Suggestions from the Medical Products Agency on the proposal for revision 3 of the 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:

Existing proposal	**Proposal by the Medical Products Agency**	**Comments**
1.2 Scope: Herbal medicinal products as defined in Article 1 (3) of Directive 2001/83/EC	1.2 Scope: Herbal medicinal products as defined in Article 1 (30) of Directive 2001/83/EC	Typo
2.1.2 Applicable delays for authorisation, tacit authorisation: However, Article 9 (5) and (6) of Directive 2001/20/EC set out important exceptions to this general rule	2.1.2 Applicable delays for authorisation, tacit authorisation: However, Article 9 (5) and (6) of Directive 2001/20/EC set out important exceptions to this general rule concerning medicinal products of biological/biotechnological origin	Clarification
2.2 Covering letter: a) the trial population	2.2 Covering letter: a) the trial population, e.g. patients not able to give legal informed consent	Clarification
2.2 Covering letter: (c) IMPs and non-IMPs, such as GMOs, radiopharmaceuticals, narcotics and psychotropics	2.2 Covering letter: (c) IMPs and non-IMPs, drawing attention to unknown or anticipated safety issues	Relevance
2.2 Covering letter: The applicant shall set out precisely in the cover letter where the reference information is contained as regards the assessment whether an adverse reaction is a suspected unexpected serious adverse reaction (“SUSAR”) as defined in Directive 2001/20/EC and implementing Community guidelines.	2.2 Covering letter: The applicant shall set out precisely in the cover letter where the reference safety information is contained as regards the assessment whether an adverse reaction is a suspected unexpected serious adverse reaction (“SUSAR”) as defined in Directive 2001/20/EC and implementing Community guidelines.	Reference safety information is the term used in ICH E2F
2.5 Protocol: A justification for including subjects who are incapable of giving informed consent or other special populations	2.5 Protocol: A justification for including subjects who are incapable of giving informed consent or other special populations such as minors	Clarification

2.6 Investigator's Brochure The current IB or equivalent document (e.g. SmPC for marketed products) will be the reference document for the assessment of the expectedness of any adverse reaction that might occur during the clinical trial.	2.6 Investigator's Brochure The current IB or equivalent document (e.g. SmPC for marketed products) should contain the reference safety information document for the assessment of the expectedness of any adverse reaction that might occur during the clinical trial.	Adaptation to ICH E2F
2.7.1 Quality data: • certification by the qualified person that the manufacturing complies with good manufacturing practices ("GMP") at least equivalent to the GMP in the Community; • certification of the CMP compliance of the manufacturing of any active biological substance.	2.7.1 Quality data: • certification by the qualified person (QP) that the manufacturing complies with good manufacturing practices ("GMP") at least equivalent to the GMP in the Community; • certification of the GMP compliance of the manufacturing of any active biological substance. If the national competent authority finds the QP declaration insufficient, a copy of the relevant audit report may be requested. The national competent authority may also ask for verification by an EU inspection if the IMP is imported to EU from a non-ICH country.	Additional requirements are considered necessary in some cases Typo
3.3.1. Amendments as regards the clinical trials protocol:	3.3.1. Amendments as regards the clinical trials protocol: Major changes which affect the study design or have an impact on the conduct of the study and/or planned primary and/or major secondary statistical analyses	New example of protocol-related substantial amendment
3.3.3. Amendments as regards other initial scientific documents supporting the Request for authorisation of the clinical trial: Any change to the IB that alters the product safety profile and safety monitoring arrangements.	3.3.3. Amendments as regards other initial scientific documents supporting the Request for authorisation of the clinical trial: Any change to the IB that alters the reference safety information or safety monitoring arrangements.	To be consistent with ICH E2F To clarify that either a change in the reference safety information or a change in the safety monitoring arrangements constitute a substantial amendment (both are not simultaneously required)
4.1. Legal Basis and Scope: "End of the trial" is not defined in Directive 2001/20/EC. The definition of the end of the trial should be provided in the protocol and any change to this definition for whatever reason should be	4.1. Legal Basis and Scope: "End of the trial" is not defined in Directive 2001/20/EC. The definition of the end of the trial should be provided in the protocol and any change to this definition for whatever reason should be notified as a substantial amendment even if	To clarify that a decision to prolong the follow-up of patients in a clinical trial should be notified as substantial amendment

notified as a substantial amendment.	the trial has already been declared ended.	
4.2.2. Shortened deadline for early termination/premature end: “Premature end” is considered as “early termination”.	4.2.2. Shortened deadline for early termination/premature end: “Premature end” is considered as “early termination”. Premature end should be notified even if patients continue to be followed-up for safety reasons.	For consistency between temporary halt and premature end. The decision not to recommence the trial can be made as early as the decision to halt the trial. The possibility should be considered to indicate the end of follow-up of patients followed-up for safety reasons.