Writing for medical devices compared to pharmaceuticals: An introduction

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Abstract

The inherent differences between medical devices and drugs have implications for clinical research and medical writing. In view of the current move to more stringent regulatory requirements for the medical device industry, an increasing demand for suitably experienced medical writers is anticipated. The present article introduces writing for medical devices, highlights differences compared to communicating drug information, and explores the relevant regulatory guidelines. Our focus is on the European environment.

What is a medical device?

The term "medical device" refers to any instrument, apparatus, software, implant, reagent, material, or other article intended to be used for medical purposes and which does not achieve its principal action by pharmacological means.[1] This could mean anything from a simple syringe to a new hip implant. Confusingly, some devices do exert a pharmacological effect, e.g. a drug eluting vascular stent. But what is important in terms of classification is that this is not their principal mode of action. Another important subclassification is an "active device", this refers to a medical device which depends on a source of energy or power for its action, e.g. the battery in a cardiac pacemaker (Table 1).

What are the main differences compared to medicinal products?

There are a number of important differences between medical devices and medicinal products of which the most visually obvious is that the former may also be used outside of the body (e.g. *in-vitro* diagnostics, blood bags, or MR scanners).

Most importantly, as medical devices do not achieve their principal action by pharmacological means, they have fewer opportunities to interact with the human body as compared to the myriad possible systemic effects associated with a medicinal product. Nevertheless, medical devices still have the potential to cause harm, e.g., by introducing infection, promoting thrombosis, stimulating allergy, or causing conduction disturbances. Such complications are generally caused by biophysical mechanisms and can usually be anticipated. This means that a smaller cohort of subjects are needed to confirm safety and performance of a medical device, which in turn results in a faster product approval process compared to a medicinal product. For the latter, it is recognised that unexpected side effects can still occur despite extensive routine testing in large numbers of patients. Such adverse events have resulted in a number of high profile disasters and drug withdrawals, but also some unexpected benefits; e.g. Viagra™ was originally developed as an antianginal treatment.[2] Similarly, minoxidil, now a blockbuster for hair loss, was previously marketed as an antihypertensive agent.[3] Certainly, a knowledge of pharmacokinetics, pharmacodynamics, and pharmacogenomics is very relevant in the development process of medicinal products, something which is not the case for most medical devices.

A further difference between drugs and devices resulting from their different modes of action is that the latter is relatively simple to alter and changes rarely have detrimental effects. It is not unusual, for example, to see several product

Table 1. Definitions

Term	Definition	Further explanation / Examples
Active medical device[1]	A medical device that depends on a source of power, usually electrical.	e.g. cardiac pacemaker
Clinical data[5]	Safety and/or performance information generated from clinical use of a device.	Clinical data are related to the device in question or a similar device for which equivalence has been demonstrated. Clinical data can be sourced from (a) clinical investigations, (b) scientific literature, or (c) published and/or unpublished reports on other clinical experience.
Clinical evaluation[5]	A methodologically sound ongoing procedure to collect, appraise, and analyse clinical data pertaining to a medical device and to evaluate whether there is sufficient clinical evidence to confirm compliance with relevant essential requirements for safety and performance when using the device according to the manufacturer's Instructions for Use.	Submission of clinical evaluation report (CER) is required as part of the approval process allowing market access (CE-mark) for a medical device.
Clinical investigation[17]	Any systematic investigation or study in or on one or more human subjects undertaken to assess the safety, or performance of a medical device.	Synonym: Clinical study
Device deficiency[7]	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. This includes malfunctions, use errors, and inadequate labelling.	e.g. balloon rupture, unsterile packaging, kinking of the device
Device registry[17]	An organised system that uses observational study methods to collect defined clinical data under normal conditions of use.	Similar to Phase IV studies in drug research.
Equivalent device[5]	A device for which equivalence to the device in question can be demonstrated.	The equivalent device shall have similar technical, biological, and clinical characteristics, e.g. same intended purpose, similar design, made of same materials
Feasibility study[5]	Clinical investigation that is commonly used to capture preliminary information on a medical device (at an early stage of product design) to adequately plan further steps of device development, including needs for design modifications or parameters for a pivotal study.	Not all novel medical devices require feasibility studies.
Investigator's brochure[7]	Compilation of the current clinical and non-clinical information on an investigational medical device(s), relevant to the clinical investigation.	Also called "Clinical Investigator Brochure"; is required for studies involving a non-approved, investigational medical device.
Medical device[1]	Any instrument, apparatus, software, implant, reagent, material, or other article intended to be used for medical purposes and which does not achieve its principal intended action by pharmacological means.	e.g. plasters, blood bags, catheters, sutures, surgical instruments, bone cements, hip implants, stents, heart valves, CT scanner, hospital laboratory equipment etc.
Pivotal study[13]	A clinical investigation adequately designed and powered to collect definitive evidence of benefits to the patients, clinical risks, clinical performance, and/or clinical aspects of a device for a specified intended use.	Pivotal studies are commonly used to gain CE-certification

iterations being tested throughout the course of a study to "fine-tune" the design. By comparison, in the pharmaceutical industry, making a small change to a molecule can have major consequences. Again, a positive example: acetylation of salicylic acid to make acetylsalicylic acid (ASA) was found to significantly reduce the associated side effects resulting in the success story we now know as aspirin.[4]

How are devices classified?

As mentioned, medical devices can be anything from a pair of surgical scissors to an implantable heart valve. Because the associated dangers are very different, four risk profiles have been established: Class I, IIa, IIb, and III (Table 2). The approval pathway of a device depends on the risk class and becomes increasingly more demanding with ascending risk. For Class I devices (low risk), scientific data are commonly not needed while (with a few exceptions) information from clinical research studies are essential for high risk Class III devices.

To simplify getting your product onto the market, it had until recently been relatively easy to use data from "equivalent devices" which look and function in a similar manner, instead of seeking new data from the investigational device itself. Expressing this in simple terms, you could claim that because your new urinary catheter was made of similar material to that of another urinary catheter on the market, approval was justified. This approval route has now been made more difficult by the recently released MEDDEV 2.7/1 Rev4 guideline (see below).[5] It now requires more technical details to be provided in an application in order to demonstrate equivalence. Such information is commonly not published and is unlikely to be made freely available by a competitor company. Therefore, in the future, more clinical trials will be required for market approval.

> The usual procedure is to first "bench-test" the device, e.g. study a certain physical property of a device such as the elastic recoil of a stent. Thereafter, research in animals may be required.

Once market approval is obtained, the product is allowed to display the *CE* (*Conformité Européene,* literally "European conformity") mark – the same sign you may see on the side of a hair dryer – allowing you to distribute your product throughout Europe subject to periodic review.

How is a medical device developed?

Medical devices are specifically developed to meet a clinical need; the first step is to come up with a possible solution for this need and the second step involves building prototypes. This is commonly undertaken by engineers, often in close cooperation with physicians. For instance, the first heart valve was developed by a retired engineer with a background in hydraulics and fuel pump technology in cooperation with a surgeon.[6]

The usual procedure is to first "bench–test" the device, e.g. study a certain physical property of a device such as the elastic recoil of a stent. Thereafter, research in animals may be required. While such studies work well for certain parameters, e.g. toxicity testing or assessing degenerative behaviour, they are often insufficient to predict ultimate behaviour in humans. For example, positioning of the device, frequency of rapid pacing, acceptance of paravalvular leakage, and degree of oversizing were just a few of the many issues that had to be addressed during the first transcatheter heart valve studies. Consequently, devices requiring complex implantation techniques are often subject to feasibility studies to see if the whole procedure works as intended before embarking on pivotal studies.

How do study types and clinical investigation plans differ for medical devices?

Medical device studies are not classified into Phase I to IV studies as in the pharmaceutical industry. Instead, a variety of terms with similar meanings exist. Table 1 offers some guidance on definitions and Table 3 compares the phases of drug and device development. For the latter, study numbers are usually smaller and healthy volunteers cannot be included for ethical reasons. Also, blinding or placebo treatment may be more challenging with certain devices.

The minimum content requirements for a clinical investigation plan are listed in the International Quality Standard document ISO14155: Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice (ISO14155).[7] In contrast to drug research, the Medical Dictionary for Regulatory Activities (MedDRA) coding is rarely used. Instead, disease-specific endpoint definitions (e.g. the Academic Research Consortium Guidelines)[8] may be more relevant. Indeed, a number of disease-specific guidelines exist which provide recommendations on approval pathways for medical devices (e.g. the recommendations of the European Society of Cardiology – European Association of Percutaneous Cardiovascular Interventions Task Force on the Evaluation of Coronary Stents).[9,10] Adverse event definitions *per se* are basically the same as for drug studies, but in medical device research the term "device deficiency" is also relevant as it refers to product issues that did not necessarily lead to an adverse event (Table 1).

The reader may find it useful to see how a clinical investigation plan might look by visiting EMWA's webinar archive[11] or by searching journals which require the inclusion of a clinical investigation plan as supplemental material, e.g. the New England Journal of Medicine.[12]

A central issue for the safe and effective use of many medical devices is physician's experience. This in turn requires training and practice, particularly in relation to implantable devices. Such experience can in part be gained using simulators and animal models. In order to support adoption of their product, companies need to provide comprehensive and easily understandable training material. This physician-focused material contrasts with the patient-focused information leaflets encountered in pharmaceutical practice. However, nothing is as effective as hands-on experience. This may involve engineers or "clinical specialists" providing training and local support. Alternatively, experienced physicians may visit centres to "proctor"

Table 2. Risk classification of medical devices

Class	Risk	Examples
I	low	Sticking plasters, tongue depressor, thermometer
IIa	low to medium	Endotracheal tubes, dental filling material
IIb	medium to high	X-ray machines, peripheral vascular stents
III	high	Artificial heart valves, coronary stents

colleagues during their first few procedures. This is supported by MEDDEV 2.7/2 Rev 2, which recommends that when handling complex or unfamiliar devices, risks should be mitigated by adequate training and support during the first cases.[13] Such training should be featured in the clinical investigation plan.

What are the aspects of data analysis relevant to medical devices?

Device trials often comprise different analysis groups, particularly where implants are concerned. It is important to define them clearly upfront. For instance, should the term "intention-to-treat", be defined as patients who signed informed consent or as patients in whom an implant was attempted? While the former is the more common definition of intention-to-treat, the latter might be more suitable for implants. For instance, in coronary stent trials, the final eligibility of a patient is usually determined after patient informed consent during angiography and use of the term "implant attempted" avoids contamination of the intention-to-treat group. For randomised trials, the terms "patients per allocated treatment group" and "patients per treatment received" are comparable to the pharmaceutical industry.

Early clinical studies may include "roll-in" patients. These are the first to be treated in a particular centre using a new technique in which complications might be expected as part of the learning curve. Such individuals are commonly not counted as part of the primary analysis group.

Where complex procedures are involved, e.g. implanting a heart valve, outcomes are also related to the skills and experience of the operator. Analysis per centre might be advisable for clinical study oversight, but are commonly not reported.

It is worth emphasising that as for pharmaceutical reports, all post-hoc analyses should be appropriately labelled as such in any resulting manuscript or summary.

Overview of relevant European regulations

The Declaration of Helsinki and all general guidelines relevant to medical writing (e.g. the Consolidated Standards of Reporting Trials (CONSORT) statement, Good Publication Practice for Company Sponsored Medical Research (GPP3)) apply to drugs as well as to devices, along with the requirement for trial registration (see e.g. www.Clinicaltrials.gov).

While specific medical devices regulations were previously less stringent, this is changing following recent hip and breast implant scandals.[14] Central to the current European medical device regulations are the Medical Device Directive (MDD 93/42/EEC)[1] and the Active Implantable Device Directive (AIMDD 90/385/EEC). These will be replaced by the new European Medical Device Regulation (MDR). *(Note: just prior to publication, the MDR was released and is now accessible via http://eur-lex.europa.eu/eli/reg/2017/745/oj).* A draft document specifies requirements for items such as informed patient consent forms, clinical investigation plans, investigator brochures, and clinical study reports. These are similar to the specifications described in the current ISO14155:2011 guidelines[7] (see below). Furthermore, the MDR will require several novel documents and hence offers new opportunities for medical writers. For example, for Class III and implantable devices, companies will be required to publicly provide a lay summary of the main safety and performance aspects of the device along with clinical evaluation outcomes.

The MDD/MDR is supplemented by a number guidance documents, the MEDDEV guidelines. They refer to topics such as serious adverse event reporting, clinical investigations, and post-market clinical follow-up studies (see http://meddev.info/). Most relevant for medical writers is the new MEDDEV 2.7/1 Rev 4[6] guideline on writing clinical evaluation reports (CER) released in June 2016. The main features are an emphasis for an in-depth literature search and appraisal of relevant publications along with drafting of the CER by qualified authors. This new document also more clearly describes the frequency of CER updates required during the product life cycle.

Another important guideline for medical writers referred to above is ISO14155:2011,[8] the contents of which may be summarised as mirroring the International Conference on Harmonisation – Good Clinical Practice (ICH -GCP). This comprehensive document

Table 3. Main differences between medical devices and drugs at a glance

Aspect	Medical devices compared to drugs
Principal mode of action	Not by pharmacological means
	Less interaction with human body
	Some devices work exclusively outside the human body
Development	More technical, involves engineers
	Faster development cycle
	Less patients required in clinical studies
	More frequent product updates
Clinical studies	Commonly no studies in healthy volunteers
	Blinding is often not possible
	No classification in Phase I, II, III, and IV studies, but:
	-Feasibility,[9] Pilot-, First-in-Men-, First-in-Human studies are similar to Phase II studies
	-Pivotal-, Premarket-, CE-mark studies are similar to Phase III studies
	Postmarket studies, registries are similar to Phase IV studies[11]
Miscellaneous	Success of treatment may be related to physician's skills, particularly for invasive devices such as implants
	Often smaller companies, requiring an "all-rounder" mentality

describes how to conduct a clinical investigation, as well as provide details on the required content for patient informed consent forms, case report forms, clinical investigation plans, investigator brochures, and clinical study reports. An update is expected in 2019/2020.

What skills does a medical writer need to flourish in the device world?

It helps to have an "all-rounder" mentality, with a broad knowledge of clinical research, statistics, and medical writing skills. With the exception of global players such as Medtronic with nearly 100,000 employees worldwide[15] medical device manufacturers are generally smaller than pharmaceutical businesses, with a predominance of small to medium-sized enterprises. Smaller medical device companies such as start-up companies typically have less than 20 employees and may not possess individuals with the skills to clean, analyse, and present data in the required format for regulatory approval or scientific publications, so that this task may fall to the medical writer.

Furthermore, because patient numbers are generally smaller than in drug trials, another interesting aspect of working with devices is that the experienced writer may have the opportunity to dig deeper into the data, look beyond the endpoints and seek out potential interactions. Of note, the new MEDDEV 2.7/1 Rev 4 guidance document now specifies that authors of CERs should possess a mix of relevant skills such as knowledge of statistics, clinical research, etc.[5]

But do not be put off by these requirements; writing for medical devices can also be performed by the less experienced, particularly when working on lower risk devices and with the support of suitably qualified colleagues.

Conclusion

This article has provided a brief overview of the diverse world of medical device writing. Most new products are relatively straightforward and might cause the reader to misunderstand that this field is less taxing than developing documents for the pharmaceutical industry. This is far from the case, especially with less common devices requiring complex development and novel implantation techniques. This leaves the question which is a better job: writing for drugs or devices? A survey of medical writers in the pharmaceutical and device industries found no clear differences in terms of quality of life, stress, support, or remuneration.[16] If you like a more technical environment, working in smaller teams or at a faster pace, or being an all-rounder with some opportunity to develop your own ideas, then medical device writing might be for you. There are vacancies currently with many device companies seeking to expand their writing departments. This trend seems likely to continue with the increasingly stringent regulatory requirements described above. Perhaps device writing is the new "sweet spot" in the medical communications world? ■

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