



Experience of nonclinical drug development – is it important for a medical writer?

by Carin Larsson-Backström

An EMWA workshop not only gives you valuable knowledge in the workshop topic. The exercise as a practicing component included in most of the workshops also gives you a possibility to learn more about the other participants. Recently, I attended the workshop on “The Investigator’s Brochure” (IB). The participant profile was medical writers with at least 1 year of experience in the pharmaceutical industry. The exercise consisted of the preparation of a mini-brochure based on actual data given out as a pre-course assignment. During the workshop, we worked in teams to decide about the salient findings to present in an IB. From the comments made by some of the participants within my team, it was obvious that for those who did not have very much experience in nonclinical drug development, it would be difficult to fulfil the obligations stipulated by the International Conference on Harmonisation (ICH) guidelines.

According to the ICH guidelines [1], the IB should highlight the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic (PK), metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product. In regard of the nonclinical studies, the summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic, and the possible unfavourable and unintended effects, in human. Furthermore, the relevance of the nonclinical information to the proposed human dosing should be addressed, and comparisons should be made in terms of blood/tissue levels rather than on an mg/kg basis. For those of us having experience of several years from nonclinical as well as clinical Research & Development in the pharmaceutical industry, it is not very difficult to pick out things that an investigator needs to know.

Experience of nonclinical drug development is valuable for a medical writer in quite a lot of similar situations. Certainly it should help when writing the Nonclinical Overview and Summary incorporating the new Common Technical Document (CTD) format. The Nonclinical

Overview should present an integrated and critical assessment of the pharmacologic, PK, and toxicologic evaluation of the pharmaceutical [2, 3]. Any deviation from existing relevant guidelines [4, 5] on the conduct of the studies should be discussed and justified. The Good Laboratory Practice (GLP) status of the studies submitted should be commented. Studies conducted to establish the pharmacodynamic (PD), PK and toxicokinetic effects, the mode of action, and potential side effects, should be evaluated and consideration given to the significance of any issues that arise. The Integrated Overview and Conclusions should arrive at logical, well-argued conclusions supporting the safety of the product for the intended clinical use. The same ICH guidance [3] also assists the author in the preparation of written summaries of nonclinical pharmacology, PK, and toxicology in an acceptable format. However, no guideline can cover all eventualities, and common sense and a clear focus on the need of the regulatory authority assessor are the best guides to constructing an acceptable document.

The preparation of a Clinical Development Plan (CDP) also involves many considerations concerning the nonclinical drug development. The CDP describes a schedule of studies designed to obtain a product licence and should follow the directions described in the ICH guideline (E8), “General considerations for clinical trials” [6]. To develop new drugs efficiently, it is essential to identify characteristics of the investigational medicine in the early stages of development and to plan an appropriate development based on this profile. Before any clinical trial is carried out, results of nonclinical investigations or previous human studies should be sufficient to indicate that the drug is acceptably safe for the proposed investigation in humans. Important considerations for determining the timing of nonclinical studies with respect to clinical trials include: the proposed duration and total exposure in individual patients, characteristics of the drug (e.g. long half-life), disease or condition targeted for treatment, use in special populations (e.g. women of childbearing potential), and route of administration. The selection of the initial human dose and safe duration of exposure should be sup-

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ported by sufficient information from early nonclinical studies, which also should provide information about physiological and toxicological effects of a new drug. The basis and direction of the clinical exploration and development rests on the nonclinical PK and pharmacology profile, including information such as mechanism of action, dose-response or concentration-response relationships and duration of action, routes of administration, systemic general pharmacology and studies on absorption, distribution, metabolism and excretion. It seems to me obvious that, although most of these considerations will be executed in the Nonclinical Overview, it will help a great deal for a medical writer to have experience and understanding in the preclinical drug development when preparing a CDP.

Quite a lot of knowledge of PD and PK is required for optimal reporting of these studies

Similar considerations concerning the nonclinical drug development as discussed for the CDP are also of importance for the planning, i.e. writing the study protocol [1], and reporting of the clinical studies [7] to be conducted according to the CDP. The variables of concern include:

- the selection and timing of dose,
- duration of exposure,
- route and mode of administration,
- methods of measurements of drug concentrations,
- the specific efficacy and safety variables to be assessed and laboratory tests to be conducted,
- their schedule (days of study, time of day, relation to meals, and the timing of critical measures in relation to test drug administration),
- the methods of measuring them and the appropriateness of the measurements.

These concerns are related in particular to the phase I, human pharmacology studies, starting with the initial administration of an investigational new drug into humans. The analytical methods used, the PK models and the derived parameters should be similar to those used in the nonclinical studies. Reporting the human pharmacology studies requires, however, pharmacological, and in particular, PK experience not only in the consideration of the nonclinical results but also of those from the phase I studies. For the correct reporting of the results and to draw the most correct conclusions of the PD and PK studies, and studies relating drug blood levels to response (PK/PD), requires quite a lot of knowledge of, and preferably some experience in, these specialities.

It helps to have experience in nonclinical drug development also when linking to the nonclinical issues relevant for humans, on writing the CTD Clinical Overview and Summary [8]. Similar considerations are valid when preparing the Summary of Product Characteristics (SPC;

9), which should be based on the Clinical Overview.

Experience of nonclinical drug development, including knowledge and preferably experience of PD and PK, is therefore important for a medical writer. It is definitely of help when writing all the documents mentioned: the IB, the nonclinical and clinical overviews and summaries incorporating the CTD format, the nonclinical and clinical study reports, the CDP and the SPC. When writing these documents, it is important for any medical writer, and in particular for those with no or only limited experience in non-clinical drug development, to establish team building early, and to decide the role for the medical writer. Why not also use the network of the many talented members that EMWA provides, to establish collaboration between the EMWA members?

Why not use the EMWA network to establish collaboration between members?

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References

1. ICH Harmonised Tripartite Guideline for Good Clinical Practice (E6). EU: Adopted by CPMP, July 1996; MHLW: Adopted March 1997; FDA: Published in the Federal Register, Vol.62, No. 90, May 9, 1997, pp 25691-25709
2. ICH Harmonised Tripartite Guideline for Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use (M4). Recommended for adoption, November 8, 2000
3. ICH Harmonised Tripartite Guideline for The Common Technical Document for the Registration of Pharmaceuticals for Human Use, Safety - M4S. Nonclinical Overview and Nonclinical Summaries of Module 2, Organisation of Module 4. Recommended for adoption, November 9, 2000
4. ICH Harmonised Tripartite Guideline for Maintenance of the ICH Guideline on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (M3). Recommended for adoption, July 16, 1997
5. ICH Harmonised Tripartite Guidelines for Safety Topics (S1 – S8)
6. ICH Harmonised Tripartite Guidelines for General Considerations for Clinical Trials (E8); Recommended for Adoption, July 1997
7. ICH Harmonised Tripartite Guidelines for Structure and Content of Clinical Study Reports (E3). Recommended for adoption, November 30, 1995
8. ICH Harmonised Tripartite Guidelines for The Common Technical Document for the Registration of Pharmaceuticals for Human Use, Efficacy – M4E. Clinical Overview and Clinical Summary of Module 2, Module 5: Clinical Study Reports. Recommended for adoption, November 9, 2000
9. Notice to Applicants. A Guideline on Summary of Product Characteristics, December 1999

Language Quiz

In which of the following countries is Roman writing the official form of writing and why?

- Korea
- Vietnam
- Thailand
- Japan

Answer in box on page 21