GCPs의 International Harmonization 방향

김 경 환

International Harmonization of GCPs

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= 국 문 초 록 =

Good Clinical Practice(GCP)는 1970년 후반에 미국에서 FDA가 신의약품의 제조 및 판매허가와 관련된 사항 즉 임상시험 의뢰자와 모니터의 역할과 책임, 임상시험심사위원회의 역할, 임상시험연구자의 의무, 피험자들의 보호와 동의 등에 관한 규정안을 제안하면서, 이들 관련 규정안을 총칭하여 GCP라 칭하며 현재에는 의약품의 임상시험시 관련기관들의 제규정들에 적절하게 규정한 지침을 뜻한다.

임상시험은 인간을 대상으로 하는 연구이기 때문에 임상시험에 앞서 이러한 임상시험이 윤리적이고 과학적인 방법으로 실시되어야 한다. 그러므로 GCP규정을 시행하는 목적은 임상시험에 참여하는 피험자들의 권리와 안전을 도모하고, 임상시험과정 및 임상시험 결과의 과학적 검증 및 시험결과의 정확성 및 신뢰성을 얻기 위함이라 하겠다.

미국에서 처음으로 시작된 GCP규정은 각국에 영향을 주었는데, 이로인해 미국에 수입되는 의약품에 대한 미국 GCP규정의 적용과 다국적기업 성격의 제약회사, 우루과이 라운드 등의 영향으로 세계 각국들이 GCP규정을 설정하게 되었다. GCP규정은 독일(1986년), 프랑스(1987년), 영국(1989년)에 실시되었고, 유럽공동체의 형성으로 EU의 GCP규정안이 1990년 고시되어 1992년부터 실시되고 있으며, 일본도 1985년 의약품 임상시험 시행기준안을 공포하고 임상시험 기준시행법이 1990년부터 시행되고 있다. 우리나라에서도 80년대에 들어오면서 GCP법제화를 준비하여, 1987년 “의약품임상시험관리기준”을 제정 고시하였으나, 임상시험실시기관과 관련자들의 인식미비로 그간 시행을 미루어 오다 1995년 10월부터 GCP의 전면 시행이 이루어지게 되었다.

이러한 각국의 GCP는 각 나라마다의 상황에 따라 근소한 차이는 있으나 비교적 원칙적인 사항에서는 일치한다고 할 수 있겠다. 우선 차이를 보이는 몇 가지를 살펴보면, IRB 구성원 및 내용을 볼때 차이는 아래 표 1, 2와 같다. 이러한 단편적인 차이가 보여주듯이 각국의 GCP는 근소한 차이가 있는바 GCP의 선도적 역할을 하고 있는 미국 EU 및 일본 등 3개 당사자가 GCP의 국제기준마련을 위해 협의(International Harmonization Conference on Technical Requirement for Registration of Pharmaceuticals for Human Use ; ICH)하여 왔으며 전문위원회의 최종 심의를 거쳐 실시단계에 이르고 있다. 여기에서는 1996년 5월 1일 전문위원회에서 승인되어 3개 당사자가 실시하도록 권장한 제4단계 협의결과를 기준으로 소개한다. 이 ICH GCP가 실시될 경우 우리나라를 비롯한 대부분 나라 GCP규정의 개정이 뒤따를 것으로 보인다.

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Table 1. Composition of IRB Members

	U.S.A	KGCP	Japan	E.U.
Total No.	At least 5 : both sex	More than 5 ; (medical, dental, herbal pharmacology, nursing)	At least 5	
Background	At least 1 ; Non-scientific member At least 1 ; Non-affiliated member	At least 1 ; doctor At least 1 ; Non-medical, pharmaceutical science	At least 1 ; Non-scientific member	Medical + Non-medical member
Designation		by the head of the center Deliberation No Vote	by the head of medical institution	
Participation in one's own proposal		No	No	
Function	Consultant	Advisory committee		

Table 2. Contents of IRB Regulations in GCPs

	U.S.A	KGCP	Japan	E.C.
Scope	+	+	+	+
Composition of member	+	+	+	—
Function	+	+	+	+
Review process	+	+	+	—
Approval criteria	+	—	—	—
Expedited review	+	—	—	+
Cooperative research	+	+	+	+
Suspension, termination	+	+	—	—
Record maintenance	+	+	+	+
Non compliance	+	—	—	—
Inspection & audit	+	—	—	—

THE PRINCIPLES OF ICH GCP

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighted against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol and amendment(s) that have received prior institutional review board(IRB)/independent ethics committee(IEC) approval/favourable opinion.
7. The medical care given to, and medical decisions made for, subjects must always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice(GMP). They should be used in accordance with the approved protocol and amendments(s).
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

CONTENTS OF CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)

1. General Information
2. Background Information
3. Trial Objectives and Purpose
4. Trial Design
5. Selection and Withdrawal of Subjects
6. Treatment of Subjects
7. Assessment of Efficacy
8. Assessment of Safety
9. Statistics
10. Direct Access to Source Data/Documents
11. Quality Control and Quality Assurance
12. Ethics
13. Data Handling and Record Keeping
14. Financing and Insurance
15. Publication Policy

16. Supplements

ICH Harmonised Tripartite GCP Guideline

GUIDELINE FOR ESSENTIAL DOCUMENTS FOR
THE CONDUCT OF A CLINICAL TRIAL

SECTION 1 : Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts

	Title of Document	Located in Files of	
		Investigator	Sponsor
1.1	INVESTIGATOR'S BROCHURE	X	X
1.2	SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM(CRF)	X	X
1.3	INFORMATION GIVEN TO STUDY SUBJECT	X	X
	-INFORMATION SHEET		
	-INFORMED CONSENT FORM	X	X
	-ADVERTISEMENT FOR SUBJECT RECRUITMENT(if applicable)	X	
1.4	FINANCIAL ASPECT OF THE TRIAL		
1.5	INSURANCE STATEMENT		
1.6	SIGNED AGREEMENT BETWEEN INVOLVED PARTIES		
	DATED, DOCUMENTED APPROVAL OR OPINION OF INDEPENDENT ETHICS COMMITTEE (IEC)/INSTITUTIONAL REVIEW BOARD (IRB)	X	X
1.7	INDEPENDENT ETHICS		
1.8	COMMITTEE/INSTITUTIONAL REVIEW BOARD COMPOSITION	X	X (where required)
	REGULATORY AUTHORITY		
1.9	AUTHORISATION/APPROVAL/ NOTIFICATION OF PROTOCOL	X (where required)	X (where required)
	CURRICULUM VITAE OF		
1.10	INVESTIGATOR(S) AND SUBINVESTIGATOR(S)	X	X
1.11	NORMAL VALUES FOR ANY MEDICAL/ LABORATORY/TECHNICAL PROCEDURE OR TEST INCLUDED IN THE PROTOCOL	X	X
1.12	MEDICAL/LABORATORY/TECHNICAL PROCEDURES/TESTS	X (where required)	X

1.13	SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)		X
1.14	INSTRUCTIONS FOR HANDLING OF INVESTAGATIONAL PRODUCTS AND TRIAL-RELATED MATERIALS	X	X
1.15	SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS	X	X
1.16	CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED		X
1.17	DECODING PROCEDURES FOR BLINDED TRIAL	X (or third party)	X (or third party)
1.18	MASTER RANDOMISATION LIST		X (or third party)
1.19	PRE-TRIAL MONITORING REPORT		X
1.20	TRIAL INITIATION MONITORING REPORT	X	X

SECTION II : During the Clinical Conduct of the Trial

In addition to having on file the above documents, the following should be added to the files during trial and evidence that all new relevant information is documented as it becomes available.

Title of Document		Located in Files of	
		Investigator	Sponsor
2.1	INVESTIGATOR'S BOOCHURE UPDATES	X	X
2.2	ANY REVISION	X	X
2.3	DATED, DOCUMENTED APPROVAL / FAVOURABLE OPINION OF INDEPENDENT ETHICS COMMITTEE/INSTITUTIONAL REVIEW	X	X
2.4	BOARD REGULATORY AUTHORISATIONS NOTIFICATIONS WHERE REQUIRED	X (where required)	X
2.5	CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUBINVESTIGATOR(S)	X	X
2.6	UPDATES TO NORMAL VALUES FOR ANY MEDICAL/LABORATORY/TECHNICAL PROCEDURES/TESTS	X	X
2.7	UPDATES OF MEDICAL/LABORATORY/ TECHNICAL PROCEDURES/TESTS	X (where required)	X
2.8	DOCUMENTATION OF	X	X

	INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT		
2.9	CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS		X
2.10	MONITORING REPORT FOR VISITS		X
2.11	RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS	X	X
2.12	SIGNED INFORMED CONSENT FORMS	X	
2.13	SOURCE DOCUMENTS	X	
2.14	SIGNED, DATED AND COMPLETED CASE REPORT FORMS(CRF)	X (copy)	X (original)
2.15	DOCUMENTATION OF CRF CORRECTIONS	X (copy)	X (original)
2.16	NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS INCLUDING CAUSALITY ASSESSMENTS	X	X
2.17	NOTIFICATION BY SPONSOR AND/OR INVESTIGATOR TO REGULATORY AUTHORITY(IES) OF SERIOUS ADVERSE ASSESSMENTS	X (where required)	X
2.18	NOTIFICATION BY SPONSOR TO ALL INVESTIGATORS OF SERIOUS ADVERSE EVENTS INCLUDING CAUSALITY ASSESSMENTS		X
2.19	NOTIFICATION BY EACH INVESTIGATOR TO THE RESPONSIBLE IEC/IRB OF SERIOUS ADVERSE EVENTS INCLUDING CAUSALITY ASSESSMENTS	X	
2.20	INTERIM OR ANNUAL REPORTS TO IEC/IRB	X	
2.21	SUBJECT SCREENING LOG		X (where required)
2.22	SUBJECT IDENTIFICATION LIST		
2.23	SUBJECT ENROLMENT LOG	X	
2.24	INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE	X X	X
2.25	SIGNATURE SHEET		X
2.26	RECORD OF RETAINED BODY FLUIDS/ TISSUE SAMPLES(IF ANY)	X X	X

SECTION III : After Completion of Termination of the Trial

After completion or termination of the trial, all of the documents identified in sections I and II should be in the file together with the following.

	Title of Document	Located in Files of	
		Investigator	Sponsor
3.1	INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE	X	X
3.2	DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION	X (if destroyed at site)	X
3.3	COMPLETED SUBJECT IDENTIFICATION CODE LIST	X	
3.4	COMPLIANCE STATEMENT AUDIT CERTIFICATE(if available)		X
3.5	FINAL TRIAL CLOSE-OUT MONITORING REPORT		X
3.6	TREATMENT ALLOCATION AND DECODING DOCUMENTATION	X	X
3.7	FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)	X	X
3.8	CLINICAL STUDY REPORT	(if applicable)	

GUIDELINE FOR THE INVESTIGATOR'S BROCHURE

ICH Harmonised Tripartite GCP Guideline

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 - 3.5.3 Toxicology
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APPENDIX 1 :

TITLE PAGE(Example)

APPENDIX 1 :

TITLE PAGE(Example)

SPONSOR'S NAME

Product :

Research Number :

Name(s) : Chemical, Generic (if approved)

Trade Name(s) (if legally permissible and desired by the sponsor)

INVESTIGATOR'S BROCHURE

Edition Number :

Release Date :

Replaces Previous Edition Number :

Date :