Making instructions for use available in Europe

Manufacturers need to proceed carefully and thoughtfully when posting product instructions online.

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The European Commission's guidance document MEDDEV 2.14/3 rev. 1 now allows IVD users to obtain instructions for use (IFU) online.1 The guidance document also specifies the requirements to be met by the manufacturer in providing IFU. Although these requirements are rather demanding, the guidance document creates an opportunity to reduce the cost and complications of sending multilingual IFU to the user in paper format or on CD-ROM.

Since the implementation of the European Directive 98/79/EC for IVDs medical devices (IVD Directive), manufacturers of IVD that distribute their products within the European market have been faced with finding ways to meet the diverse language requirements set forth by the various member states at the time of the transposition of the directive into national law.2

Thirty-one European countries are currently functioning within the regulatory framework provided by the IVD Directive. The majority of the member states have decided that the IFU for IVDs for professional use must be provided in their national languages. In practice, this means that a manufacturer active across Europe will need IFU in 15 to 20 languages.

The IVD Directive states that “Each device must be accompanied by the information needed to use it safely and properly.” Until last year, this requirement had to be interpreted literally, which meant that most manufacturers included IFU in each device package, usually in hard copy, or sometimes as a CD-ROM. Distributing the IFU over the Internet was not an option.

The richness of Europe's diverse cultures and languages came at considerable cost for the IVD manufacturer and for the environment.

Challenges Posed by the Traditional Means of IFU Provision

A manufacturer that wants to make its IFU available in the traditional way is confronted with many options. Table I gives an overview of how different solutions for IFU provision compare with each other according to different parameters.

	Paper IFU				CD-ROM		E-Labeling	
	In-house printing		Printing outsourced		In-house burning of small series	Outsourced pressing of large series	In-house development and operation	Outsourced to service provider
	European-wide IFU	Regional or national IFU	European-wide IFU	Regional or national IFU				
Cost								
Investment	High	High	Low	Low	High	Low	High	Low
Direct cost per copy	High	Medium	Low	Low	High	Medium	Low	Low
Operator time	Low	High	Low	High	Low	Medium	High	Low
Cost of redundant inventory	Low	Low	High	High	Low	High	Low	Low
Cost of telephone support	Low	Low	Low	Low	Low	Low	High	Medium
Operations								
Impact planning	Medium	Low	High	High	Medium	High	Low	Low
Interference in operations	Medium	Low	High	High	Medium	Low	Low	Low
Risk for technical failure	Medium	Medium	Low	Low	Medium	Low	Low	Low
Risk for error								
Risk for delivering wrong IFU to user	Low	Medium	Low	Medium	Low	High	Medium	Low
Effort to achieve regulatory compliance	Low	Low	Low	Low	Low	Low	High	Medium
Environmental								
Creation of waste in IFU life cycle	High	High	High	High	High	High	Low	Low
Use of natural resources and energy	High	High	High	High	Medium	Medium	Low	Low
User-friendliness								
Difficulties with access to IFU	Low	Low	Low	Low	Medium	Medium	Medium	Medium
Difficulties with legibility of IFU	High	Medium	High	Medium	Low	Low	Low	Low
Cost of waste disposal	High	High	High	High	High	High	Low	Low

Table I. Comparison of different solutions for the provision of IFU to the European user. Different operational, regulatory, environmental, and user-related parameters are evaluated.

The manufacturer has different options regarding the form of the IFU. Will the company use a paper format or a CD-ROM? In the case of a paper IFU, will the manufacturer provide one booklet that includes all the languages of its target markets in Europe, or will it make multiple package inserts, each with one language or group of languages? The latter decreases the cost of the IFU itself but raises additional questions: Does the firm include the specific IFU in each kit at kit assembly, which creates complications in inventory management? Or, does the firm include the specific IFU at the time of shipment when the destination of the kit is known, which causes significant complications of the shipment process?

There are decisions to be made about outsourcing of printing versus printing in-house. These decisions apply to both paper IFU and CD-ROMs.

In general, in-house printing of paper IFU provides more flexibility and facilitates keeping the inventory of IFU low by producing them for each batch separately. However, it requires

operator time, the cost per copy is relatively high, and multilingual booklets are usually voluminous and heavy and may simply not fit inside a small IVD kit.

Professional print shops can print IFU on large, thin paper sheets that are folded to fit into a small box. Although this helps manufacturers fit all the languages into the kit, these IFU—with their very small and condensed printing—are not particularly legible. Their cost per copy is low, provided that large quantities are ordered. However, most IVD manufacturers do not produce very large batches of product. In addition, they regularly update their IFU, which often results in large volumes of inventory going to waste, increasing the cost per used copy.

A similar situation applies to CD-ROMs. Burning CD-ROMs in-house offers advantages and disadvantages similar to printing paper copies in-house: flexibility and low inventory, but high cost per copy. Large quantities of CD-ROMs can be pressed at a lower cost per copy but with the same risk of discarding large quantities of unused stock.

Many factors determine the best choice for a particular manufacturer: number of products, number of languages, batch size, availability of internal resources, degree of internal organization, average size of a shipment, and more. However, whatever the solution, ensuring that the users will have their instructions in their native languages puts a significant financial and operational burden on the manufacturer.

An IVD manufacturer with a wide range of different products that makes 100,000 kits a year and prints a 40-page multilingual package insert double-sided on A4 paper (80-g quality) folded as an A5-size booklet will spend around €100,000 per year on printing costs alone. That manufacturer will use and ship five metric tons of paper per year.

The user in the laboratory usually only needs one copy of the IFU and only in his or her own language. In practice, that user will only keep one copy of that IFU. Since most IVD reagents are repeatedly sold to the same laboratory, the large majority of paper IFU or CD-ROMs are immediately thrown out. This increases the waste-disposal cost of the laboratory and places an unnecessary burden on the environment.

MEDDEV 2.14/3 Rev. 1: A New Situation

In January 2007, the European Commission published an official guidance document, “IVD Guidances: Supply of Instructions for Use (IFU) and other information for In-Vitro Diagnostic (IVD) Medical Devices” (MEDDEV 2.14/3 rev. 1). It is a “guide for manufacturers and notified bodies” that is “not legally binding” but has been jointly drafted by various interested parties including “competent authorities, the European Commission services, and industry,” according to the document's authors. As such, it can be regarded as reflecting positions taken by the stakeholders in the medical device sector, and one can assume that it will be followed within the member states and help ensure uniform application of relevant provisions of the Directive, as is stated within the document itself.

The guidance notes that the IFU for IVDs intended for professional use can be provided in either paper or nonpaper form, or they can be supplied by altogether different means, including:

- By providing a toll-free telephone number that one can call to have the IFU faxed, mailed, or e-mailed.
- By making the IFU available at a fax call-in number (i.e., “fax polling”).
- By making it available on a designated Web site.
- By distribution through the local sales organization.

Where the manufacturer elects to supply the IFU in a format other than paper, it must provide a toll-free contact number that can be used to have the IFU sent to the user.

IVDs to be used by laypersons or at the point of care are excluded from this guidance. Their instructions for use must still be delivered together with the product. Manuals for instruments must accompany the product at the time of the initial delivery also.

Provision of IFU through a Web Site (E-labeling)

The most attractive means for providing IFU is to make them available online. This practice is known as “e-labeling” (but the MEDDEV document itself does not include this term).

E-labeling sounds easy, but a closer look at MEDDEV reveals that important conditions and requirements apply.

Table II provides a summary overview of the requirements applicable to alternate means in general and to Internet-based IFU provision specifically.

The Web site itself must be a dedicated Web site or a dedicated part of a Web site and subject to further conditions (security, risk analysis, file format, etc.). Moreover, the user must have the opportunity to call a toll-free telephone number to request a hard copy of the IFU to be sent via fax or regular mail.

Both the development of a dedicated Web site that meets the requirements of the MEDDEV document and the development of a free telephone-number system in multinational, multilingual Europe represent significant challenges for the large majority of IVD manufacturers.

Requirements applicable to all alternate means of IFU provision	Requirements specifically applicable to IFU provision over the Internet
The device must only be used for professional use, excluding point-of-care applications.	Provide clear instructions to the user for readily locating the IFU on a dedicated area of the Web site.
Proper design and function of the IFU should exist for all means of supply. Provide documented verification and validation. Obtain notified body approval, if applicable.	Adhere to appropriate data security requirements in terms of physical security (availability of hardware and software and intrusion protection) and server certification (to ensure the user logs on to the appropriate server).
Perform risk assessment in light of product usage. Assessment to be reviewed by notified body.	Post files in a generic, read-only file format, such as PDF. The documents displayed and printed via the Web site must be identical in content to those included in the IVD kit in paper format.
The user should be informed that the IFU for the device will be supplied by other means.	Provide access to the reader of the provided file format; for example, a link for a download of Acrobat Reader.
The manufacturer must have a system in place to provide a paper copy of the IFU on request by the user at no additional cost in a timely manner. A toll-free telephone number must be available to the user.	

Table II. Summary overview of requirements that apply to e-labeling in the EU.

The Web Site

Many manufacturers include the IFU on their main Web site, usually for informational purposes only. The downloadable PDF document is often placed on a page with advertising or product information. This system would not meet the requirements of the MEDDEV guidance if the manufacturer were to present this as the only means of providing the IFU.

The Web site is subject to the requirements that apply to all the alternate means of IFU provision, the most significant of which are discussed here.

For starters, the manufacturer must ensure the proper design and function of the IFU for supply over the Internet and document its verification and validation as part of the quality system.

The manufacturer, informed by the views of healthcare professionals, must have carefully considered as part of its risk management the risks associated with the provision of the IFU over the Internet, especially in light of the product usage and the professional users' need. When doing such a risk analysis, the supply of the wrong version of an IFU is identified as one of the most likely errors to occur and to go unnoticed, especially when two versions are present in the market at the same time. The system must be designed in such a way that this error cannot occur.

Both the validation and risk assessment should be reviewed by a notified body, if applicable, as part of the conformity assessment process.

The aforementioned requirements also apply to the other means of IFU provision. In addition, the MEDDEV guidance contains some additional specific requirements for IFU supply through a Web site. These include the following:

The user must receive clear instructions on how to locate the IFU on a dedicated area of the Web site.

The Web site must meet appropriate data-security requirements in terms of physical security (availability of hardware and software and intrusion protection) and server certification (to ensure the user logs on to the appropriate server).

The IFU should be available in a generic read-only file format, such as PDF, and access to the reader program of the provided file format is necessary (for example, by providing a link to Adobe's Web site for downloading the Acrobat Reader software).

The documents displayed and printed this way must be identical in content to those included in the IVD kit when made available in paper format.

In practice, this means that a manufacturer will have to design a dedicated Web site, or a dedicated part of a Web site, based on risk assessment in order to minimize the probability of error or lack of access. The Web site must be validated in agreement with quality system principles, hosted in a secure environment, and certified.

Although not specifically required by the guidance document, manufacturers may consider compliance with standards and regulations on electronic records and electronic signatures, include change logs, and download statistics for quality assurance and marketing reasons, respectively.

Toll-Free Telephone Service

The MEDDEV guidance imposes the use of a toll-free telephone service that users in the laboratory can call to request IFU by mail, e-mail, or fax.

The MEDDEV guidance does not contain any specific requirements for the telephone service except that the manufacturer must have it and that it must be free for the user. What is easy

to execute in the United States (setting up one 800 number for the entire territory, in one language) becomes a gigantic task in Europe.

Each of the 31 countries has its own telephone companies, which work within their national context. Thanks to international agreements, an international 800 number system exists, but it cannot be used in all countries. Moreover, it has to be activated in each individual country and monthly fees paid for each country.

An equally challenging question is in which language the telephone operator should answer the phone. Fluency in English is growing but should not be overestimated. Many competent authorities have made their national languages mandatory for IFU. Communication problems over the telephone could lead to sending a wrong IFU or may prevent an IFU from arriving at the user's correct location. Therefore, the language question should be taken seriously. Ideally, each user should be answered in his or her own language, or at least a wide choice of languages should be offered. A call center could offer a solution but is expensive for an individual manufacturer to maintain. Most call centers offer a limited selection of languages anyway.

Outsourcing E-labeling

To avoid the costs of and efforts required for developing a compliant Web site and establishing a complicated European wide telephone service, outsourcing e-labeling is an option to be taken into consideration.

Outsourced e-labeling services are currently available to IVD manufacturers via a Web site specifically designed for this purpose and a continental, multilingual, free telephone service.

Outsourcing to a specialized service provider enables every IVD manufacturer to take advantage of the opportunity offered by the MEDDEV guidance. Each company will have to assess its supplier and its service with respect to the requirements of the guidance and of quality in general. It will also have to do some work to meet the labeling requirements. Nevertheless, for most manufacturers, the advantages in terms of cost, efficiency, and flexibility will quickly outweigh the initial effort to implement e-labeling.

E-labeling and the User in the Laboratory

Providing the IFU over the Internet creates a certain inconvenience for the user in the laboratory. That user must go to a computer and download the IFU in order to have a printed copy. If the user has no access to a computer with an Internet connection, he or she will have to call the free telephone number in order to request a copy of the IFU by fax, mail, or e-mail.

However, e-labeling also has clear advantages for the user. The manufacturer can make a user-friendly IFU available in an easily legible font on a practical paper size, such as Letter or A4. Many users will appreciate the reduced waste disposal cost and the benefits for the environment.

In March 2004, the German Federal Institute for Drugs and Medical Devices conducted a survey on different types of electronic labeling of medical devices. Whereas the users of the general medical devices had diverse opinions on the use of electronic labeling, in this study the IVD users' responses were generally “extremely positive.”

Conclusion

The publication of MEDDEV 2.14/3 rev. 1 creates a situation in which IVD manufacturers can more efficiently tackle the challenges presented by the language requirements in Europe by the provision of the IFU by alternate means. The latter includes the option to make IFU available on a dedicated Web site. Meeting the additional requirements applicable to this solution, including making available to all users in Europe a toll-free telephone number, is still an important challenge for most IVD manufacturers. Outsourcing to a professional e-labeling service provider should bring e-labeling within the reach of each manufacturer.

References

1. IVD Guidances: Supply of Instructions for Use (IFU) and other information for In-Vitro Diagnostic (IVD) Medical Devices, MEDDEV 2.14/3 rev. 1 (European Commission, Enterprise and Industry Directorate-General, Cosmetics and Medical Devices, 2007).

2. Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices, Official Journal of the European Community, L331/1, 1998.