Image: iStockphoto

Clinical Studies in Italy

Maria Donawa

First published in *Medical Device Technology*, **20**, 7 (November/December 2009).

The requirements for conducting medical device clinical studies in Europe are not identical in all Member States. That is, variations exist in the way that the requirements in the European Directives are interpreted and enforced. This article provides an overview of the requirements that currently apply in Italy.

Transposition of the revising Directive

New European medical device requirements, including those concerning the conduct of medical device clinical investigations, will come into force on 21 March 2010 as a result of changes introduced by the revising Directive 2007/47.[1] At the time of writing, these changes, as they will be transposed into Italian law, have not been made publicly available by the Italian Ministry of Health (MOH). For this reason, this article will discuss only current requirements for conducting clinical studies in Italy; however, readers should check the new regulations as soon as they become available. In the meantime, it is hoped that this discussion will be beneficial to companies needing to meet current requirements until the new ones come into force. In addition, the differences between the Italian requirements and the European Directives provide an example of the differences that can occur as a result of national preferences. Readers should be aware that all the MOH documents referenced or referred to in this article are in the Italian language only. The article will not discuss performance evaluation studies of in vitro diagnostic medical devices.

Notification process

The European Directive for Active Implantable Medical Device Directive (AIMDD) (90/385/EEC) was transposed into Italian law by the Decreto Legislativo 14 Dicembre 1992, N. 507 (Legislative Decree of 14 December 1992, No. 507).[2] The Medical Device Directive (MDD) (93/42/EEC) was transposed into Italian law by the Decreto Legislativo 24 Febbraio 1997, No. 46 (Legislative Decree of 24 February 1997, No. 46).[3] Information on the requirements for conducting medical device clinical investigations in Italy can be found on the Italian MOH's website.[4]

The requirements to notify the MOH of clinical investigations of AIMDs and medical devices subject to the MDD are virtually identical to the principal notification requirements in the AIMDD and MDD. That is, the manufacturer or his authorised representative must notify the Competent Authority (CA) of plans to conduct clinical investigations at least 60 days before the initiation of the investigations. The CA in Italy is the Italian MOH. The information that must be included in the notification is specified in Annex 6, Statement Concerning Devices Intended for Special Purposes, of the AIMD; and Annex VIII, Statement Concerning Devices for Special Purposes, of the MDD.

Companies wishing to conduct clinical studies in Italy must follow the procedures outlined in the Decreo 2 Agosto 2005 (Decree of 2 August 2005), Modalità di presentazione della documentazione per notifica di indagine clinica con dispositivi medici (Procedures for presenting documentation for the notification of medical device clinical investigations). The Decree, which can be obtained from the MOH's website,[5] includes requirements on the

- need to provide the notification in the Italian language
- procedures for transmitting the notification to the MOH
- fee to be paid
- contents of the notification
- declarations required from the manufacturer

Dr Maria E. Donawa

physician, pathologist and pharmacist with nearly 30 years' regulatory experience, worked with the US FDA before becoming President of what is now Donawa Lifescience Consulting, an international consultancy company, which provides regulatory, quality and European Authorised Representative services to life science companies and is a full service European CRO.

- attachments that must be included with the notification
- procedures to follow if the clinical protocol is amended.

A form, Modello riassuntivo per la richiesta di valutazione delle indagini cliniche con dispositivi medici (Summary form for requesting the evaluation of medical device clinical investigations), which is part of the Decree of 2 August 2005 must be used when transmitting the notification to the MOH; this form can be downloaded from the MOH's website.

The fee charged by the Italian MOH to review medical device clinical investigation notifications is €1859.25. Instructions on how and when payments should be made are included in the Decreto 2 Agosto 2005 and also in the Circolare del 5 Dicembre 2007 (Circular of 5 December 2007), which is discussed later. A receipt indicating that the payment has been made must accompany the notification.

Sixty-day waiting period

Paragraph 2 of Article 7 of the Italian transposition of the AIMDD specifies that the active implantable medical device cannot be used in the clinical study if, based on an opinion of the Consiglio superiore di sanità (the Higher Council of Health) (CSS), the MOH denies approval of the study and informs the interested parties within 60 days. It also indicates that the European Commission will be informed of the denial. Thus, this portion of the requirement in the Italian transposition is similar to the analogous requirement in the AIMDD, except for the involvement of the CSS in the decision-making process.

The second subparagraph of Article 10 of the AIMDD states that Member States may authorise manufacturers to start the clinical investigations before the expiry of the 60-day period, provided the relevant ethics committee has delivered a favourable opinion. The Italian MOH, in its transposition of the AIMDD, has decided to require CA approval in addition to ethics committee approval. It is important that manufacturers are aware of the requirement for CA approval so that they can avoid initiating a clinical investigation of an AIMDD before the expiration of the 60-day period, even though they may have obtained a favourable opinion from the ethics committee. An action of this type would constitute a violation of Italian law.

The requirements in Article 14 of the Italian transposition of the MDD are virtually identical with paragraphs 2 and 3 of Article 15 of the MDD, which allow the possibility of initiating a clinical study before the expiration of the 60-day waiting period, provided a favourable opinion has been issued by the relevant ethics committee(s). For example, paragraph 3 of Article 14 of the Italian transposition states that clinical investigations may begin before the expiration of the 60-day waiting period if the ethics committee has expressed a favourable opinion on the study(ies).

Nevertheless, the MOH has expressed an opinion that clinical studies should not be initiated until the entire 60 day period after notification has elapsed. This opinion is included in a letter (circular) sent by the MOH to Italian ethics committees.[6] This opinion is not legally binding, but it means that manufacturers are advised to wait until 60 days have elapsed before initiating a clinical study. Otherwise, if the MOH identifies problems within the 60 day period, there is a danger that an ongoing study would have to be stopped, which is likely to have significant negative effects on study time and costs. It is hoped that this type of difference will be avoided in coming revisions of the Italian transposition of the MDD and any associated nonbinding policy documents.

Clinical site requirements

Paragraph 4 of Article 7 of the Italian transposition of the AIMDD states that medical device clinical studies can be conducted only in public hospitals and institutions in accordance with procedures and methods established by MOH decree, taking into consideration opinions expressed by the CSS. No other details are provided in paragraph 4. The relevant decree to take note of, however, is the Decreto Leglislativo 30 Dicembre 1992, N. 502 (Leglislative Decree 30 December 1992, N. 502), Riordino della disciplina in materia sanitaria, a norma dell'articolo 1 della L. 23 ottobre 1992, N. 421 (Reorganisation of healthcare operations in accordance with Article 1 of Law 23 October 1992, No. 421), which is discussed below. This Decree outlines the requirements that public hospitals must meet if they are to be considered "Aziende ospedaliere" and "Presidi ospedalieri." There is no satisfactory English translation of these terms, which approximate to hospital corporations and hospital facilities.

Paragraph 4 of Article 14 of the Italian transposition of the MDD states that clinical investigations must be conducted in the Unità Sanitarie Locali (Local Health Units) and hospital corporations or facilities that meet the requirements in Article 4 of the Legislative Decree of 30 December 1992, N. 502 and subsequent amendments. The "Unità Sanitarie Locali" are now called "Aziende Sanitarie Locali" or Local Health Corporations. Furthermore, this paragraph states that the conduct of clinical investigations in other public and private health institutions must be approved in advance by the MOH. In addition, the Circular of 26 February 2007, which is discussed below, states that the approval process should be completed within 90 days; however, written approval is required from the MOH before the study can begin.

Manufacturers unaware of the clinical site requirements, which are not included in the AIMDD or the MDD, may spend considerable time and resources negotiating with clinical sites that will need prior approval by the MOH before a medical device clinical investigation can be conducted at the site. Therefore, it is important that manufacturers determine early in the process of identifying prospective clinical sites in Italy whether or not these will need to be approved by the MOH before the clinical investigations can be conducted at the site. →

➔ Clinical studies with CE-marked devices

The requirements for conducting clinical studies with CE-marked medical devices are in paragraph 7 of the Italian transposition of the MDD. This paragraph states that paragraphs 1, 2 and 3 do not apply if the clinical investigation is conducted with a device affixed with the CE mark, unless the investigation involves an intended use of the device that differs from the one covered by the CE mark. Paragraphs 1, 2 and 3 concern the need to notify the study and the 60-day waiting period. However, the requirements of Allegato X (Annex X), Valutazione Clinica (Clinical Evaluation) still apply. Although the AIMDD and the Italian transposition of the AIMDD do not specify requirements related to clinical studies with CE-marked devices, the MOH applies the requirements in paragraph 7 to clinical studies with AIMDs and devices covered by the MDD.

It is essential that manufacturers recognise that paragraph 4 of Article 14 of the Italian transposition of the MDD is not excluded by paragraph 7 of the transposion. This means that clinical studies with CE-marked devices used for their intended purpose, for example, for post-marketing clinical studies, must be conducted in public hospitals and institutions that meet the requirements set out in the Legislative Decree 30 December 1992, N. 502; or the clinical sites must be approved in advance by the MOH. This is further explained in the Circolare del 26 febbraio 2007 (Circular of 26 February 2007), which outlines the requirements and administrative procedures for conducting clinical studies with CE-marked medical devices. Additional clarification on this issue is provided in the Circolare del 5 Dicembre 2007 (Circular of 4 December 2007), which includes more information on the documentation needed to notify the MOH of a medical device clinical study. The Circulars can be obtained from the MOH website. A detailed discussion on the contents of these two important Circulars is beyond the scope of this article; however, manufacturers are urged to become informed of the procedures that the Circulars describe. Similar requirements are not in the AIMDD or the MDD.

Significant changes

This article has discussed some of the more important existing requirements for conducting clinical studies in Italy. It must be remembered, however, that the Italian MOH and other Member States are in the process of developing and publishing updated medical device requirements that will implement the revisions included in the revising Directive 2007/47. It is expected that significant changes related to the entire set of requirements for conducting medical device clinical studies in Italy will be introduced during this process to eliminate certain differences between Italian law and the European Directives and to introduce overall improvements to the current system. This will be welcomed by all parties involved in conducting medical device clinical studies in Italy.

References

1. Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007 amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices and Directive 98/8/EC concerning the placing of biocidal products on the market; http://ec.europa.eu/enterprise/medical_devices/legislation_en.htm
2. The document can be downloaded in Italian: www.ministerosalute.it/imgs/C_17_normativa_516_allegato.pdf
3. The document can be downloaded from www.normativasanitaria.it/normsan-pdf/0000/28917_1.pdf
4. www.ministerosalute.it/dispositivi/paginaMenu.jsp?menu=sperimentazione
5. www.normativasanitaria.it/jsp/dettaglio.jsp?id=1954
6. Lettera (Circolare) del 4 marzo 2005 ai comitati etici (Letter of 4 March 2005 to Ethics Committees), page 2; www.normativasanitaria.it/normsan-pdf/0000/23779_1.pdf

mdt

Maria E. Donawa
Donawa Lifescience Consulting, Piazza Albania 10, I-00153 Rome, Italy,
tel. +39 06 578 2665, e-mail: medonawa@donawa.com
www.donawa.com

First published in *Medical Device Technology*, **20**, 7 (November/December 2009).