Chapter 12

Labeling, Label, and Language: A Truly Global Matter

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12.1 Introduction

For most medical devices, the label on the product is the primary interface between the user and the product. As an integral part of the product proper, it provides a visual way to verify that the product in the packaging is what the user intends to use and ensures the packaging is used as intended (e.g., for a sterile, double packed product). But labeling is a lot more—it encompasses the whole interface between the user and the manufacturer. Labeling tells the reader what the product may be used for and when not, what benefits and risks it is expected to have, and which precautions the user should take or consider when used as intended. Some legal labeling definitions include any and all promotional utterances, while others restrict its remit to the printed materials

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that accompany the product. Labeling also establishes the use intended by the manufacturer and depending on the classification of the product, may have been reviewed in the regulatory submission.

But all labeling must be based on the risk management performed by the manufacturer during design and development, no exceptions. This pivotal document dictates not only in essence the labeling content but also the fundamentals upon which the clinical evaluation of the product should be based. So, as the product is on the market, the experience gained in the "post-market" phase will dictate through its feedback on the risk management an evolution of the labeling content commensurate with the stage in the life cycle of the device.

Labeling and languages are often mentioned in one breath. However, languages required by the respective countries or economies are just a subsection of the need to adapt the language of the instruction for use to the intended user or users. Complicated use of even absence of the native language of a user may defy the purpose of communicating the essential elements of the information required to use the device safely and for its intended use. So, labeling language should be interpreted in those two distinct ways. It constitutes a critical aspect of Human Factors in Design and other core considerations when creating a new product or adapting an existing one.

An aspect not always appreciated is that "world" languages such as English, French, Spanish, and increasingly, Mandarin Chinese, have an (often unintended) impact beyond the national borders of the jurisdiction for which they were intended. This may lead to conflicting versions of label content in different countries and, thus, cause confusion among the readers. This calls for a global harmonization of labeling content—a lofty but often elusive goal. Note that label content is distinguished from the indications for use, which is also conveyed by the labeling. There can often be different indications for use based on what the manufacturer was able to substantiate in their regulatory submission in a particular market. (Or stated another way, what the regulatory authorities in a particular market were comfortable to accept as indications for use based on the clinical data.)

Finally, the revolution in information has impacted the requirements put forward by notably hospitals and other electronically advanced users. While we included the information available at this time, this is most certainly the aspect that will need to be updated in the next five years.

12.2 Definition of Labeling

Labeling means different things in different countries. The European Medical Devices Directive 93/42/EEC as amended by Directive 2007/47/EC (the MDD) does not define labeling per se or its constituent components. Apart from the ubiquitously present stipulations in the MDD when and where the CE-marking must be affixed, par. 13 of Annex I (Essential Requirements) spells out in great detail which information must be supplied by the manufacturer. The elements of labeling mentioned there are limited to the information accompanying the device (i.e., package insert or instruction for use, which includes a manual for large or complex devices) and the label(s) proper for individual units either on the product itself or on the unit packaging, on the "sales packaging." Terms such as "shipping carton," labeling for double packaging, and other commonly used designations have not been codified in the law.

One of the key elements of labeling in the near future will be the use of a UDI, a unique device identifier. While the idea itself makes eminent sense, it must be feared that in absence of a well-defined electronic structure allowing for the proper handling and management of the huge quantity of data influx, the objective of the electronic tracing of individual products from the manufacturer to the user will stay an illusion for many years to come. To this end, the Global Harmonization Task Force (GHTF) has issued guidance on UDI [1] (UDI System, September 16, 2011) which implores countries to consider the GHTF guidance in promulgating regulations on UDI. It would appear the USA FDA will be the first in line to publish a draft rule (expected in the fall of 2011) [2]. The FDA has published this draft UDI as a proposed rule (Federal Register, Vol. 77, No. 132, 10 July 2012). http://www.gpo.gov/fdsys/pkg/FR-2012-07-10/

html/2012-16621.htm; however, the EU, with their revision of the medical devices directives, will similarly seem to require UDI [3]. The draft Medical Device Regulation introduces the use of UDI. http://www.gpo.gov/fdsys/pkg/FR-2012-07-10/html/2012-16621.htm.

As the concept of "labeling" in Europe means different things in the respective EU Member States, vastly different regulatory regimens exist. France, Germany, the United Kingdom, and even Italy and Spain show an increasingly strong enforcement of their respective laws concerning promotion, including the Internet. The enforcement of a harmonized label content (especially concerning intended uses, indications, and claims as well as contra-indications) is just beginning, enhanced by the COEN (Committee of Enforcement), and lately by the CMC (Central Management Committee), two Member State-only committees that promotes a coordinated approach toward interpretation and implementation of laws and regulations for devices.

Based on Title 21, Section 820.1 of the Code of Federal Regulations (CFR), the United States has had a long and historically driven tradition of strong and sometimes even heavy-handed enforcement of labeling compliance. Labeling in the United States means any written or verbal expression of information accompanying or concerning the device and controlled in any way by the manu-facturer, including but not limited to labels in the strict sense, promotional materials, any verbal statement by company representatives, the Internet, and even information about products not yet approved but shown to the public at trade fairs. The FDA is strictly monitoring the compliance of labeling content with the claims approved. Any proof that a manufacturer is intentionally or commercially exploiting the often gray area of "off-label" use can lead to draconian fines and/or criminal prosecution.

In Korea, a medical device label is one attached onto the outer most packaging though there does not appear to be an official reference to the definition of labeling. In China, NMPA (National Medical Products Administration) Order No. 10 regulates the labeling (Instructions, Labels, and Packaging of Medical Devices). There are 23 Articles in the Order. Countries such as Singapore and Hong Kong, which use more GHTF (or

AHWP)-like regulatory systems, have similarly defined labeling as in the EU.

12.3 Elements of Labeling

Labeling may consist of the following:

- The label proper (see above) increasingly including the UDI code.
- A manual, instruction for use, package insert, etc., intended for the intended user(s).
- Where applicable or demanded by laws or regulations, promotional materials where they relate to the "approved" claims or intended uses. For instance, where an insulin pump must not be used when the user is swimming, the manu-facturer or distributor cannot show a lady on the beach wearing that pump. (Historic example! The case was whistle-blown by a competitor and the manufacturer cancelled the ad.)
- Materials placed by a manufacturer or a distributor of the product on the Internet or spread by e-mail, social media, involuntary pop-ups, etc. This is such a growing and complicated subject that we will treat it separately further in this chapter. Suffice it to say here that electronic utterances that are in perfect compliance with the laws in one country may be offensive in another, even when the national language of the latter country is not used. A historic example springs to mind: When a representative of a UK-based company showed a training video to illustrate the use of a new invasive surgical device (hardly glamorous) to physicians, he was arrested in Libya for "pornography." The video had used a female patient.

A good source for labeling content guidance is the GHTF document "SG1-N70:2011 Label and Instructions for Use for Medical Devices," issued on September 22, 2011. It is a bit general but gives a solid basis for which aspects of labeling should absolutely be considered before placing a device on the market. Also, while there are country differences and deviations, there is

generally a core set of elements in labeling, which is captured in the GHTF guidance.

In many countries in Asia, South America, and even North America (Mexico specifically), there is a requirement that the medical device registration number be included on the labeling.

In Korea, labeling is generally a sticker that is attached onto every product intended for the Korean market, which must include the information about the following: KFDA registered model number, manufacturer information, Korean license holder information, KFDA registration number, manufacturing date/lot number, etc. In China in particular, the NMPA Order No. 10, Article 8, stipulates the number of the Import Medical Device Registration Certificate (IMDRC) number as well as the reference to the relevant technical standards.

The Australian system leverages the EU system, and generally labeling developed for the EU can be used in Australia with the addition of the Australian Sponsor. In New Zealand, the Medicines Regulations 1984, Regulation 12(4) [4], establishes the requirements for the labeling of medical devices. The regulation states, "No person shall sell any medical device that does not bear the name of the manufacturer of the medical device or the name of the manufacturer's distributor in New Zealand."

In Hong Kong, the Medical Device Administrative Control System (MDACS) is modeled on the recommendations of the GHTF, and, thus, compliance should not be particularly burdensome for products that have already met the criteria in the EU. The labeling requirements are delineated in Appendix 3, Additional Medical Device Labelling Requirements of the guidance, GN-01. Again, the device's Listing Number ("HKMD No. ####") needs to be on the label. There is guidance on labeling in the form of the Singapore Health Sciences Authority (HSA) GN-23 Guidance on Labelling for Medical Devices, August 2009; and, again, the medical device regulatory system in Singapore is largely based on the GHTF guidance documents.

The applicable Brazilian labeling requirements are described in Resolution RDC No. 185, Annex III.B, information on the labeling and IFU for medical devices. The name and address of the Brazilian importer should be included if appropriate (2.1),

but more specifically, the Brazilian Registration Holder, technical expert certified by ANVISA, technical expert's name must be delineated on the label (2.11). Also, once ANVISA has accepted the application, the ANVISA registration number must be included on the product label preceded by "ANVISA" (2.12). For the most part, Resolution RDC No. 185, Annex III.B, resembles the MDD, Annex I, ER, Section 13. Information supplied by the manufacturer.

In Chile, at the writing of this section, only a limited number of products are subject to mandatory control by the ISP: examination gloves, surgical gloves, condoms, and sterile hypodermic needles and syringes for single use. The regulatory framework for medical devices is based on Law 19,497 and Products Control Regulations and Medical Use Elements (DS No. 825/98), and Article 26 discusses the labels. Again, as observed in many countries, the Chilean device registration number issued by the ISP must be included as well as all the standard elements.

12.4 Risk Management, Clinical Evaluation and Labeling: The Core Triangle for Safe and Effective Use of the Device

Few risk analyses are concluded without specific inclusion of risk mitigating statements in the labeling, mostly in the instructions for use. These statements are commonly divided into contra-indications, warnings when used as intended, precautions to be taken before or after device use, and which side effects may be expected, as well as other considerations. Most countries do not define under which header a particular statement must be placed; however, this aspect is usually emphasized by a regulatory authority whenever a risk mitigating statement is insufficiently complied with by the user, sometimes replete with the instruction to print bold or similar.

Clinical evaluation and investigation are the tool to validate critical labeling content, e.g., under what conditions the device should be used, what performance specifications may be expected, what precautions need to be taken, etc. Very important, the specific nature, relevance and incidence of adverse events or

incidents must be critically evaluated, as it directly relates to the expectations expressed in the initial risk assessment. The final conclusion about the risk/benefit ratio is frequently determined by the capability to address the residual risks adequately by explicitly stated warnings in the instruction for use or the manual. Any risk that turns out to have been underestimated in any way will have to be reassessed, especially whether it can be mitigated by improved design and/or labeling content, or poses an insurmountable block to further use.

So, even though the labeling content is drafted in the course of the design development, the adequacy of the instruction for use can only be verified when it is applied in practice, i.e., in a clinical investigation or in the post-market phase. (Note also, the regulatory authority review of the regulatory submission can lead to changes in the labeling content as well.) Consequently, the post-market surveillance (PMS) is the single most important feedback phase in the life cycle of a label. This is where refinements of the actual handling, expanded indications (if they do not require further corroboration), more detailed warnings, precautions, etc., as well as government-dictated insertions occur. For instance, in a case not too long ago, the United Kingdom demanded that for a relatively low-risk device, a cautionary statement be included about the lack of data for pediatric use, and consequently, the restricted use in patients under 16. In another case, the French agency determined that the package insert of mammary implants must display a warning that such products may interfere with the effectiveness of classic mammography.

This leads to one more consideration: In this global age, any intervention at the government level of one country will lead to inquiries by other regulatory authorities, especially if the initial intervention originated in one of the GHTF founding countries, but increasingly also in emerging economies. This puts a big stake in the proper formulation of label content.

In conclusion, any significant deviations between the risk assessment, the results of clinical evaluation, and the labeling will likely lead to problems for the manufacturer. Both competitors and regulatory authorities are watching this matter closely!

12.5 Labeling and Promotion

A general rule is that promotion must be consistent with labeling. A medical device cannot be promoted beyond the comments delineated in the labeling for which the manufacturer obtained the regulatory approval, clearance, or registration. It is not common for manufacturers of medical devices to be marketing professional-use medical devices to consumers.

Widely different regulatory regimens exist for promotional materials for devices. For example, in the EU, promotion and advertising are not explicitly discussed in the MDD, nor in the proposed Draft Revision of the Directives.

Promotion directed to patients or lay users may also be regulated differently [5]. This is specifically the case in Australia, where a code exists: the Therapeutic Goods Advertising Code 2007 [6]. Advertisements related to medical devices directed to consumers must comply with this code.

Many lesser developed economies do not have specific regulations for promotional materials, or they may be regulated by pharmaceutical laws.

12.6 e-Labeling, Web Sites, Internet, and Social Media: A Brave New World for Labeling

While the term e-labeling has been widely accepted to mean electronic labeling, the official reference to the source was not readily apparent, of course, an adoption from the moniker electronic mail, "email." For the purposes of this discussion, electronic should mean non-paper though this is a moniker that each regulatory environment will need to define.

At the time of this writing, Europe appeared to have made the greatest accomplishment with e-labeling. A European guidance, MEDDEV, was published in 2007 on e-labeling of IVDs [7]. The guidance established the use of the other-than-paper format IFUs (different media) by different means of supply for certain categories of in vitro diagnostic devices. There were, of course, very stringent provisions that needed to have been addressed

in order to supply IFUs by different media and through different means of supply, not withstanding a toll-free telephone number. A toll-free number within the 27 EU member states as well as Norway, Iceland, Lichtenstein, and Switzerland is quite a feat! In the summer of 2011, the European Commission issued draft regulations on electronic labeling (e-labeling) and shared these publically as part of their WTO Technical Barriers Trade activities [8]. At that time, the publication date was December 14, 2011. While this date has passed, this legislation is expected in Q1 2012. There is now published an EU Commission Regulation (Regulation (EU) No 207/2012) on electronic instructions for use of medical devices. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:072:0028:0031:EN:PDF.

While recitals are in essence background comment without legal merit, Recital (3), of the draft indicates: "In order to reduce potential risks as far as possible, the appropriateness of the provision of instructions for use in electronic form should be subject to a specific risk assessment by the manufacturer." Ultimately, provided the medical device meets the provisions of the legislation, this still needs to be considered. This, of course, is similar to the recommendation for labeling, provided the device in the EU is a category that qualifies for e-labeling; ultimately, the decision is risk management related.

> *"The draft Regulation sets out conditions according to which instructions for use in paper form may be replaced by electronic instructions for use. It limits the possibility of providing instructions for use in electronic form to defined medical devices and accessories intended to be used in specific conditions. Furthermore, it contains a range of procedural safeguards. Thus instructions for use have to be provided in paper form on request, and a specific risk assessment by the manufacturer and information on how to access to the instructions for use is needed."*

The draft Regulation also sets up a few basic safety requirements for the following:

- *instructions for use in electronic form which are provided in addition to complete instructions for use in paper form*
- *Web sites containing such instructions for use*

Article 1 of the draft legislation states the premise that information supplied by the manufacturer may be in "electronic form instead of in paper form." Article 2(2) describes electronic

IFUs: electronic form by the device, electronic storage medical with the device, and on a Web site. Only manufacturers of explicit categories of medical devices can consider e-labeling (Article 3(1)): fixed installation, implanted medical devices, devices built-in system visually displaying the IFUs, software, and professional use.

As it stands, many of the AHWP members do not accept e-labeling. In Korea, the package insert including intended use, instructions for use, etc., can be provided in an electronic format such as a CD ROM [9]. In China, e-labeling is not permitted, *per se*, but can certainly be provided in addition to the paper version.

At this time, one can comfortably assert that there is nothing to preclude provision of hard copy labeling with e-labeling. Whether e-labeling alone is accepted is an entirely different matter and will likely be increasingly permitted over time.

Early 2012, social media have yet to make a visible impact on the sale or promotion of medical devices. It is to be expected that we will see an increased use of sale channels especially for "OTC" devices. This is addressed cursorily in the proposed European Draft Regulation to become enforceable later in this decade.

12.7 Language, Language Level, and Intended User

One of the more critical aspects of the labeling content is the language. The famous non-verbal IKEA® "manuals" and labels do not use any language predicated on the assumption that every individual will recognize certain pictures and symbols. The same is true for the universally recognized symbol for "exit." So, the problem posed by the limited space (as well the high cost) on most devices relative to the need for translation in national languages has been partially resolved by the use of symbols. Insofar these have been included in the "Harmonized Standard" European standard EN 980, there is a "presumption of compliance" with the respective subsections of the ER 13 of Annex I of the MDD. Any other symbols, including but not limited to those in ISO 15223, must be explained in the instruction for use in all

applicable languages. That said, EN 980:2008 at the time of publication of this text will have been withdrawn, and the EN harmonized standard EN ISO 15223-1:2012.

In the United States, the use of symbols is much less appreciated. There, as well as in many other mainly Anglosaxon jurisdictions, culture dictates a graphic description of details in the instruction for use, which in the United States is also driven by the fear of liability for anything not explicitly expressed in the labeling. Health Canada does not explicitly state that symbols are accepted and Health Canada does not recognize EN 980 or ISO 15223 though Health Canada appears to accept symbols. While this attitude is most outspoken in the Anglosaxon cultures, it tends to become also increasingly prominent in other ones. The ultimate result is an instruction for use or manual that is for most intended readers, at best difficult to access or comprehend.

Brazilian RDC No. 185, Annex III.B, Section 1.4, permits the use of symbols; however, symbols must comply with regulations and technical standards. If there are no regulations or technical standards applicable, symbols used must be described in the IFU. The standards that are published by Associação Brasileira de Normas Técnicas (ABNT) include ABNT NBR ISO 15223-1:2010 titled *Productos para a saúde—Símbolos a serem utilizados em rótulos, rotulagem e informações a serem fornecidas de produtos para saúde*.

This dilemma between readability and completeness has been partially resolved by demanding that manufacturers develop and enclose instruction for use that represents a language comprehension of a 12-year-old individual, taking into account that the language used is native. The use of a language other than the native language(s) is in most countries of the world restricted to higher professional users or specialists. For instance, an insulin pump might be used by an array of users from a highly educated physician diabetologist to a semi-literate elderly person. An implantable left ventricular assist device (LVAD) may have up to four different manuals for the respective users of the device and its accessories.

The EU requires that the knowledge and experience of the user be considered (MDD Annex I, Section 1). In the United States, there

has been greater emphasis on human use factors [10]. One should not dismiss the standard of IEC 62366:2007, Medical Devices—Application of Usability Engineering to Medical Devices. Human use factors have implications on the labeling, which should also be considered.

Then there is the language proper. Especially in multi-country or -language areas (most of the world, actually….), it is very difficult for a manufacturer to develop an instruction for use with sufficient coverage of languages to satisfy the users' needs. Oddly enough, it is here that e-labeling (see elsewhere in this article) accessible by smartphones could provide a very legitimate solution. This appears to be a very cost-effective, environmentally friendly, and practical solution for many sparsely populated or developing regions of the world, with the only limitation being expressed by the saying "you can lead the horse to the well, but you cannot make it drink": The user—even an educated one—should at least a few times, read the instructions for use and not discard them unread when opening the package.

12.8 Conclusion

Labels and labeling are among the most important parts of a medical device. While cultures, educational levels, reading proficiency, and familiarity with a product do vary, manufacturers must pay utmost attention to the formulation of content for the respective components of labeling to ensure the safe use of the device when used as intended. The use of language commensurate with the various intended users is critical, as is the effort by the manufacturer to keep the labeling contents current to the knowledge gained by the use of the product in practice.

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