Structure for the documents to be submitted in the case of electronic submission of applications for clinical trials at the BfArM (Federal Institute for Drugs and Medical Devices) / Paul-Ehrlich Institut (PEI)

Preliminary notes

- In the case of an electronic submission and in contrast to the current official practice, the documents to be submitted should include one paper version of the application dossier with signatures and one data carrier comprising all documents in electronic form. As of now it is required to submit one copy of the paper version only.
- The submission of the files by email or EudraLink will not be accepted.
- The files must be submitted in pdf format without password protection. The only exceptions to the PDF format are the xml file of the EudraCT form and the SNIF form (MS Word) of the Joint Research Center designed to report studies with GMOs. For details, please refer to the table below.
- With regard to the file structure on the electronic data carrier, please use the folder structure below with the folder names provided.
- If no documents are submitted for a particular subject (e.g. no GMO application), the appropriate folder on the CD or any separation sheets in the paper version, whichever may apply, should be omitted. The numbering of the folders should be retained even if the omission of some folders would have the effect that no continuous ascending order is maintained, so that for instance the folder "Other Documents" would always be No 14.
- For additional documents provided at a later date, answer letters to objections, and modifications, too, only those files on the CD should be provided which contain submitted documents. The appropriate folders should bear the original numbering indicated as well as the original folder names.
- References to the *Communication from the Commission 2010/C82/01 (CT1 guidance")* are given with the restriction that the items mentioned in this guidance do not contravene the regulations laid down in the AMG (Arzneimittelgesetz, German Medicines Act) or the GCP-V (Ordinance on Good Clinical Practice). In the case of doubt, the regulations governed by the AMG shall apply, which – if necessary – are communicated to the applicant in a formal list of grounds for non-acceptance or in the letter of reasoned objections pursuant to § 9 (2) GCP-V.

No	*Folder Name*	*Documents included*	*Explanation*
🗀01	Cover Letter	• Cover letter to authority/response letter	Pursuant to § 7 (2) GCP-V: Cover letter in German (*) or in English bearing the EudraCT number, the protocol code of the sponsor and the title of the clinical trial, emphasizing the special features of the clinical trial and indicating where said information is to be found in the other documentation. If a national scientific advice procedure is conducted, the latter (incl. date) should be mentioned. (*) The BfArM/PEI also accepts cover letters in English. See also *Communication from the Commission 2010/C82/01 ("CT1 guidance")*, subsections 28 and 29 (application for authorisation) and subsections 133 and 134 (application for substantial amendments).
		• Response/Comments to Grounds for non-Acceptance (GNA)	Response to GNA, if these constitute an independent document and do not form part of the cover letter
🗀02	EudraCT	• Application form as PDF file	Application form generated in the EudraCT database, as a PDF file / or print-out of the form in the same format See *Communication from the Commission 2010/C82/01 ("CT1 guidance")*, subsections 34 – 40 (application for authorisation) and 133e (application for substantial amendments).
		• Application form as XML file	Application form generated in the EudraCT database, as an XML file The XML file needs to be included only in the submission CD. It is not required to provide a print-out of the XML file with the paper version of the XML file
		• EudraCT number confirmation email	Pursuant to § 7 (2) No 1 GCP-V Copy of the letter of confirmation for the EudraCT number for the protocol issued by the European database The latter is the confirmation email from the EudraCT database which links the EudraCT number with the protocol code See also *Communication from the Commission 2010/C82/01 ("CT1 guidance")* subsection 26.
		• Form for amendments (Substantial Amendment Notification Form)	In the event of substantial amendments, measures to be taken for the protection against immediate danger, temporary hold of the clinical trial, resumption of the clinical trial, use the *"Substantial Amendment Notification Form"*. See *EudraLex Volume 10*.
		• Declaration of the End of Trial Form	The *"Declaration of the End of Trial Form"* must be used in the event of reporting the end of a trial only. See *EudraLex Volume 10*. See also *Communication from the Commission 2010/C82/01 ("CT1 guidance")*

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			Subsection 160 (regular termination of trial) and subsections 162 – 163 (early termination).
🗀03	Protocol	• Protocol	Pursuant to § 7 (2) Nr 3 GCP-V Protocol signed by the principal investigator of the clinical trial and the sponsor or his representative, giving the full title of the clinical trial, the EudraCT number, protocol codes of the sponsor, the version and date See also *Communication from the Commission 2010/C82/01* ("CT1 guidance") Subsections 41 – 42
🗀04	IB	• Investigator's information / investigator's Brochure (IB) or document which replaces the IB, if applicable	Pursuant to § 7 (2) No 7 GCP-V Investigator's brochure [IB] or documents replacing investigator's information, e.g. Summary of Product Characteristics (SmPC). See also *Communication from the Commission 2010/C82/01* ("CT1 guidance") Subsections 52 – 58 and subsection 122 (Amendments as regards the IB) Note with regard to amendments to the IB: Information must be provided as to whether the new pre-clinical and/or clinical data involve a change in the risk-benefit assessment for on-going clinical trials with the investigational medicinal product; furthermore, information must be provided whether new adverse effects are to be included in the IB which would modify the basis of the SUSAR reporting, and, if yes, the type of adverse effects. These points should be explicitly addressed in the cover letter or in a separate document.
🗀05	IMPD	• IMPD-QUA or simplified IMPD	Pursuant to § 7 (4) No 1 a GCP-V: Documents pertaining to quality and manufacture For investigational medicinal products with chemically defined and herbal active ingredients: Pursuant to the *"Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (CHMP/QWP/185401/2004 final)".* For investigational medicinal products with biological active ingredients: Pursuant to the *"Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials (EMA/CHMP/BWP/534898/2008)"*. As well as concerning the viral safety of investigational products: Guideline on virus safety evaluation of biotechnological investigational medicinal products (EMEA/CHMP/BWP/398498/2005)

No	*Folder Name*	*Documents included*	*Explanation*
			See also *Communication from the Commission 2010/C82/01 ("CT1 guidance")* Subsections 68 – 70.
		• IMPD-TOX	Pursuant to § 7 (4) No 1b GCP-V: Documents pertaining to the pharmacological-toxicological studies. See also *Communication from the Commission 2010/C82/01 ("CT1 guidance")* Subsections 71 – 76. Note: Reference to the pre-clinical part of the IB is possible. See also *Communication from the Commission 2010/C82/01 ("CT1 guidance")* Subsection 84 (possible reference to the investigator's brochure
		• IMPD-KLI: Results of previously conducted clinical trials	Pursuant to § 7 (4) No 1 f GCP-V: Documents showing results from clinical trials conducted previously and any other additional clinical findings See also *Communication from the Commission 2010/C82/01 ("CT1 guidance")* Subsections 77 – 80. Note: Reference to the clinical part of the IB is acceptable. See also *Communication from the Commission 2010/C82/01 ("CT1 guidance")* Subsection 84 (possible reference to the investigator's brochure)
🗀06	Risk - benefit	• Risk and benefit assessment	Pursuant to § 7 (4) No 1 g GCP-V: Overall risk and benefit assessment for the clinical trial for which the application is made. See also *Communication from the Commission 2010/C82/01 ("CT1 guidance")* Subsections 81 – 82. Note: Reference to the relevant section of the protocol is acceptable.
🗀07	Non-IMPD	• NIMP dossier Documentation for "non-investigational medicinal products" (NIMP)	Dossier on NIMP pursuant to *"Guidance documents applying to clinical trials guidance on investigational medicinal products (IMPs) and 'non investigational medicinal products' (NIMPs") [SANCO/C/8/SF/cg/a.5.001(2011)332855].* See also *Communication from the Commission 2010/C82/01 ("CT1 guidance")* Subsections 92 – 94.
🗀08	GMP	• Manufacturing authorisation	Pursuant to § 7 (4) No 1 d GCP-V: Copy of the manufacturing authorisation of all manufacturers located in the EU/EEA.
		• Import licence	Pursuant to § 7 (4) No 1 e GCP-V: Copy of the import licence of the importer with office in the EU / EEA.
		• QP declaration	Declaration on the manufacture in third countries in accordance with standards of good manufacturing practice pursuant to Article 13 (3) of Directive 2001/20/EC.
🗀09	Labelling	• Texts for labelling the investigational medicinal products	Pursuant to § 7 (4) No 1 g GCP-V:

No	*Folder Name*	*Documents included*	*Explanation*
			Intended texts for the labelling of investigational medicinal products on the basis of § 5 CGP-V. For radioactive medicinal products: supplemented by the specifications pursuant to Section 3 No 2 AMRadV (Verordnung über radioaktive oder mit ionisierenden Strahlen behandelte Arzneimittel, Decree on radioactive drugs or drugs treated with ionizing radiation).
10	Administrative Documents	• Sex distribution	Pursuant to § 7 (2) No 12 GCP-V Justification of the suitability of the selected sex distribution of the group of trial subjects to identify potential sex-specific differences in the efficacy or safety of the medicinal products investigated.
		• Further treatment	Pursuant to § 7 (2) No 13 GCP-V Plan for further treatment and medical care of the trial subjects when the clinical trial is completed.
		• Declaration on data protection (pseudonymised data)	Pursuant to § 7 (2) No 15 GCP-V The confirmation that trial subjects have been informed of the transmission of their pseudonymised data within the framework of the duties of keeping records and notification as defined by § 12 and § 13 to the recipient specified therein; this must include a declaration that trial subjects who do not agree to their data being passed on will not be included in the clinical trial.
		• List additional countries where an application for the authorisation of the clinical trial has been submitted	Pursuant to § 7 (4) No 4 GCP-V Designation and address of the competent ethics committee according § 42 para. 1 sentence 1 and 2 of the German Medicinal Products Act and designation and address of the competent authorities of other Member States of the European Union and of other participating States of the European Economic Area agreement in which the clinical trial is conducted.
		• Unfavourable opinions of authorities	Pursuant to Section 7 (2) No 14 GCP-V Reasoned statements of negative opinions of the competent ethics committees of other Member States of the European Union or other participating States of the European Economic Area agreement and any refusals of authorisation requests by the competent authorities of other member States of the European Union or of other participating States of the European Economic Area agreement; if conditions have been issued to any positive opinion of an ethics committee or an authorisation by the competent authority, these must be added.
		• Opinions of the ethics committees Unfavourable opinions, and if applicable, also favourable opinions from Germany	Pursuant to Section 7 (2) No 14 GCP-V Reasoned statements of negative opinions of the competent ethics committees of other Member States of the European Union or other participating States of the European Economic Area agreement and any refusals of authorisation requests by the competent authorities of other member States of the European Union or of other participating States of the European Economic Area agreement; if conditions have been issued to any positive opinion of an ethics committee or an authorisation by the competent authority, these must be added.

No	*Folder Name*	*Documents included*	*Explanation*
			If applicable: Favourable opinions of ethic committees from Germany .
		• Powers of attorney	Applies only, in cases where the application is not submitted by the sponsor. Power of attorney issued by the sponsor authorising the applicant to submit the application for authorisation of a clinical trial at the competent federal authority.
		• Declarations on whether the costs will be borne	If relevant: Statement of invoice deviating invoice addresses or declarations on who will bear the costs in the authorisation procedures.
🗀11	Scientific Advice	• Scientific Advice / national or EMA)	Results of Scientific Advice at the EMA or other national authorities (incl. BfArM/PEI) See also *Communication from the Commission 2010/C82/01 ("CT1 guidance")* Subsection 29 (specific features to be emphasised in the cover letter).
		• PIP (Paediatric Investigation Plan)	Paediatric Investigation Plan According the communication from the Commission – detailed instructions for the application for authorisation of the clinical trial of a medicinal product for human use submitted to the competent authorities, for notification of significant changes and report on the completion of the clinical trial ("CT 1") (2010/C 82/01) – subsections 29 and 95: Statement on whether the trial is part or is intended to be part of a Paediatric Investigation Plan (PIP) as referred to in Title II, Chapter 3 of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use. If the Agency has already issued a decision on the PIP, the cover letter should contain the link to the decision of the Agency on its website. See also *Communication from the Commission 2010/C82/01 ("CT1 guidance")* Subsection 29 (specific features to be emphasised in the cover letter).
🗀12	GMO	Only for genetically modified organisms: • SNIF application form of the Joint Research Institute	For information to the public pursuant to Article 24 of Directive 2001/18/EC and on the basis of § 14 (3) sentence 3 GCP-V The information is provided via the (GMOINFO) database of the Joint Research Centre of the European Commission. The database contains a summary of the reports of the national authorities (Summary of Notification Formats [SNIF]). To prepare for publication, the appropriate form must be attached in Microsoft® Word format.

No	*Folder Name*	*Documents included*	*Explanation*
		• Documents on environmental risk assessment	Pursuant to § 7 (4) No 3 GCP-V For Investigational medicinal products that are derived from or containing a genetically modified organism or a combination of genetically modified organisms, according to Annex II of Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC (Official Journal L 106 p.1), an description and assessment of the risks to the health of the general public and the fabric of the living environment and an description of the intended measures and in accordance with Annex III of this directive, information relating to the genetically modified organism, information relating to the conditions of the clinical trial and the environment potentially receiving the genetically modified organism, information relating to the interaction between the genetically modified organism and the environment, a monitoring plan to identify the effects on human health and the environment, a description of the intended monitoring measures and particulars of any residual substances and the treatment thereof and also any emergency response plans. The sponsor may to this extent also refer to documents which a Third Party has presented in a previous procedure, in as much as this does not involve confidential information.
🗀13	Xenogenic products	For xenogenic cell therapeutics only • Evidence of insurance	Pursuant to § 7 (4) No 2 GCP-V: Evidence of insurance as defined in § 40 para. 1 sentence 3 No. 8 and para. 3 German Medicinal Products Act, if the investigational medicinal product involved is a xenogenic cell therapy
🗀14	Other documents	• Other documents	Other documents that cannot be included in any of the above mentioned folders.
🗀15	Reporting	• Reports on a review the risk-benefit assessment	Reports on a review of the risk-benefit assessment pursuant to § 13 (4) GCP-V
		• Information on measures for the protection against immediate risk	Reports on measures pursuant to § 11 GCP-V in connection with § 13 (5) GCP-V See also *Communication from the Commission 2010/C82/01 ("CT1 guidance")* Subsections 142 – 145 (Notification of urgent safety measures).
		• Annual safety reports	Annual safety reports pursuant to § 13 (6) GCP-V See also *Communication from the Commission 2010/C82/01 ("CT1 guidance")* Subsections 124 – 130 (annual safety reports of the sponsor to the national competent authorities…).
		• End-of-trial report/study reports	Summary of the report on the clinical trial which covers all the essential results of the clinical trial pursuant to § 13 (9) GCP-V.