Medical writing for early clinical development

by Biddy Schilizzi

How does one become a medical writer in early clinical drug development? Having recently taken the plunge from salaried employee to go freelance, I've become aware of an apparent need for writers with experience in this in area, in particular in pharmacokinetic (PK) writing. Because the question has been asked as to how one gets started in this line of medical writing, I'll present my own observations and experience gained from working in a large Phase I/IIa CRO.

Early clinical drug development means Phase I and IIa trials, conducted in small groups of healthy volunteers or patients, respectively. For the medical writer there are a number of interesting and distinguishing features about Phase I/IIa work.

First, these trials are often 'first-in-man' studies, so safety is paramount; second, there may be an exploratory study of pharmacodynamic (PD) endpoints; and last but not least important PK data will be collected. This data will help determine the subsequent dosing level and frequency in the intended therapeutic population. Since many therapeutic agents are 'killed' in Phase I/IIa, the quality of work delivered in these early trials can sometimes make or break a particular drug.

The focus here will be on PK/PD reporting (as medical writers are generally better informed about safety writing) with a brief illustration of how regulations and guidelines are relevant to Phase I/IIa medical writing.

Becoming a Phase I medical writer

Medical writers who write for Phase I/IIa in my experience come from various backgrounds. Writers typically come from one of the biomedical sciences, clinical medicine or pharmacology, and usually have a PhD. To ease the transition from academia to industry, many universities now offer post-graduate courses comprising specialised training for careers in the pharmaceutical industry.

Writers are, however, often recruited at a junior level directly from university, with no prior experience in the pharmaceutical industry. More experienced individuals with several years in clinical or pre-clinical research may have a pure research, project management or regulatory background. In my case, I'd worked in clinical research (immunology) at a university hospital, followed by product management at a biotech company. Whatever the background, an interest in clinical research and affinity with the interpretation and presentation of data is a prerequisite. Prior knowledge of the principles of Good Clinical Practice (GCP), is desirable.

Training

The skills and experience required for Phase I reporting are gained through a combination of on-the-job training, and specialised courses in PK.

The best form of training for any Phase I medical writer, regardless of background, is to work with a mentor, usually a senior colleague with PK and medical, or regulatory writing experience. In-house statistics and PK specialists, who, in larger organisations generally act as internal consultants, also play a valuable role in the learning process. In a reasonably sized pharmaceutical company or full-service CRO, there will be opportunities to work on a range of documents from pre-study (e.g. Protocol, Investigator Brochure [IB]), to final Clinical Study Report (CSR). CRO employees benefit from working for different sponsors, ranging from big pharmaceutical to small biotech companies. This provides exposure to a variety of therapeutic areas and study designs; drug products ranging from traditional chemical entities to recombinant proteins, and not least, working across national boundaries. These varying aspects broaden the range of skills and enrich the PK experience.

An understanding of PK is certainly required to interpret and describe the PK data in the CSR. This understanding is an advantage at an even earlier stage when writing or reviewing the Study Protocol or IB. Another prestudy document, the Investigational Medicinal Product Dossier (IMPD), contains summaries of information relating to the quality, manufacture and control of the Investigational Medicinal Product (IMP), and may be submitted as an addendum to the IB. A background in pharmacology or pre-clinical drug development is an added asset when it comes to preparing this rather technical document. When reviewing the Statistical Analysis Plan (SAP), a good understanding of PK enables you to contribute to discussions with the statistician and/or PK expert. All this contributes to the overall quality of the final CSR.

Completion of several CSR's containing a PK section gives a good idea of the desired structure and content of a Phase I/IIa CSR. Then follows the ideal moment to deepen or refresh PK and statistical know-how. Commercial courses (at commercial rates) are relatively easy sourced, however

a local university pharmacology department may also offer courses suitable for medical writers. In our department, medical writers usually followed a 3-day post-graduate course in PK. Though it was not wholly applicable to the type of PK data we worked with, it was very valuable in improving the depth of our PK knowledge. A typical course should cover the kinetics of drug absorption, distribution, metabolism and excretion, and include discussion of issues such as the role of genetic polymorphism, biomolecular drugs and PK-PD modelling.

EMWA members have the opportunity to follow more specific PK courses, tailored to reporting clinical trials, such as those offered by John Carpenter (Pharmacology, Parts 1 & 2).

Once on the job (pharma or CRO), medical writers should take advantage of in-house PK training, remembering to collect certificates for all completed courses and make CV updates as proof of continuing professional development. CVs are required for the trial master file and are added to the CSR appendices.

PD reporting requires the writer to draw chiefly on their research interests and skills gained as a medical scientist without necessarily being an expert in the particular therapeutic area. The PD endpoints, or biomarkers, at this stage of clinical development are often exploratory, and interpretation of results can lead to interesting, sometimes heated, discussions with the sponsor and the study team. This is where one really gets to know one's colleagues! In my experience, Phase I/IIa medical writers really enjoy the opportunity to report results of biomarker investigations (PD studies), perhaps because it is a happy reminder of the excitement/frustrations of our lab days.

Guidelines

Equally as important as the scientific training is the need to keep abreast of the national and international regulations and guidelines relating to the conduct of clinical trials. With the exception of writers with regulatory experience most will need to build this knowledge on-the-job. In this respect, it is a welcome development for freelancers that EMWA has begun offering courses in GCP.

In general, regulations and guidelines fall into two categories; those which medical writers must apply in their documents, and those they need to be aware of and possibly refer to in their writing.

The first category concerns content, format and structure of study documents. A good example is the International Conference on Harmonisation (ICH) E3 [1], relating to the structure and content of CSRs. It is important to note here that ICH E3 is a guideline, not a template, and that a PK section actually needs to be included for Phase I/IIa studies. Also applicable to Phase I, is the guideline relating to the Common Technical Document (ICH M4 [2]), containing, for example, technical guidelines on document layout, margins and font for electronic submission.

The second category includes regulations and guidelines such as GCP, relating to the ethics, safety and/ scientific conduct of a clinical trial, as well as guidelines on the design and analysis of particular trials. In Europe, the most recent GCP legislation results from the European Clinical Trial Directive (EU-CDT 2001/20/EC; [3]), which has now been translated into law by the member states of the European Union. This legislation governs the implementation of GCP in the conduct of clinical trials on medicinal products for human use. Final responsibility for implementation of GCP usually lies with the pharmaceutical company or CRO (the Investigator), but the medical writer must ensure that the prestudy documents and CSR reflect the correct implementation of the legislation and make reference to the regulations as appropriate.

Specific regulations and guidelines relating to Phase I/IIa are too numerous to adequately cover here. Full guidance is available via the ICH, FDA or European Medicines Agency (EMEA) websites; however it's worth mentioning some examples.

In 2006, the US Food and Drug Administration (FDA) published Guidance on Exploratory Investigational New Drug (IND) Studies [4]. This guidance refers to Phase 0, or microdosing, trials which are exploratory, first-in-human trials using sub-therapeutic doses. They are designed to accelerate the development of promising drugs by establishing very early on whether the drug or agent behaves in human subjects as was anticipated from preclinical studies. PK is the prime objective. Safety and tolerability at sub-therapeutic doses are not expected to be an issue and safety assessments are kept to a minimum.

Other guidelines relate to the design and analysis of a particular study e.g. a bioequivalence [5]; or QTc [6] study.

An important recent European guideline with impact on the design of Phase I trials was published in 2007 following the TeGenero trial in the UK [7]. This guideline focuses on factors influencing risk and drug quality, and considers designs for first-in-human clinical trials.

Keeping abreast of guidelines and regulations for clinical trials may not be anyone's idea of bedside reading. However, there is absolutely no escaping their importance! Understanding the content and the events leading up to the introduction of a guideline increases professional confidence and adds to the quality of the documents produced. One of the easiest ways to digest this sometimes dry material is to follow expert discussions in journals such as the *Good Clinical Practice Journal*. They provide background on the regulatory, strategic and clinical issues that directly impact clinical studies globally. Discussions on the FDA, ICH or EMEA websites during the consultation stages may also be helpful.

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Conclusion

There are many ways of getting into Phase I/IIa medical writing. However I remain unaware of any 'regulatory' writers who venture out on their own directly after leaving university. The best way to gain the requisite professional skills and experience is through on–the-job training inside a pharmaceutical company or CRO.

I've found it stimulating to be involved in this early phase of drug development as new drugs emerge, and new guidelines are published to reflect changes within the industry and the demands of society for increased safety and protection of volunteers. Writing for Phase I/IIa provides opportunity for continuing professional development and the satisfaction of working in a dynamic phase of drug development.

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7. Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. 2007. EMEA/CHMP/SWP/28367/07
   To assist sponsors in the transition from non-clinical to early clinical development. It identifies factors influencing risk for new investigational medicinal products and considers quality aspects, non-clinical and clinical testing strategies and designs for first-in-human clinical trials. Strategies for mitigating and managing risk are given, including the calculation of the initial dose to be used in humans, the subsequent dose escalation, and the conduct of the clinical trial http://www.emea.europa.eu/pdfs/human/swp/2836707enfin.pdf

Elephants too?

"Males and females can't understand each other's calls, and the female vocabulary is much larger." This quote relates to elephants and comes from *The Book of Animal Ignorance* by John Mitchinson and John Lloyd.

Advance notice of the EMWA book group book for discussion at Ljubljana

At the EMWA Spring conference we will once again be encouraging delegates who are interested to join the EMWA book group to discuss our chosen book. To give advance notice, the book we have chosen to read for the Ljubljana conference (26-30 May 2009) will be *Lucky Man: A Memoir* by Michael J. Fox.

Last year book group discussions took place as a topic on the lunchtime networking tables. The activity is intended to be voluntary and recreational and to be enjoyed by anyone who reads for pleasure and who wants to take part.

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"More than €4 million <u>were</u> invested ..." or "More than €4 million <u>was</u> invested ..."?

Adam Jacobs asked me which of the above I would choose, and here I am clearly on the side of the plural.

There are prescriptivists who claim that the €4 m in the above sentence should be regarded as a single item and therefore must always be construed with the singular (like those who insist that 'none' must always be followed by the singular [1]). You can do this if you want, but for more reasonable folk I have a good reason for using the plural: because we say *More than 100 patients **<u>have</u>** ...* and *More than 5 infusions **<u>were</u>** ...*, we say *More than €4 million **<u>were</u>** ...* . And it's as simple as that. Ah! you are saying, but people and infusions are in the plural, and million is in the singular. It is in the singular because it is being used as 'unit', but what you are actually saying is *More than 4 million **<u>euros</u>** ...* (read it out loud), and it is the euros here that carry the grammatical weight and not the millions.

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