Agenzia Italiana del Farmaco

AIFA

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DETERMINATION of January 7, 2013.

Management of clinical trials with drugs following the transfer of the role of Competent Authority to the Italian Medicines Agency.

(Determination no. 1/2013).

(Published in the Official Journal of the Italian Republic no. 10 of January 12, 2013)

THE DIRECTOR GENERAL

Having regard to Legislative Decree no. 300 of July 30, 1999, and subsequent modifications and additions, and in particular articles 8 and 9;

Having regard to art. 48 of Decree Law no. 269 of September 30, 2003, amended and transformed into Law no. 326 of November 24, 2003, establishing the Italian Medicines Agency;

Having regard to Decree no. 245 of the Minister of Health, in agreement with the Ministers for Public Administration and Simplification and of Economy and Finance, of September 20, 2004, laying down rules on the organization and functioning of the Italian Medicines Agency, issued in accordance with the above-mentioned art. 48, paragraph 13, as modified by Decree no. 53 of the Minister of Health, in agreement with the Ministers for Public Administration and Simplification and of Economy and Finance of March 29, 2012;

Having regard to Decree of the Minister of Health of November 8, 2011, registered by the Central Budget Office in the "Visti semplici" register, sheet no. 1,282, on November 14, 2011, appointing prof. Luca Pani as Director General of the Italian Medicines Agency;

Having regard to Directive 2001/20/EC of the European Parliament and of the Council of April 4, 2001, on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use;

Having regard to Legislative Decree no. 211 of June 24, 2003, concerning the "Transposition of Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for clinical use";

Having regard to Decree of the Minister of Health of December 21, 2007, giving "Directions for submitting the request for authorisation of a clinical trial on a medicinal product for human use to the Competent Authority, for communicating substantial amendments, for declaring the end of the trial and for the request of an opinion to the Ethics Committee" and, in particular, to art. 8, according to which any update of and modification to the annexes to the same ministerial decree and to the notification procedures are established by provisions of the Director General of the Italian Medicines Agency, in compliance with the regulations of the European Community;

Having regard to AIFA Determination of March 7, 2011, published in the Official Journal of the Italian Republic no. 64 of March 19, 2011, concerning the "Modifications to Appendixes 5 and 6 to the Decree of the Minister of Health of December 21, 2007, relating to forms and documents to fill for submitting the request for authorisation to the Competent Authority, for communicating substantial amendments, for declaring the end of the trial and for the request of an opinion to the Ethics Committee";

Having regard to the Guidelines of the European Commission "Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1) (revision 3 of March 2010)", related to the requests for authorisation, the modifications and the declaration of the end of the trial, within the scope of Directive 2001/20/EC;

Having regard to Decree Law no. 158 of September 13, 2012, amended and transformed into Law by art. 1, paragraph 1, of the Law no. 189 of November 8, 2012, providing for "Urgent measures to promote the country's development through a higher level of protection of health, amended and transformed into Law no. 189 of November 8, 2012 (Ordinary Supplement to the Official Journal of November 10, 2012)" and, in particular, to art. 12, paragraph 9, transferring to the Italian Medicines Agency the expertise in the field of clinical trials of medicinal products granted by Legislative Decree no. 211 of June 24, 2003, and subsequent modifications and additions, to the National Institute of Health, and the role of Competent Authority pursuant to art. 2, paragraph 1, letter *t)*, numbers 1) and 1-*bis*) of the above-said Legislative Decree no. 211/2003;

Having also regard to art. 12, paragraph 12, of the above-said Decree Law no. 158/2012, which requires that, with effect from July 1, 2013, documentation of clinical trials on medicinal products ruled by Legislative Decree no. 211 of June 24, 2003, have to be managed exclusively by electronic means, through the standard models of the AIFA's National Monitoring Centre on Clinical Trials of Drugs (hereinafter "OsSC");

Deemed necessary, following the transfer of the role of Competent Authority to AIFA, to provide operators with guidance on how to submit requests for authorization of clinical trials of drugs;

Determines:

Art. 1.

1. With effect from September 14, 2012, the expertise in the field of clinical trials of medicinal products previously granted by Legislative Decree no. 211 of June 24, 2003, to the National Institute of Health are transferred to AIFA.

2. With effect from November 11, 2012, the expertise in the field of clinical trials of medicinal products provided for by art. 2, paragraph 1, letter t), points 1 and 1-bis) of the Legislative Decree no. 211 of June 24, 2003, are transferred to AIFA.

Art. 2.

1. Requests for authorisation of all clinical trials on medicines, substantial amendments made to the trials, declaration of start and conclusion in each clinical site, declaration of the overall conclusion of the study and results, in accordance with the procedures laid down by the Decree of the Minister of Health of December 21, 2007, shall be transmitted, together with the documents referred to therein, to AIFA through OsSC.

2. Until the adoption of the Decree of the Minister of Health, no fee is due to AIFA to carry out the functions of Competent Authority.

3. Ethics Committees continue to receive and validate documents, even on paper, in accordance with the provisions of checklist I.a, as amended by this determination, and of checklist I.b of Appendix 5 to the Decree of the Minister of Health of December 21, 2007.

4. AIFA is responsible for validating in OsSC requests for authorisation of phase II, III and IV clinical trials, limited to documents pertaining to AIFA.

5. The legal responsible of the clinical site is responsible for signing the contract with the sponsor or his representative, as provided for by art. 6, paragraph 6, of the Legislative Decree no. 211 of June 24, 2003.

Art. 3.

1. Until the adoption of the Decree of the Minister of Health referred to in art. 12, paragraph 9, of the Decree Law no. 158/2012 mentioned in the introduction, the National Health Institute, continuing to operate according to the procedures already in force, support AIFA for phase I trials; AIFA arranges the authorisation to be granted together with the Institute.

2. Until the adoption of the Decree of the Minister of Health referred to in art. 12, paragraph 9, of the Decree Law no. 158/2012 mentioned in the introduction, the National Health Institute is responsible for validating phase I trials requests for authorisation.

3. Phase I clinical trials and clinical trials on products for advanced therapies and related substantial amendments are authorised by an AIFA's specific decision.

4. For all phase II, III and IV trials, except trials on products for advanced therapies referred to in art. 9, paragraph 6, of the Legislative Decree no. 211 of June 24, 2003, provisions set forth in the just-mentioned art. 9 are applied, without prejudice to any reasoned objection within the period prescribed in the same art. 9, from the date of the application submission through OsSC.

Art. 4.

1. Appendix 5 in the Decree of the Minister of Health of December 21, 2007, is modified as regards the contents of list I.a, according to the specimen attached to this determination.

2. This determination shall enter into force the day after its publication in the Official Journal of the Italian Republic.

Rome, January 7, 2013

The Director General: PANI

I.a	**DOCUMENTS CHECK LIST**			
Information to be sent to AIFA (only by electronic means through OsSC), to the National Institute of Health for phase I studies and to the Ethics Committee (EC) granting the single opinion *Thick "NA" (Not Applicable) when the document is not envisaged for the study / provided for by rules*				
	1.	**General information**		
		1.1	Cover page with EudraCT number, printed from OsSC	
		1.2	Cover letter (*containing elements specified in the European Commission guidance - CT1*)	
		1.3	Clinical Trial Application form, printed from OsSC	
	❑ NA	1.4	List of other countries' Competent Authorities to which the request has been submitted and their decisions *(if available when the request is submitted)*	
	❑ NA	1.5	Copy of the summary of scientific advice Copy of the EMA decision and of the *Paediatric Committee* opinion on the *PIP (if not published; if published, please mention the link in the cover letter)* Specify:	
	❑ NA	1.6	If the applicant is not the sponsor, letter authorising the applicant to act on behalf of the sponsor	
	2.	**Information concerning subjects *(to be transmitted for evaluation to EC only)***		
		2.1	Informed consent form, date and version number	
	❑ NA		2.1.1	Additional informed consent forms, date and version number (consent form for minors, foreigners, etc.) Specify:
		2.2	Patient information leaflet, date and version number	
	❑ NA	2.3	Recruitment arrangements Specify:	
	❑ NA	2.4	Material subjects must be provided with (diaries, questionnaires, etc.) Specify:	
	3.	**Information concerning protocol**		
		3.1	Study protocol, date and version number	
	❑ NA		3.1.1	Documents related to the protocol (date and version) Specify:
		3.2	Protocol synopsis in Italian, date and version number	
	❑ NA	3.3	*Peer Review* of the study *(if available)*	
	❑ NA	3.4	If not in the protocol yet, risk-benefit assessments, expected risk of treatments and procedures to be implemented (including pain, discomfort, respect for the right to physical and mental health of subjects and means to prevent and/or manage unexpected or unintended events), a justification for including participants belonging to vulnerable populations (such as minors, subjects temporarily or permanently incapable, etc.).	
	❑ NA	3.5	If not in the protocol yet, ethics assessment by the coordinating investigator (or principal, if the trial is mono-centre).	
	4.	**Information concerning the IMP**		
		4.1	*Investigator's Brochure*, date and version number	

		4.2	IMPD, date and version number	
			4.2.1	Specify the IMP the dossier refers to:
	❑ NA	4.3	Other IMPDs	
			4.3.1	Date and version number
	❑ NA	4.4	Description of all on-going clinical trials with the same IMP	
		4.5	If the IMP is manufactured in the European Union but has not a marketing authorisation in the EU	
	❑ NA		4.5.1	Copy of the manufacturing authorisation, as referred to in art. 13, paragraph 1, of the Legislative Decree no. 211/2003 and Directive 2001/20/EC
		4.6	If the IMP is not manufactured in the EU and does not have a marketing authorisation in the EU	
	❑		4.6.1	Certification by the qualified person in a Member State that: a) the manufacturing site complies with good manufacturing practice (GMP) at least equivalent to the GMP in the EU; or b) each production batch has undergone all analyses, tests or checks relevant and necessary to confirm its quality.
	❑		4.6.2	Certification of GMP status of each active biological substance
	❑		4.6.3	Copy of the importation authorisation in the Member State and of the manufacturing authorisation granted to the third country site the IMP is imported from, as referred to in art. 13, paragraph 1, of the Legislative Decree no. 211/2003 and Directive 2001/20/EC
		4.7	Certificate of analysis for the test product in exceptional cases:	
	❑ NA		4.7.1	Where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected
	❑ NA	4.8	Studies on viral safety *(to be included in the IMPD)*	
	❑ NA	4.9	Provisions for medicinal products having particular characteristics (e.g. status of authorisations needed for bio-safety of IMP containing GMO, narcotics)	
		4.10	Examples of label in Italian	
	❑ NA	4.11	Certificate of suitability for TSE *(if necessary, following the sponsor's evaluation)*	
	5.	**Information concerning GCP inspections results the sponsor received**		
	❑ NA	5.1	Summary letters AIFA received	
	6.	**Information concerning structures and staff *(to be transmitted for evaluation to EC only)***		
		6.1	Structures the trial will be conducted in	
		6.2	CV of the coordinating / principal investigator	
	❑ NA	6.3	Information concerning auxiliary staff, if present	
	7.	**Information concerning financial aspects *(to be transmitted for evaluation to EC only)***		
		7.1	Provisions for indemnity, in case of damages or death due to the clinical trial	
		7.2	Provisions for insurance coverage of investigator's and sponsor's liability Certificate of insurance (data concerning the policy)	
	❑ NA	7.3	Any compensation for loss of earnings or reimbursement of expenses for the trial subjects	
	❑ NA	7.4	Contract proposal between the sponsor and the clinical site where the trial will be conducted	