The Clinical Development Plan – The Importance of Getting it Right

The challenge of mixing marketing, pre-clinical, production, pharmacovigilance, and regulatory groups throughout the CDP process should not detract from its simplicity when clinical experts work together in tandem

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"By failing to prepare, you are preparing to fail." – **Benjamin Franklin**

"Every battle is won or lost before it is ever fought." – **Sun Tzu, The Art of War, 5th century BCE**

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The wisdom of the ages, for thousands of years, has been that good planning is essential for the success of any project, and generally, the more complex the project, the more important the planning is for it. Many historical disasters can rightly be attributed to poor or non-existent planning.

Given the extreme complexity and difficulty of developing new pharmaceutical products, one would think that the planning for such an endeavour would be taken very seriously. Yet, somewhat surprisingly, it frequently is not. As medical writers specialising in regulatory submission dossiers, we have seen many clinical development programmes that are nearing their end and heading towards submission to authorities for marketing application, and, yet, seem to be lacking any real master plan. It is astonishing how little cohesive thought has sometimes been put into the series of studies performed, such that, at the time of submission, some key questions remain unanswered. As a result, writing the submission dossier is a bit like trying to weave together a piece of swiss cheese – we need to dance around the holes in the storyline, while still trying to defend and support the planned label claims.

These glaring holes in clinical development programmes are sometimes attributed to the inherently unpredictable nature of drug development and the challenges of knowing what will come out of planned studies. Yet, on close inspection, it frequently seems to bea result of poor planning and foresight from the start of the clinical programme, and the lack of a well-thought through clinical development plan (CDP). It has happened more than once that at the time of finalising Phase III studies, when we ask to see the CDP and the target product profile (TPP) to get an idea of the strategic concept the programme was following, we are given half-finished drafts of one or both of these documents that never really got the attention they deserved. Unfortunately, teams often do not take time to sit down at the start and begin envisioning the summary of product characteristics, or product label, and pre-emptively plan to run precisely those studies that will provide the data to support the desired claims. When so much is at stake, getting the CDP right can be a defining point between potential success or failure of the sought-after marketing approvals.

The CDP goes hand in hand with the TPP for a product (1). Before a CDP can be conceived, the TPP needs to cover some important ground including what the product is going to be used to treat (i.e., the planned target indications and populations), how it will be applied (routes of administration and conceivable treatment regimens), details of what is known about how the drug works (initially from pre-clinical testing but to be developed as the clinical programme proceeds), what other treatments are already available, and what the regulatory strategy will be for developing the product. Only once these ideas are clear can a team begin to plan the studies that will be needed to develop the product for clinical use. It is, therefore, important that these documents be developed early and kept in sync with each other over the course of the development programme.

> *To produce a CDP that will take the product down the right path from the start, important cross-functional decisions and strategies need to be made in the early stages*

In theory, clinical drug development might be considered difficult to plan, as each study in the development process is part of a sequence, and the objectives and design of many studies can only be based on the findings of previous studies. However, experience with many development programmes over the years has shown us that just as there are clear phases of the development process (Phases I to IV), there are a number of basic concepts that will always need to be addressed in the development of almost all drugs. For example, the basic pharmacokinetics of every drug will need to be investigated in initial studies to elucidate how a drug enters the body, where it goes, how it is metabolised, and how it is eliminated. Likewise, pharmacokinetic studies examining drug interactions with medications commonly associated with the intended indication are also usually required as are those in special populations likely to be receiving the medication. Thereafter, Phase II and III studies will be needed to establish the optimum dose, the size of the therapeutic effect, and the safety in large numbers of patients. Some form of this information must be collected for any medical product to be approved and eventually made available to patients. So, mapping out a CDP is not really that unexpected in terms of knowing the basic game plan of what will be needed.

Which is not to say that a CDP is not a complex document. Input will be needed from several different people

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who have the right experience in many different areas – who can foresee and imagine what data will need to be collected in the clinical studies to fully elucidate the pharmacological characteristics, efficacy, and safety of the product. A CDP must reflect both the scientific and the commercial rationale for development to ensure that at the end of development, all the data needed to have a product that can be marketed in a meaningful way are available. The document needs to be structured and written in a way that makes the flow of logic in the plan clear. This is where the aid of an experienced medical writer can be invaluable to turn a CDP from a jumble of ideas into something coherent with clarity of thought and purpose.

Additionally, the CDP is a living document. As the results of studies come in, this may change what we know about a product; the plan has to react to this new knowledge and adapt accordingly. New directions for what to explore that nobody had previously anticipated may become obvious. This means the writing and development of a meaningful CDP demands an investment of time from many people throughout the lifecycle of the product.

This is probably the most challenging aspect of preparing a good CDP: organising the necessary cooperation of the right people from across functions who otherwise rarely work together. Although the marketing, pre-clinical, production, pharmacovigilance, and regulatory groups will certainly make contributions at the time of preparing the regulatory approval dossiers, these functions often only start collaborating very late in the development process, and their input tends to be made in parallel and not involve true teamwork. Having an experienced medical writer on board who is adept at pulling together ideas and input from multifunctional teams, and who can manage and coordinate the writing and updating of the document, can make the process much more efficient.

To produce a CDP that will take the product down the right path from the start, important cross-functional decisions and strategies need to be made in the early stages, as these will have direct consequences on later stages of the programme. The decisions made by teams designing the pharmacology studies in Phase I need to be aligned with the plans and objectives of the later efficacy and safety studies. It would be a mistake to design these early studies in isolation from the therapeutic area experts who will design the later studies since the dosage used and the objectives of the later studies will be defined and influenced by the results of these early studies. It is important that everyone is heading in the same direction from the start. The CDP is going to be the hymn sheet everyone should be singing from for several years to come, and taking the time to have all the right functions in place from the start, including a medical writer who can help craft the thoughts into a cohesive whole, will help ensure that everyone is singing in harmony from start to finish.

References

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Barry Drees received his PhD in Molecular Genetics at the University of California, US. Following his postdoctoral work as a fellow of the National Institute of Health, he worked as a Medical Writer at Hoechst/Aventis for 12 years. Barry is a frequent speaker on medical writing, statistics, and other scientific communication topics for a number of associations and companies in the pharma industry. He is a past President of the European Medical Writers Association (EMWA) and is a former Editor-in-Chief of the EMWA journal. He is currently a Co-Founder and Senior Partner of **Trilogy Writing & Consulting**, continuing to personally lead submission teams and provide training for the industry around the world.

After receiving her PhD in developmental neurobiology, **Julia Forjanic Klapproth** started her career as a medical writer in the regulatory group at Hoechst Marion Roussel (later Sanofi) in 1997. Since then, she has been President of the European Medical Writers Association twice (2001-2002, 2007-2009). In 2002, Julia co-founded **Trilogy Writing & Consulting**, a company specialised in providing regulatory medical writing. In addition to managing the company as President/ Senior Partner, she writes a wide array of clinical documents including study protocols, study reports, and is specialised in the clinical parts of CTD submission dossiers.

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