PEER REVIEWED

Hamdi Akan, MD, FACP, CCTI | Hilal İlbars, MSc, PhD | İsmail Hakki Ayhan, MD, PhD | Emin Kansu, MD, PhD, FACP | Murat Akova, MD | Oğuz Akbaş, MD, PhD | Nurşah Ömeroğlu, PhD, CCRA | Çiğdem Ari, MD, CCRA | Emel Tetik, PhD, MSc | Edibe Taylan, MD

New GCP Rules in Turkey

The first mention of clinical trials in a legal document occurred in Turkey many years before the Helsinki Declaration or Belmont report; issued in 1926, the Code of Pharmaceutical Products and Preparations No. 1262 law carries the statement: "Experimental drugs can be used in a patient only by his/her permission."

After periods of misconducted and ill-designed studies, the modern era of clinical trails began in 1993 with the introduction of the "Drug Research Bylaw." This document was directly influenced by the initial drafts of ICH-GCP Guidelines, and some parts were very similar. (Table 1 presents a comparison of the two.) This became the main document that regulates the conduct of clinical trials in Turkey; a good clinical practice (GCP) guidelines document was added in 1995. After that, good laboratory practice (GLP) and good manufacturing practice (GMP) guidelines were also published and issued by the Ministry of Health.

Although these were quite early and impressive achievements, the growing number of different clinical trials and clinical investigators over time increased the need for new and updated regulations. This demand was partly covered by documents such as regulations on compassionate use, observational trials, patient rights, and articles in the Turkish penal law. During that time, major changes in the national policies of Turkey occurred, turning the face of Turkey dramatically toward the European Union (EU), and a new period began that required a complete revision of all legal documents and adaptation to EU rules and principles.

Major changes in the national policies of Turkey occurred, turning the face of Turkey dramatically toward the European Union (EU), and a new period began that required a complete revision of all legal documents and adaptation to EU rules and principles.

All these factors prompted an initiative begun by the Turkish health authorities and supported by academia, resulting with a new draft bylaw in the last days of 2005 that regulates drug-related trials. It contains eight articles:

Article 1—Aim, scope, legal support, and definitions
Article 2—Safety of subjects, informed consent, and responsibilities
Article 3—Starting clinical trials
Article 4—Approved ethics committees
Article 5—Clinical trial sites, investigators, and basics of conducting clinical trials
Article 6—Investigational medicinal products
Article 7—Adverse events, monitoring, and reporting of adverse events
Article 8—General and final statements

Table 2 presents a summary of the differences between the current and the new bylaw.

The name of the 1993 bylaw is "Bylaw on Drug Research"; the new document is "Bylaw on the Clinical Trials Conducted by Medicinal Products Used in Humans," which reflects the fact that the new bylaw has a broader reach. The 26 paragraphs in the current bylaw increased to 47 in the new one. The 1993

Table 1. Comparison of ICH-GCP Guidelines and Turkish Drug Res		
	CH-GCP Guidelines	**Turkish Drug Research Bylaw (GCP Guidelines)**
Approval	IRB/IEC approval	Competent Authority approval
Submission to IEC	IRB/IEC	First local IRB; after approval of central ethics committee
Notification of the regulatory authority	Sponsor	Investigator
Nontherapeutic trials	Decision to be made by the IRB/IEC	Not defined
Ethical Committee membership	At least one member whose primary area of interest is in a nonscientific area and at least one member who is independent of the institution/trial site.	No such member
Impartial witness for informed consent	Under specific conditions	For every informed consent
Adverse event notification	Sponsor	Investigator
Timetables: • SAE (fatal and life-threatening) reporting	7 days	24 hours
• AE (non-life-threatening) reporting	15 days	Not defined
• Retention of the source documents	2+ years	15 years

bylaw is based on previous local legal documents; the new bylaw states that it is in parallel to the 2001/20/EC and 2005/28/EC directives.

Both documents start with definitions. The current document defines regulating authority, drug, clinical research, ethics committee, and local ethics committee; these five were expanded to 39 in the GCP guideline published in 1995. The new bylaw has 23 definitions. The current bylaw covers only drugs used in humans, but the new bylaw covers all medicinal products that can be used in humans.

Subjects

The current bylaw has a narrow explanation on subjects, declaring that the rules of Helsinki should be applied and written consent is necessary. Minors and incapacitated subjects are covered in two sentences: "Unless there is a necessity, Phase I and II trials should not be conducted on children under 18 years old, pregnant woman, and incapable subjects. Phase III trials can be conducted in incapable subjects with a written permission from their legal representatives."

Due to the arguments on conducting trials in children after 1993, the new Turkish penal law accepted by the Parliament in 2005 detailed the rules of conducting trials in children in accordance with EU directives. The new bylaw has a separate article for trials in children and persons incapable of giving their consent. The paragraph on children includes issues that were absent in the current bylaw, such as assent of children, direct benefit and minimal risk, and the notion of no incentives or financial inducements except compensation.

Also, although current bylaw requires a witness to sign for all informed consents, the new bylaw requires this only for subjects who cannot give a written informed consent for any reason. In addition, the new bylaw states that "no clinical trial should be conducted that affects the genetic identity of the germ cells of the subject."

Ethics Committees

There are major changes in the types and configuration of the ethics committees. The central ethics committee that is currently working in the Ministry of Health will be renamed as the Clinical Research Advisory Board (the Board), and the local ethics committee will be called the Approved Ethics Committee. Membership on the Board requires five years of experience in the individual's field of specialty; the current requirement is 10 years. There will be additional Board members, including members from the Bar Association, the Department of Religious Affairs, a biostatistician, a deontologist or medical ethics specialist, and a nonmedical, university-graduated layperson. The Board will also control and audit the Approved Ethics Committees and will be responsible for the standard operating procedures (SOPs). Theoretically, the Board serves as an advisory board, and the single opinion of the competent authority is possible without the approval of the Board.

An approved ethics committee can work only in university hospitals and fully equipped state hospitals. The member configuration will be changed to require that one-third of the members be selected outside the institution. A lawyer and a nonmedical, university-graduated

Table 2. Comparison of the Current and the New Bylaw		
	Current Bylaw	**New Bylaw**
Origin	ICH Guidelines	2001/2005/EC Directives
Ethical committee submission	First local, then central ethics committee (double-tract)	Simultaneous application (Single opinion)
Ethical committee approval	Both local and central ethics committee	Single opinion
Application responsibility	Clinical investigator	Sponsor
Site of clinical trial	Only university and state education and research hospitals	Plus A1-Class private hospitals
Ethical committee configuration	No layperson	One-fifth of the members outside the institution (incl. laymen)
Ethical committee membership	10 years of experience in their field of specialty	Five years of experience in their field of specialty
Investigator	Five years of experience in the field of expertise	PhD or specialty in a field of medicine

layperson will also be required. All phase trials and bioavailability and bioequivalence trials will be subject to approval by ethics committees, and all applications must be answered within 45 days. These committees must be approved by the regulating authority (i.e., Ministry of Health). For approval, the curriculum vitae of the members, written SOPs, archive facilities, fax, phone, data bank, GCP expertise, and five years of clinical experience are required.

Clinical Trial Sites, Application, and Conduct

The current bylaw states that clinical trials can be conducted only in university or state education and research hospitals that offer graduate education. According to the new bylaw, these trials can also be conducted in A1-Class private hospitals with adequate infrastructure, manpower, and laboratory facilities. Except for university and state education and research hospitals, which fulfill these requirements, all clinical trial sites have to apply to the Ministry of Health for approval. After an audit process, these sites can be approved.

According to the current bylaw, the principal investigator is responsible for the clinical trial application and other procedures related to the trial. Soon the sponsor will be responsible for these procedures. In the submission process, both the competent authority and Approved Ethics Committee application can be done at the same time. Currently, when applying to the Central Ethics Committee, the protocol first has to be approved by the local ethics committee.

An important change that can speed up the process of approval will be obtaining a single opinion from the competent authority (i.e., Ministry of Health). Approved Ethics Committees will only be informed about the study, and the final opinion of the competent authority is mandatory to start a trial. The competent authority has a maximum of 60 days from the date of receipt of a valid application to give its reasoned opinion to the applicant. This can be extended 30 days for trials involving medicinal products for gene therapy, somatic cell therapy, or medicinal products containing genetically modified organisms.

Currently, the opinion of the local ethics committee is sufficient for Phase IV trials, and only the notification of the Central Ethics Committee is required. Soon, final evaluation by the competent authority will be required. According to the current bylaw, all protocol amendments are sent to the Central Ethics Committee. In the future, if these amendments are substantial and are likely to have an impact on the safety of the trial subjects, or to change the interpretation of the scientific documents in support of the conduct of the trial, or if they are otherwise significant, the sponsor shall notify the Approved Ethics Committee.

Other Issues

Currently, five years of experience in the field of expertise is required to be a responsible investigator. Soon, a PhD or specialty in a field of medicine will be enough. Another addition in this section is the possibility to have a co-investigator from another institution for outpatient follow-up.

Clinical research organizations (CROs) that will take part in a research activity will have to be audited and approved by the Ministry of Health for clinical trial purposes. After the approval, they can be qualified as a CRO.

The new bylaw states that the investigator shall report all serious adverse events immediately to the sponsor, except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting. Currently, all adverse events are reported to the Central Ethics Committee by the investigator or sponsor.

The sponsor ensures that all relevant information about suspected serious unexpected adverse reactions that are

fatal or life-threatening is recorded and reported in seven days to the competent authority and Approved Ethics Committee. Under the new bylaw, other serious adverse reactions must be reported in 15 days; this period is 24 hours now.

Responsibilities

According to the 2005/28 EC Directive, due to the specific conditions under which noncommercial trials are conducted, member states foresee specific modalities to be applied to these trials. This is the case not just when conducted with authorized medicinal products and on patients with the same characteristics, but also to comply with the principles imposed by this directive, in particular as far as the manufacturing or import requirements for authorization and the documentation to be submitted and archived for the trial master file are concerned. The conditions under which the noncommercial research is conducted by public researchers, and the sites where this research takes place, make the application of certain GCP details unnecessary or guaranteed by other means. This paragraph is reflected in the new bylaw by this statement: "The Ministry of Health will prepare a draft after receiving the opinions of the other involved ministries and institutions in this respect."

The legal and economic responsibilities of a clinical research trial belong to the clinical investigator, institution sponsor, and/or CRO. The costs related to the investigational medicinal product and any other products, equipment used in the manufacturing of these products, and laboratory analysis in clinical trials can by no means be paid by the patient or social security system. The investigator or the sponsor pays all the costs related to the clinical trial. There is a similar statement in the current bylaw.

An important addition in this section is the penalties. The current bylaw states that, if a clinical trial is conducted against the rules of the bylaw, the Ministry of Health can suspend the trial after the positive opinion of the Central Ethics Committee. The new bylaw says that, if a clinical trial is conducted and published against the principles mentioned in the bylaw, the ministry will suspend the clinical trial application of the responsible investigator for two years and has the right to make public the identities involved, using the press, if necessary.

Clearly, the new bylaw is an important step in Turkey's integration process into the EU. The new bylaw will be effective in 2007. This will be followed by new guidelines on SUSAR reporting and competent authority submission. Although there are some differences between the EU directives and the Turkish Bylaw, the main articles are similar. The discrepancies between the two documents will be resolved during the talks through the EU integration process. **ACRP**

Hamdi Akan, MD, FACP, CCTI, received his MD from the Ankara University School of Medicine, where he works in the Division of Hematology, principally on febrile neutropenia and clinical trials. He is the webmaster of two Turkish websites on febrile neutropenia and coffee and has served as managing editor of the only "GCP journal" in Turkey. The first ACRP-certified clinical trial investigator in Turkey, Akan is currently an active member of the Health Ministry National Central Ethics Committee. He can be reached at hamdiakan@gmail.com.

Hilal Îlbars, MSc, PhD, received a bachelor's degree in pharmacy and a master's degree in pharmaceutical toxicology from the pharmacy faculty of Gazi University. Currently a PhD student in pharmacy management of the pharmacy faculty of Ankara University, she worked one year in the Eğirdir Osteopathic Hospital under the Ministry of Health (MoH) as an hospital pharmacist. She has been working in the General Directorate of Drug and Pharmacy for 12 years in various departments in cosmetics, licensing, and the last five years in clinical research. She is now head of the MoH clinical trials department and can be reached at hilbars1970@yahoo.com.

Ísmail Hakki Ayhan, MD, PhD, is a pharmacology professor who chairs the Ethics Committee and Department of Pharmacology and Clinical Pharmacology, Ankara University Faculty of Medicine; he is also an adviser to the university president. He has been president of the National Central Ethics Committee, member of the executive committee of the European College of Neuropsychopharmacology, and a board member of the board of the Vienna School of Clinical Research. He can be reached at hayhan@dialup.ankara.edu.tr.

Emin Kansu, MD, PhD, FACP, received his MD from Hacettepe Faculty of Medicine, Ankara, Turkey, and completed internal medicine residency and hematology clinical and research fellowship training at Thomas Jefferson University, Philadelphia, Pa. He has been a faculty member and chairman of the Department of Basic Oncology and the director of the Hematopoietic Stem Cell Transplantation Unit at the Hacettepe University Institute of Oncology. He can be reached at ekansu@ada.net.tr.

Murat Akova, MD, obtained a degree in medical microbiology from London Hospital Medical College, UK. After serving a year as visiting scientist at the Center for Adaptive Resistance and Microbiology at the Tufts University School of Medicine, Boston, Mass., he obtained a subspeciality degree in infectious diseases from Hacettepe University where he is now a tenured professor of medicine. Since 2002 he has been an active member of the Health Ministry National Central Ethics Committee. He can be reached at makova@hacettepe.edu.tr.

Oğuz Akbaş MD, PhD, received his MD from Ankara University in 1981 and his PhD in pharmacology at the Hacettepe University in 1985. After employment with various pharmaceutical companies, he received training as a clinical study monitor. He worked on several projects as a freelance study monitor, and since 1999 he has been the general manager of MONITOR Clinical Research Organization Company. He can be reached at oguza@monitorcro.com.

Nurşah Ömeroğlu, PhD, CCRA, received her BSc from the Bogazici University Department of Molecular Biology and Genetics and her PhD from Ankara University. Currently she is the director of the Clinical Operations Unit at Sanofi-aventis Turkey. She has worked in different positions of clinical research since 1998. She is also an ACRP-certified clinical research associate (CCRA). She can be reached at nursah.omeroglu@sanofi-aventis.com.

Çiğdem Ari, MD, CCRA, received her MD from the Ankara University Medical School and completed a residency program in the Department of Physical Medicine and Rehabilitation at the Hacettepe University. Having worked in several positions in the pharmaceutical sector since 1995, she is currently the quality manager of Sanofi-aventis Turkey. She has been in clinical research as an investigator, CRA, and Clinical QA, and is a member and certified CRA of ACRP and member of BARQA. She can be reached at cigdem.ari@sanofi-aventis.com.

Emel Tetik, PhD, MSc, received her PhD in molecular genetics and her MSc in biotechnology from the Middle East Technical University, Department of Biological Sciences. She has been a faculty member and lecturer of the Department of Pharmaceutical Biotechnology at the Marmara University, Faculty of Pharmacy. Having worked in different positions in the clinical research field, she is currently the director of the Clinical Research Unit at Sanofi-aventis Turkey. She can be reached at emel.tetik@sanofi.aventis.com.

Edibe Taylan, MD, received her MD from the Istanbul University-Cerrahpasa Faculty of Medicine. Having served in several directorate positions in the pharmaceutical sector since 1987, she is currently the medical director and member of the Management Committee of Sanofi-aventis Turkey. As head of the medical team, she has key responsibilities in medical and regulatory affairs, clinical operations, pharmacovigilance, quality, and health economics. She is also a member of the Turkish Association of Research-Based Pharmaceutical Companies. Taylan can be reached at edibe.taylan@sanofi-aventis.com.