Public consultation on draft guidance on harmonised requirements for non-investigational medicinal products in CTA submissions

September 2010

Cancer Research UK welcomes the opportunity to comment on the draft guidance for non-investigational medicinal products (NIMPs) in Clinical Trial Authorisation (CTA) submissions. In our response to the consultation on the Clinical Trials Directive (CTD) in January 2010, we welcomed the aims of the Directive but felt that these aims had not been fully realised and that more detailed guidance in a number of areas, including NIMPs, would improve comprehension of the Directive. We therefore welcome that this draft guidance has been published and we have the opportunity to provide comments. We have focused our response on the new guidance but we hope that this is an interim measure, and look forward to working with the Commission, the Medicines and Healthcare products Regulatory Authority (MHRA) in the UK, and others to develop further improvements in the medium term.

About Cancer Research UK

Cancer Research UK (CR-UK)[1] is the world's leading charity dedicated to cancer research and the largest independent funder of cancer research in Europe. Over half of all cancer research in the UK is carried out by our doctors and scientists. Cancer Research UK's work is entirely funded by the public and in 2008/09 we spent £355 million on research, supporting the work of more than 4,800 scientists, doctors and nurses.

CR-UK funds research into all aspects of cancer from exploratory biology to clinical trials of novel and existing drugs as well as population-based studies and prevention research. Our scientists and doctors have made significant contributions to the development of half of the top 30 drugs used to treat cancer patients worldwide today. At CR-UK, we are involved with all stages of clinical trials, and we have a perspective both as a funder of academics conducting trials and as a Sponsor of early phase trials.

Since CR-UK began funding trials in 1988, we have funded almost 300 therapeutic trials and more than 100,000 patients have taken part in these trials. In the same time period, the Drug Development Office (DDO) has sponsored and conducted over 100 early phase exploratory studies, with more than 2,000 patients entered on these trials. These exploratory studies were on new clinical agents, of which five have been taken to market by subsequent business partners.

Acknowledgements

Our response has been collated following internal staff discussion and with contributions from the follow additional groups/individuals:

- Jabeen Ahmad, Head of Quality, Regulatory and Pharmacovigilance, and Vi Ung, Regulatory Affairs Manager, Drug Development Office (DDO)[2]

[1] Cancer Research UK is a registered charity in England and Wales (1089464) and in Scotland (SC041666)

[2] This draft document was reviewed in detail during the internal CR-UK DDO Regulatory and Guideline Review Forum at a meeting of Regulation and Guidelines Forum, 21st July 2010.

- Julie Hearn, Head of Clinical Trials, and Silvia Grisendi, Clinical Trials Manager, and the Clinical Trials Units (CTU) Governance Leads

This response does not represent the views of any one individual or organisation listed above, but is the product of collaboration between all listed parties.

Comments

In our response to the initial consultation in January 2010, we highlighted a number of points relating to the use of NIMPs in clinical trials, including requesting clarification on the definition of NIMPs and for an improved risk-based approach.

We found the draft guidance document was useful in specifying dossier requirements for NIMPs in CTA submissions as no such guidance previously existed. This is especially helpful when submitting CTAs in multiple member states to ensure harmonisation; however, the impact on a single member state submission is not as significant.

In summary, the document helped to address some of the current issues faced by sponsors in relation to what documents are required to support the use of NIMPs in CTA applications. However, and although not significantly the remit of this document, clearer guidance on IMP and NIMP classification and examples would still be welcomed as there is still some confusion relating to what is considered a NIMP in a trial and what is not.

A several points regarding the format of the guidance were raised:

1. The document had to be read in conjunction with the existing guidance on use of medicinal products in clinical trials ('Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in clinical trials'). We believe that these documents should be amalgamated in the future and perhaps the information from the new guidance presented in a summarised table format possibly in an annex to the existing guidance on IMPs in trials.
2. The document was very repetitive and from a reader's perspective, not straightforward to follow. One suggestion could be (as with the suggestion above) for the pages of different options to be summarised in a table which would reduce the number of pages and potentially make it easier for a sponsor to identify their individual situation and hence the data they need to submit.

As is our concern with the Clinical Trials Directive more broadly, we feel that the guidance does not go far enough in terms of distinguishing between the different types of sponsors (pharmaceutical company/drug manufacturer or a university/hospital which has no involvement in the manufacture or distribution of IMPs) or the different levels risk involved. Furthermore, the guidance does not make appropriate allowances for trials in high morbidity diseases where patients will inherently be receiving a vast array of treatments (established and experimental), often over a considerable period of time, to treat their disease. Our concern is that if this document is implemented and strictly interpreted, cancer trials will become unworkable.

Whilst the document summarises very clearly what documents need to be submitted for the various scenarios, it's still unclear what a NIMP is, since the definitions are vague and, most worryingly, may have unintended implications for cancer trials.

A few additional detailed comments are as follows:

- Background therapy (3.1): We are unclear as to whether this includes cancer treatments given sequentially. For trials of neo/adjuvant treatment, we are unclear whether this means every bit of adjuvant treatment the patient may receive after trial treatment, which could be any number of combinations of chemotherapy drug and any hormone treatment, which may or may not be specified in the protocol count as a background therapy. Although this could be covered simply and briefly in the covering letter, we could never state with certainty that they would always have drugs within their licensed indication because they are able to enter adjuvant treatment trials which might use drugs that are not within these indications. Also, what is considered standard therapy differs between Member States and even between health authorities and similar organisations within a Member State.

- Rescue medication (3.1.2): Within cancer trials, we only know an IMP was 'not satisfactory' when the patient relapses and receives treatment for metastatic disease, and the point of trials in early disease is to find out if we can reduce the incidence of that happening. Does this mean that every conceivable treatment for metastatic disease counts as rescue medication? New treatments for metastatic disease could become available between adjuvant treatment ending and the patient relapsing, or the patient might enter a trial of treatment for metastatic disease which might not be used within its licensed indication. Any information we gave would be meaningless and probably inaccurate, so we are unclear as to whether we are expected to provide updates, and for how long after the trial has ended.

- The other type of rescue medication is if the effect of the IMP is 'too great' (3.1.2). This is a vague term with little meaning. If it means it causes adverse events, within cancer treatment, every chemotherapy in use has an effect which is arguably 'too great', and the possible supporting medications are many and varied. By this reasoning, all anti-emetics, diarrhoea remedies or drugs that might be given to patients who have a blood transfusion, antibiotics for infections that might have been contracted because the patient was on chemotherapy, pain killers – an endless list – could be included.

- The statement in section 2: "In this context, the sponsor should implement a system allowing traceability of medicinal products which allows adequate reconstruction of NIMP movements and administration, taking into account the purpose of the trial and trial subjects' safety. It has at least to include a procedure, established with the investigator and if applicable, with the hospital pharmacy, to record which patients received which NIMPs during the trial with an evaluation of the compliance." We feel that setting up a procedure to track and monitor NIMP compliance in a clinical trial is in most cases an unnecessary burden as generally NIMPs are well established long-used licensed drugs. Tracking their use and monitoring patient compliance is additional work/data collection which interferes with the ability of the CTU to achieve far more important aspect of trial management. We strongly believe that there should be a risk based approach to the extent to which NIMPs are tracked/monitored for compliance and in most cases this would amount to very little.

We thank you again for the opportunity to provide comments and look forward to working with the Commission to develop further improvements to the Clinical Trials Directive. We have also provided comments on the reviewed guidance on SUSAR (suspected unexpected serious adverse reaction) reporting and have shared copies of both responses with the MHRA. If you would like to discuss these comments further, or have any queries, please do not hesitate to contact us (publicaffairs@cancer.org.uk).