US and European Postmarket Clinical Data Requirements

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Under United States regulations, the Food and Drug Administration may require manufacturers to collect postmarket clinical data. In Europe, the role of postmarket clinical follow-up is described in a guidance document, but not specifically mentioned in the European Directives. This article discusses the two systems, which are similar, but also different in important aspects.

US postapproval requirements

Before discussing United States (US) regulations on the collection of postmarket clinical data, it should be mentioned that in the US devices are classified into three risk-related categories: Classes I, II and III. Class I devices are those associated with the lowest risk and Class III, the highest. The discussion of postapproval requirements concerns Class III devices and the premarket approval (PMA) regulations in the US Code of Federal Regulations (CFR), 21 CFR Part 814, Premarket Approval of Medical Devices.

Under section 814.82, Postapproval requirements, the Food and Drug Administration (FDA) may impose requirements in an order approving a PMA application. For example, FDA may require

- prominent display in the labelling of the device and in the advertising of any restricted device, warnings, hazards or precautions that are important for the safe and effective use of the device
- inclusion of identification codes on the device
- the continuing evaluation and periodic reporting on the safety, effectiveness and reliability of the device for its intended use; in this case, FDA will state in the approval order of a PMA the reason or purpose for the requirement, the number of patients to be evaluated, and the reports that must be submitted.

Readers should refer to the regulation, which lists other types of postapproval requirements that may be imposed.

For example, as a condition of approval of a cardiovascular implant, FDA required a study to evaluate the longer-term safety and effectiveness of the device during three years of implantation. The study was required to include a certain number of patients from three clinical studies that had been conducted to support the PMA. The details of the clinical data to be collected were also specified. In addition, another postapproval study, including a larger number of patients enrolled from a specified number of geographically disbursed sites, was also required. Readers can find examples of approval orders for medical devices that require clinical studies to be conducted by searching the FDA's PMA Database on the FDA Center for Devices and Radiological Health's website: www.fda.gov/cdrh

It is important to note that a device may not be manufactured, sterilised, packaged, stored, labelled, distributed or advertised in a manner that is inconsistent with any conditions of approval specified in the PMA approval order. Furthermore, failure to comply with any postapproval requirement constitutes a reason for withdrawing a PMA.

US postmarket surveillance studies

In addition to including requirements in an approval order of a PMA, FDA can order postmarket surveillance for any Class II or Class III device under the regulation specified in 21 CFR Part 822, Postmarket Surveillance. This regulation implements section 522 of the US Federal Food, Drug and Cosmetic Act (FD&C Act) by providing procedures and requirements for postmarket surveillance →

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of any Class II and Class III device:
- the failure of which would be reasonably likely to have serious adverse health consequences
- which is intended to be implanted in the human body for more than one year, or
- which is intended to be a life-sustaining or life-supporting device used outside a device user facility.

In spite of the criteria listed above, there is no need for manufacturers to automatically submit postmarket surveillance data. Instead, FDA notifies manufacturers when the need for this type of information or data has been identified during the review of the marketing application or after the device has been marketed. For example, postmarket surveillance studies may be ordered to collect information on an unanticipated adverse event.

After receiving an order from FDA to conduct a postmarket surveillance study, manufacturers must submit a postmarket surveillance plan for approval within 30 days of receiving the order. The required elements of the plan are specified in the regulation. After receiving the proposed plan, FDA has 60 days to determine if the person designated to conduct the surveillance is qualified and experienced, and if the plan will collect useful data that can reveal unforeseen adverse events or other information necessary to protect the public health. It should be mentioned that FDA states that the collection of clinical data may take many forms and that prospective clinical study data will be necessary in only about 10% of all instances of postmarket surveillance.[1]

European postmarket surveillance

The conformity assessment annexes of the European medical device Directives require manufacturers to institute and keep up-to-date a systematic procedure to review experience gained from devices in the postproduction phase and to implement appropriate means to apply any necessary corrective actions. This requirement includes the obligation to notify the Competent Authorities of certain types of serious incidents. Table I shows the requirement as stated in Annex VII of the Medical Device Directive (93/42/EEC). Although there is some slight variation in the language in the various annexes and Directives, the requirements are the same. That is to say, manufacturers are required to implement a postmarket surveillance procedure or programme, which includes an obligation to report serious incidents to the relevant Competent Authorities.

The types of postmarket systems that should be implemented to satisfy the Directives has been widely debated. A Notified Body guidance document on postmarket surveillance[2] helps to address this issue, but it is extremely general. For example, the document states that postmarket surveillance systems are an integrated part of a manufacturer's quality assurance system. That is, in most cases, postmarket surveillance systems already exist as a part of the quality system to meet internal company needs and/or to meet the requirements of third parties. The guidance document also lists sources of information on postmarket surveillance data such as expert users groups, customer surveys, customer complaints and warranty claims and post-CE-mark clinical studies. Others are also listed.

European postmarket clinical follow-up

In May 2004, the European Commission issued a guidance document: Guidelines on Postmarket Clinical Follow-Up.[3] The purpose of the document is to provide guidance on the role of postmarket clinical follow-up (PMCF) in fulfilling European postmarket surveillance obligations. The document states that while clinical evidence is an essential element of the premarket conformity assessment process, there are limitations inherent to premarket clinical investigations. That is to say, the extent of the data that can be gathered in the premarket phase does not enable the detection of infrequent complications or problems, which become apparent only after widespread use, nor do they enable the detection of long-term performance issues. Therefore, appropriate postmarket surveillance programmes as part of the manufacturer's quality system are needed to identify and investigate the risks associated with the use of medical devices placed on the market. The guidance also states that manufacturers should have not only general postmarket surveillance systems, but a defined postmarket surveillance strategy for each product or product range. The document states that PMCF through clinical studies and registries has an important role in these possible strategies.

One of the more useful aspects of the guidance document is that it provides certain criteria to assist manufacturers in deciding whether or not PMCF is appropriate. For example, it states that PMCF should always be considered when assessment of a product is performed through the concept of equivalence. It also states that PMCF should always be considered for devices where the identification of possible emerging risks and the evaluation of long-term safety and performance are critical. The criteria that should be taken into account in identifying emerging risk should include:
- innovation, when the design of the device, the material,

Table I: Annex VII, Medical Device Directive (93/42/EEC).

The manufacturer shall institute and keep up-to-date a systematic procedure to review experience gained from devices in the post-production phase and to implement appropriate means to apply any necessary corrective actions, taking account of the nature and risks in relation to the product. He shall notify the Competent Authorities of the following incidents immediately on learning of them:

(i) any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which might lead to or might have led to the death of a patient or user or to a serious deterioration in his state of health

(ii) any technical or medical reason connected with the characteristics on the performance of a device for the reasons referred to in subparagraph (i) leading to systematic recall of devices of the same type by the manufacturer.

the principles of operation, the technology or the medical indication is new
- severity of the disease
- sensitive target population
- risky anatomical location
- well-known risk from the literature
- well-known risk of similar marketed devices
- identification of an acceptable risk during preCE clinical evaluation, which should be monitored over a longer term and/or through a larger population
- obvious discrepancy between the premarket follow-up timescales and the expected life of the product.

The document also stresses the importance of the PMCF plan, which can take the form of extended follow-up of patients enrolled in premarket studies, a prospective study of a representative subset of patients after the device is placed on the market, open registries, or a combination of these approaches. It also states that the Notified Body should review the appropriateness of general postmarket surveillance procedures, incorporating PMCF, as relevant, as well as PMCF plans and results for specific products. This evaluation would take place as part of the conformity assessment procedures and auditing of the quality management system.

Similarities and differences

It is evident that there are similarities between US and European policies and requirements for collecting postmarket clinical data, which may be in the form of clinical studies, registries or by other means. However, there are important differences and manufacturers should be aware of them. For example, in the US, the need to collect postmarket clinical data is determined by FDA, although manufacturers may voluntarily collect these data. It is an established process and defined in US regulations. In Europe, a guideline, which is not legally binding, describes European expectations for these types of data. This provides manufacturers with more flexibility in determining the need for postmarket clinical data and the type of data to be collected. At the same time, there will be more uncertainty regarding the correctness of these decisions and the adequacy of the postmarket clinical data that are collected until more experience is gained.

References

1. US Federal Register, 21 CFR Part 822, "Postmarket Surveillance," **76,** 109, p. 38879, 6 June 2002 (67 FR 38878).
2. Co-ordination of Notified Bodies Medical Devices (NB-MED) on Council Directives 90/385/EEC, 93/42/EEC and 98/79/EC Recommendation, Post-Marketing Surveillance (PMS) post market/production, NB-MED/2.12/Rec1 is downloadable from www.team-nb.org
3. European Commission, Guidelines on Post-Market Clinical Follow-Up, MEDDEV 2.12-2, May 2004. Downloadable from http://europa.eu.int/comm/enterprise/medical_devices/meddev/2_12-2_05-2004.pdf mdt

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