Hammersmith Medicines Research Ltd.

Comments on Draft revision 3 of the EC 'Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial'.

1. General comment: the document is less user-friendly than Rev 2 of the guideline. Rev 2 is generally less legalistic, less wordy, and clearer. See, for example, the section 'scope'. Readability of draft 3 could be improved by referring in-text to regulations only by their reference numbers, and placing the full reference in a footnote: use of full titles of regulations and directives interrupts the flow of sentences. Also, it should be possible to read the guidance as a standalone document, without needing to cross refer to specific articles of Directives.

2. Section 2.1.2. Second paragraph. First sentence is unclear.

3. Section 2.5. 1st bulleted list, 4th bullet. This repeats information in the 2nd paragraph of this section.

4. Section 2.8.3. Title: 'Possibility to refer to the' is repeated.

5. Section 2.8.3. Please confirm that, for phase I (healthy volunteer) studies, the SmPC will be sufficient for studies using approved dosing regimens or doses lower than those that are approved.

6. Section 2.10. Are IMP labels to be submitted? They are not listed in sections 2.7.1 or 2.10, but section 3.3.2 refers to labels in the context of amendments.

7. Section 3.3. We welcome the discouragement of over-reporting.

8. Section 3.3.1. 1st bulleted list, 2nd bullet. Does this refer to 'monitoring' the conduct of the trial (checks of CRFs, consent and trial procedures), rather than medical monitoring of safety variables, eg ECG, laboratory safety variables?

9. Section 3.3.1. 1st bulleted list, 3rd bullet. Replacement of the primary endpoint would be substantial. Surely, addition of extra endpoints to satisfy the same objectives would not always be substantial.

10. Section 3.3.1. 2nd bulleted list, 4th bullet. Such documentation does not form part of the CTA application, so changes couldn't be considered as substantial amendments.

11. Section 3.3.2. See item 6 above.

12. Section 3.5 (c). In certain cases, where an amendment affects information that is repeated throughout a document, it is unnecessarily burdensome to list every change to the document. So, some flexibility should be allowed. For example, if the volume of a pharmacokinetic (PK) blood sample changed from 2 mL to 3 mL, and the sample volume was quoted repeatedly throughout the protocol, would it not be acceptable to state in the amendment that PK samples of 2 mL are replaced with PK samples of 3 mL throughout the protocol? Similarly, if Laboratory A is replaced with Laboratory B, is it not sufficient to say that every occurrence of 'Laboratory A' in the document is replaced with 'Laboratory B'?

13. Section 3.6. Please confirm that the sponsor can implement the amendment if the Competent Authority does not respond within 35 days.

14. Checklist. Please reinstate a table of checklist of the documents that need to be submitted as part of the CTA application.