungsanleitungen für Australien veröffentlicht
- Entwurf der TGA-Blätter veröffentlicht
- Private Label-Produkte: Entwurf einer Anleitung für Kanada
- SBD und ND Dokumente für Produkte auf dem kanadischen Markt
- Sicherheitshinweise von Health Canada zu elektrisch bedienten Betten
- Antimikrobische Mittel auf Produkten in Kanada
- Produktneuigkeiten aus China
- Verwaltungskontrollsystem für Medizinprodukte in Hongkong
- Freihandelsabkommen
- Kasachstan tritt dem IEC bei
- EC/US MRA zu elektromagnetischer Kompatibilität
- Japan veröffentlicht Gesetzesentwurf für IVDs
- Medizinprodukte mit niedriger Risikostufe in Japan – Drittparteien-Zertifizierung
- Japans Bestimmungen für Inhaber von Marktzulassungen
- Thailands *Medical Device Bill*
- Thailändische FDA: Allround-Service Center
- Dokumentation von Qualitätssystemen in Thailand
- Weitere Nachrichten von der thailändischen FDA

Umwelt Update

- Verpackung und Verpackungsmüll
- Elektrische und elektronische Gerätschaften
- Batterien und Akkus

Standard Update

- ISO/TR 14969: 2004
- ISO 14155 zu klinischen Untersuchungen
- Empfehlungen für Standardisierung von Nanotechnologie veröffentlicht
- Digitale Bildwiedergabe und Kommunikation in der Medizin

Wissen

- Tagungsbericht: Liegt in der Technologiekonvergenz die Zukunft der Medizinprodukte?
- Das Kleine Einmaleins: Harmonisierte Standards
- New Approach Bestimmungen - Teil 2
- Länderfokus: China

Contenu

Système de revue par tiers du CDRH

Contrairement au premarket autorisation processus pour les nouveaux dispositifs médicaux en Union Européenne où les fabricants/ promoteurs déposent leurs dossiers techniques ou dossier de conception aux Organismes Notifiés, l'Office Americain d'évaluation des dispositifs médicaux au sein de la FDA (Food and Drug administration), Center for Devices and Radiological Health (CDRH) a été jusqu'à récemment la seule institution à examiner toutes les demandes de premarket y inclus demande pour Investigational Device Exemption (IDE), premarket notification et premarket approbation des demandes. Eventuellement, le grand nombre de demandes traitées annuellement aboutissait à une progression de temps d'examination et dans des bouchons des demandes. En 1996, le CDRH a initialisée un programme pilote qui autorisait des tiers de passer en revue des propositions sélectionnées pour accèss au marché. Un deuxième programme pour tiers fut lancé plus tard. Les deux systèmes sont facultatifs et le fabricant/promoteur a toujours la possibilité de présenter la Premarket Notification directement auprès de la FDA, même les dispositifs qui peuvent être examinés par des tiers.

Dans cet article **Rosina Robinson** explore la revue par tiers du point de vue d'un fabricant de dispositif médical /promoteur d'une Premarket Notification sans adresser les exigences et les procédés nécessaires pour l'accréditation par les tiers ni les exigences nécessaires pour maintenir le statut des tiers. Plusieurs de ses références citées dans cet article inclues déscriptions de ces exigences.

Vers un système de management de risques à base de technologie de l'information

Face aux indices manifestants une croissance de la consommation de médicaments, les institutions de réglementation ont pris conscience des limites qu'envisagent les méthodes et les outils traditionnels de management de risques dans l'emploi commercial de dispositifs médicaux et de médicaments. Dans cet article, **Terry Knapp** examine quelques éléments spécifiques d'un projet de la FDA intitulé *Risk Management Program* et commente sur la manière les solutions à base de technologie de l'information peuvent assister les fabricants, médecins, pharmaciens et patients à obtenir un maximum de bénéfice et, en même temps, à courir un risque minimal utilisant des pharmaceutiques, des dispositifs biologiques ou médicaux.

Données cliniques dans l'UE

Les règles pour un placement sur le marché de dispositifs médicaux sont fixées dans les différentes CE-directives, pourtant elles ne sont pas précisément définies. **Haroon Atchia** prend l'exemple de la Council Directive 93/42/EEC (mieux connu sous le nom de Medical Device Directive, MDD) pour expliquer les exigences, pour montrer les différences entre les différentes possibilités de démontrer le bénéfice clinique d'un dispositif médical spécifique et pour explorer le rôle des autorités compétentes dans le processus de la présentation de propositions en vue de commencement d'essais cliniques pour obtenir le marquage CE.

Positionnement des dispositifs médicaux quand le remboursement n'est pas une option (2)

Les perspectives de remboursement d'une technologie concernent trois processus reliés: les perspectives de couverture d'assurance, les codes de facturation et de processus attribués, et puis le payement effectif, si un payement se fera du tout, quand la technologie est utilisée. Dans la plupart des cas l'utilisation de la technologie engendre le remboursement, et non pas la technologie elle-même. Par la suite, le prix de la technologie peut constituer une barrière majeure pour l'acceptation du produit; sauf si on prévoit des payements supplémentaires au cours du processus de remboursement ou bien si l'acheteur est convaincu que la technologie remporte des valeurs cliniques et économiques qui ne sont pas reliées au remboursement même. Pour positionner un dispositif médical avec succès sur le marché, les fabricants doivent quantifier la 'valeur' de la technologie de telle manière à ce que les acheteurs et utilisateurs la comprennent.

Dans la première partie de cet article, qui a été publiée dans l'édition de Novembre 2004, **Nancy L Reaven** a donné quelques raisons à savoir pourquoi le remboursement de technologies médicales n'existe pas aux Etats-Unis et a discuté les stratégies pour contourner les obstacles qui en résultent pour l'acceptation du produit. Dans la deuxième et dernière partie elle se concentre sur les incentives et perspectives qui sont une motivation pour les acheteurs et propose plusieurs approches pour une analyse de 'valeur'.

Actualité Européenne

- Plan d'autorisation des tissus et cellules humaines au Danemark
- Révision de la directive Européenne pour les dispositifs médicaux
- Dispositifs utilisants tissus animaux
- Directive sur la compatibilité électromagnétique
- Protection des données
- Dispositifs pour mammographie en France
- Dispositifs médicaux de diagnostics in vitro: nouvelles réglementations en France
- Compromis lors de la deuxième modification du DRG en Allemagne
- Instructions pour notification d'effets défavorables des dispositifs de diagnostics In vitro en Irlande
- Dispositifs contenant du tissu animal au Portugal
- Payements au SUKL en Slovaquie
- Informations sur l'utilisation de lasers à haute performance en Suisse
- Instruction pour balances médicales en Suisse
- Alertes de sécurite publiées par le MHRA
- Groupe de projets chargé de l'industrie sanitaire au Royaume-Uni

Actualité aux États-Unis

- Reclassification de deux dispositifs d'embolisation
- Dispositifs externes de rigidité pénile: classification
- Systèmes laser pour reproduction assistée: classification
- Dispositifs de chimie clinique et toxicologie: classification
- Dispositifs d'utilisation hospitalière et personnelle: classification
- Révocation de propositions de loi
- HDE, contrôles spéciaux et exemption d'examens environnementals
- Reclassification de dispositifs d'iontophorèse
- Retraitement des dispositifs à usage unique
- Sommaire MDTCA/MDUFMA procurable
- Sommaires finaux d'instructions de la FDA procurables

Actualité Internationale

- Produits qui ne sont pas des dispositifs médicaux en Australie
- Emballages certifiées
- Produits de diagnostic d'origine humaine
- Plan de remboursement de prothèses en Australie
- Publication de guides de classification en Australie
- Ébauche de papiers TGA publiée
- Dispositifs à étiquetage privé: guidance cannadienne
- Documents SBD et ND pour les dispositifs lancés sur le marché canadien
- Conseil de Health Canada sur la securité des lits électriques
- Agents antimacrobiens sur les dispositifs utilisés au Canada
- Nouvelles sur les dispositifs en Chine
- Système de contrôle d'administration pour dispositifs médicaux à Hong Kong
- Accord de Libre-Échange
- Kazakhstan adhère à l'IEC
- MRA de l'UE et des États-Unis sur la compatibilité électromagnétique
- Ébauche de réglementation pour dispositifs de diagnostic in vitro publiée au Japon
- Dispositifs médicaux à risque bas au Japon – Certification par tiers
- Réglementations pour titulaires d'admission au marché
- Règlementation des dispositifs en Thaïlande
- FDA Thaïlandaise : Centre de service complet
- Documentation de systèmes de qualité en Thaïlande
- Autres nouvelles de la FDA Thaïlandaise

Actualité Environnement

- Emballage et ordures d'emballage
- Équipement électrique et électronique
- Batteries et accumulateurs

Actualité des Normes

- ISO/TR 14969: 2004
- ISO 14155 sur les essais cliniques
- Recommandations pour la standardisation de la nanotechnologie
- Images digitales et communication digitale en médecine

Références

- Compte rendu: Le future des dispositifs médicaux, est-il dans la convergence des technologies?
- Abécédaire: Standards harmonisés
- Règlement du New Approach - Partie 2
- Foyer de pays: Chine

Visión del Contenido

El Programa de Revisión Independiente del CDRH

A diferencia del proceso de autorización de pre-mercado usado en la Unión Europea para dispositivos médicos nuevos, donde los fabricantes/patrocinadores someten sus archivos técnicos o expediente de diseño a Cuerpos Notificados (Notified Bodies), la Oficina de Evaluación de Dispositivos del Centro de Dispositivos y Salud Radiológica (CDRH) de la Administración de Alimentos y Drogas (FDA) en los Estados Unidos, ha hasta recientemente sido el único revisor de todas las aplicaciones para pre-mercado incluyendo aplicaciones para la Excepción para Dispositivos Investigativos (Investigational Device Exemption), notificaciones de pre-mercado, y aplicaciones para aprobación de pre-mercado. Eventualmente el gran número de aplicaciones procesadas anualmente resultaron en períodos de repaso más largos y la acumulación de aplicaciones. En el 1996, CDRH comenzó un programa piloto que autorizó a entidades independientes, no asociadas con el FDA, a repasar aplicaciones de pre-mercado selectas. Un segundo programa de revisión independiente fue agregado más adelante. Ambos programas son voluntarios y el fabricante/patrocinador de la aplicación de pre-mercado todavía tiene la opción de someter la aplicación de pre-mercado directamente al FDA, aunque esos dispositivos sean elejibles para la revisión independiente.

En este artículo, **Rosina Robinson** mira al Programa de Revisión Independiente desde la perspectiva del fabricante/patrocinador del dispositivo médico, y no se dirige a los requisitos o procedimientos que hay que seguir para la acreditación del revisor independiente, o los requerimientos necesarios para mantener su condición independiente. Muchas de las referencias hechas en este artículo incluyen descripciones de estos requisitos.

El Movimiento Hacia un Sistema de Administración de Riesgos Basado en Tecnología de Computadoras (IT)

Dentro de las más obvias manifestaciones del consumerismo progresivo de la medicina, las agencies reglamentarias están reconociendo las limitaciones de los métodos tradicionales de adminitración de riesgos en el despliegue comercial de dispositivos médicos y farmacéuticos. En este artículo, **Terry Knapp** discute elementos específicos del Ensayo de Concepto del FDA, *Programas de Administración de Riesgos* (*Risk Management Programs*), y comenta en la manera en la cual soluciones modernas basadas en IT pueden ayudar a fabricantes, doctores, farmacéuticos y pacientes a derivar el mayor beneficio combinado con el menor riesgo en el uso de farmacéuticos, biologicos, y dispositivos médicos.

Información Clínical en la Unión Europea

Las regulaciones para el colocamiento de dispositivos médicos en el Mercado en la Unión Europea son prescriptos por varias Directivas de la Unión Europea, pero no están bien definidas. Concentrandose en la Directiva del Consejo 93/42/EEC (comunmente conocida como la Directiva de Dispositivos Médicos, MDD), **Haroon Atchia** explica que los requerimientos distinguen varias opciones disponibles para demostrar la utilidad clínica de un dispositivo médico dado, y exploran el papel de la Autoridad Competente en cuanto a lidiar con las aplicaciones de comienzo para investigaciones clínicas con el fin de obtener 'CE marking'.

Ubicación de los dispositivos médicos cuando el reembolso no es una opción (2)

La expectativa de 'reembolso' para una tecnología es asociada con tres procesos relacionados entre sí: la expectativa de que sea cubierto por seguros médicos, la factura y códicos de tratamiento que se le han asignado, y el pago actual, si es que lo hay, que genere cuando sea usada. En casi todos los casos, los procedimientos donde se usa la tecnología, y no la tecnología en sí, genera el reembulso. Como consecuensia, el precio de la tecnología puede ser la barrera más grande para la aceptación del producto a no ser que pagos adicionales sean incorporados en el reembolso de los procedimientos, o el comprodor se convenza de que la tecnología trae un valor clínico y económico intrinsico, que no esta atado al reembolso del procedimiento. Los fabricantes necesitan quantificar el 'valor' de la tecnología en maneras que sean significativas para los compradores y usarios para poder tener éxito con los dispositivos médicos.

En la primera parte de este artículo, que fue publicado en la edición de noviembre del 2004, **Nancy L Reaven** dio ejemplos de algunas de las razones más comunes por las cuales el reembulso no está disponible para tecnologías médicas en los Estados Unidos, y discutió estrategias para sobrepasar las barreras para la aceptación de productos. La segunda parte de este artículo enfoca en los incentivos financieros y las perspectivas que motivan a los compradores de tecnología, y sugiere varias vias de análisis para determinar el 'valor' apropriado.

Europa al Día

- El esquema de autorización en Dinamarca para tejidos y células humanas
- Reviciones del MDD
- Dispositivos que utilizan tejidos de animales
- Directiva sobre compatibilidad electromagnética
- Protección de información
- Equipo de mamografía en Francia
- Dispositivos diagnósticos *in-vitro*: nuevas regulaciónes en Francia
- Convenio de la segunda enmienda de la ley de DRG en Alemania
- Documento de guía Irlandes sobre el reportaje de incidentes adversos
- Dispositivos conteniendo tejidos de origen animal en Portugal
- Pagos al SUKL de la República Eslovaca
- Información Suiza sobre el uso de laseres de alta energía
- Documento de guía sobre balanzas médicas en Suiza
- Alertas de dispositivos médicos publicados por el UK MHRA
- Grupo en la UK de las industrias de mantenimiento de la salud

Estados Unidos al Día

- Reclasificación de dos dispositivos médicos de embolización
- Clasificación para dispositivos médicos externos para la rigides del pene
- Clasificación para sistemas de laser usados para asister en la reprodución
- Clasificación para dispositivos usados para quimica y toxicología clínica
- Clasificación para dispositivos de hospitales generales y de uso personal
- Reglas propuestas eliminadas
- HDEs, controles especiales y excluciones para la evaluación del ambiente
- Reclasificación de dispositivos para iontoforesis
- Dispositivos de un solo uso que han sido reprocesados
- Resumenes disponibles del MDTCA/MDUFMA
- Resumenes de documentos de guía finalizados por FDA

Internacional al Día

- Productos que no son dispositivos médicos en Australia
- Empaque indicativo de adulteración
- Productos diagnósticos de origen humano
- Esquema de reembolso para prótesis en Australia
- Guía de clasificación es publicada en Australia
- Borador de hechos del TGA es publicado
- Borador de documento de guía Canadiense para dispositivos con etiquetas privadas
- Documentos de SBD y ND para dispositivos vendidos en Canada
- Consejo de seguridad del Ministerio de Salud en Canada para camas eléctricas
- Productos antimicrobianos usados en dispositivos médicos en Canada
- Noticia de dispositivos en la China
- Sistema de Control Administrativo para Dispositivos Médicos en Hong Kong
- Acuerdos de Mercado Libre
- Kazakhstan se une al IEC
- Compatibilidad electromagnética para MRA en EC/US
- Japón publica borador sobre las regulaciones para IVD
- Dispositivos médicos de riesgo bajo en Japón – ceritificación de revision independiente
- Regulaciones en Japón sobre entidades que reciben autorización para vender al mercado
- Proyecto de Ley de Dispositivos Médicos en Tailanda
- El centro de servicio de una sola parada del FDA Tailandes
- Documentación del sistema de calidad en Tailandia
- Otras noticias del FDA Tailandes

El Medio Ambiente al Día

- Empaque y desperdicios de empaque
- Maquinas eléctricas y eléctronicas
- Baterias y acumuladores

Normas al Día

- ISO/TR 14969: 2004
- ISO 14155 sobre investigaciones clínicas
- Recomendaciones sobre la normalización de la nanotecnología
- Imágenes digitales y comunicaciones en la medicina

Información de Referencia

- Reporte de reunión: Es la convergencia de tecnología el futuro de los dispositivos medicos?
- Elementos Esenciales: Normas Armonizadas
- Regulaciones con un Nuevo Enfoque – Parte 2
- Resumen de País: La China

Information for Authors

When preparing an article for publication in the *Journal of Medical Device Regulation*, please ensure that you follow the guidelines set out below. We do accept unsolicited articles, Letters to the Editor or reference charts, but we recommend that you submit a short synopsis first. The Journal cannot guarantee publication of material submitted.

Content and style

- Articles should be original material and be current and educational in nature.
- Articles should be written in English, in a clear and concise manner using headings, bullet points, tables and figures where necessary.
- An abstract or summary of approximately 250 words should be provided with each article.
- A short biography of about 10 words should be provided for each author of an article.
- Authors are responsible for all statements in their work and for obtaining permission to use any previously published tables and figures. Authors will be asked to sign a copyright waiver form for the article before it is published.
- Any abbreviations should be defined in full the first time they are used followed by the abbreviation in parentheses.
- References should be provided at the end of the article and numbered sequentially. Please do not use codes that place references at the bottom of each page or reference managing programs to create reference lists.

Length

The following word counts may be used as a guide. Topics that require extended coverage can be submitted as a series (e.g. Part 1, Part 2).

Guest editorial	2000 words
Focus article	4000 words
News update	1000 words
Meeting report	1000 words
Case study	2000 words

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Articles will be edited for style, content, grammar and punctuation. Authors will be sent a copy of the edited article for review prior to publication.

Submission procedure

Ideally, articles should be sent by email as an attachment to editor@globalregulatorypress.com. Alternatively they may be submitted on a 3.5" diskette, preferably in Word for Windows or plain text format (ASCII). Please fax or send a hard copy of your article to:

Victoria Clark, Editor, *Journal of Medical Device Regulation*
Oaklands, 1 Glendinning Avenue, Weymouth, Dorset DT4 7QF, United Kingdom
Tel: +44 (0)1305 783020
Fax: +44 (0)1305 767379
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