



Regulations and Guidelines

Affecting Clinical
Research in the
ICH Regions

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Overview of the ICH products relating to clinical development – the ‘Efficacy’ section

The work of the ICH process is divided into four major categories: Quality, Safety, Efficacy and Multidisciplinary.

ICH Topic Codes Q, S, E and M are assigned according to these categories.

Topics in each of these sections are selected and developed by Expert Working Groups. The guidance progresses in a stepwise fashion. For example, at Step 3 there is ongoing consultation on a draft. Step 4 is when consensus is reached. Documents defined as Step 5 are agreed and implemented.

In this section we summarise the guidelines that have been produced in the Efficacy section. New topics are continually being developed. To keep up to date it is necessary to regularly visit the ICH website, the source of these documents <www.ich.org>.

Q – Quality Topics, ie. those relating to chemical and pharmaceutical Quality Assurance.

Examples: Q1 Stability Testing, Q3 Impurity Testing.

S – Safety Topics, ie. those relating to *in vitro* and *in vivo* pre-clinical studies.

Examples: S1 Carcinogenicity Testing, S2 Genotoxicity Testing. Safety reporting in clinical trials is presented in the Efficacy section.

E – Efficacy Topics, ie. those relating to clinical studies in human subjects.

Example: E6 Good Clinical Practices.

M – Multidisciplinary Topics, ie. cross-cutting topics which do not fit uniquely into one of the above categories.

Abbreviations: CHMP, Committee for Medicinal Products for Human Use; CIOMS, Council for International Organizations of Medical Sciences; CPMP, Committee for Proprietary Medicinal Products; EFPIA, European Federation of Pharmaceutical Industries and Associations; EU, European Union; FDA, US Food and Drug Administration; ICH, International Conference on Harmonisation; ICSR, individual case safety report; IRB, institutional review board; MHLW, Japanese Ministry of Health, Labour and Welfare; PhRMA, Pharmaceutical Research and Manufacturers of America.

Clinical safety

E1

The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life Threatening Conditions

- Step 5
- Recommendations on the numbers of patients and duration of exposure for the safety evaluation of drugs intended for the long-term treatment of non-life-threatening conditions.

EU: Adopted by CPMP, November 1994, issued as CPMP/ICH/375/95

MHLW: Adopted May 1995, PAB/PCD Notification No. 592

FDA: Published in the *Federal Register*, Vol. 60, March 1, 1995, page 11270

E2A

Clinical Safety Data Management: Definitions and Standards for Expedited Reporting

- Step 5
- Standard definitions and terminology for key aspects of clinical safety reporting and guidance on mechanisms for handling expedited (rapid) reporting of adverse drug reactions in the investigational phase of drug development.

EU: Adopted by CPMP, November 1994, issued as CPMP/ICH/377/95

MHLW: Adopted March 1995, PAB/PCD Notification No. 227

FDA: Published in the *Federal Register*, Vol. 60, No. 40, March 1, 1995, pages 11284–11287

E2B(R3)

Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports

- Revision under Consultation (Step 3)
- This guideline aims to standardise the data elements for transmission of individual case safety reports by defining the data elements for the transmission of all types of individual case safety reports, regardless of source and destination. This guideline includes data elements of case safety reports for both pre- and post-approval periods and covers both adverse drug reaction and adverse event reports. For adverse reactions encountered in clinical trials, this format should be used only for those subject to expedited reporting. It incorporates adjustments based on the experience gained after the implementation of the guideline in the three regions. Should be read in conjunction with the companion document: M2 ICSR Message Specification. E2B(R3) Final Concept Paper, November 2003 (revision of E2B(R2)).

EU: Transmission to CHMP and Interested Parties in May 2005. Issued as EMEA/CHMP/ICH/166783/2005

MHLW: Released for consultation on July 21, 2005, PFSB/SD

FDA: Published in the *Federal Register*, Vol. 70, No. 190, October 3, 2005, pages 57610–57611

The regulatory authorities in Europe, Japan and the USA

A summary of the organisation of the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

Food and Drug Administration

The US FDA (<www.fda.gov>) sits within the Department of Health and Human Services and comprises seven centres and offices. Of these seven, the first three play a critical role in the regulation of medicinal products and devices for human use:

Center for Biologics Evaluation and Research (CBER)

Regulates biological products that are inherently more complex than chemically synthesised drugs, eg. blood and blood products, vaccines, allergenic products and protein-based drugs such as monoclonal antibodies
<www.fda.gov/cber/>

Center for Devices and Radiological Health (CDRH)

Ensures new medical devices are safe and effective before they are marketed. It also monitors devices throughout their lifecycle via a nationwide post-marketing surveillance system. In the near future, CDRH will be responsible for resolving issues relating to emerging technological and

demographic developments, eg. diagnosis and treatment options related to the Human Genome Project.
<www.fda.gov/cdrh/>

Center for Drug Evaluation and Research (CDER)

Promotes and protects health by assuring all prescription and over-the-counter drugs are safe and effective. It also monitors advertising and plays a crucial role in providing health professionals and consumers with information on safe drug use.
<www.fda.gov/cder/>

Center for Food Safety and Applied Nutrition (CFSAN)

Responsible for the safety of approximately 80% of all food consumed in the USA.
<www.cfsan.fda.gov>

National Center for Toxicological Research (NCTR)

Conducts innovative, integrative research to support and anticipate FDA's current and future regulatory needs.
<www.fda.gov/nctr/index.html>

Office of the Commissioner (OC)
Implements FDA's mission. It has

validity of opinions reached by the Committee. CHMP members are nominated by the Member States and are chosen on the strength of their qualifications and expertise with regard to the evaluation of medicinal products. They serve on the Committee for a renewable period of 3 years.

- The Committee for Orphan Medicinal Products (COMP) reviews applications from persons or companies seeking orphan medicinal product designation for products they intend to develop for the diagnosis, prevention or treatment of life-threatening or very serious conditions that affect not more than five in 10,000 persons in the EU. The COMP also advises the EC on establishing and developing policy on orphan medicinal products in the EU, and assists the EC in producing detailed guidelines and liaising internationally on matters relating to orphan medicinal products.
- The Committee on Herbal Medicinal Products (HMPC) was established in 2004, replacing the CPMP Working Party on Herbal Medicinal Products.

The HMPC's activities aim to assist the harmonisation of procedures and provisions concerning herbal medicinal products in EU Member States, and to further integrate herbal medicinal products within the European regulatory framework. The HMPC has also established a draft Community list of herbal substances and preparations for use in traditional herbal medicinal products, plus Community herbal monographs.

- The Paediatric Committee is primarily responsible for assessing the content of paediatric investigation plans and for adopting opinions on these, including the assessment of applications for a full or partial waiver and assessment of applications for deferrals. It fulfils other responsibilities aimed at improving the availability of pharmaceutical products specifically developed for the treatment of paediatric diseases, but is not responsible for marketing authorisation applications for medicinal products for paediatric use (this remains within the remit of the CHMP).

Japan's Ministry of Health, Labour and Welfare

Chapter 1 of the Japan Pharmaceutical Manufacturers Association updated documentation of "Pharmaceutical Administration and Regulations in Japan" covers the organisation and function of Japan's Ministry of Health, Labour and Welfare (MHLW).

The MHLW was established in 2001 and is responsible for the improvement and promotion of social welfare, social security and public health in Japan. It consists of the ministry plus various affiliated institutions and councils. The MHLW is in charge of pharmaceutical regulatory affairs in Japan and operates through various groups, including

- the Pharmaceutical and Food Safety Bureau (PFSB), which undertakes the approval and licensing of drugs
- the Health Policy Bureau, which handles the promotion of research and development (R&D), production and distribution policies (ie. functions related to pharmaceutical companies)
- the Pharmaceuticals and Medical Devices Evaluation Centre (Evaluation Centre) in the National Institute of Health Sciences, which also contributes to approval reviews.

In 2004, the Evaluation Centre, the Organisation for Pharmaceutical Safety and Research and part of the Medical Devices Centre were integrated to form a new independent administrative organisation known as

the Pharmaceutical and Medical Devices Agency (PMDA). PMDA offers consultation on clinical trials of new drugs and medical devices, conducts approval reviews and undertakes surveys of the reliability of application data. The MHLW and PMDA are thus now able to handle a wide range of activities from clinical studies to approval reviews, post-marketing reviews and safety measures.

The Pharmaceutical and Food Safety Bureau

The PFSB also tackles problems directly related to the lives and health of the general public, including those linked to blood supplies, blood products, narcotics and stimulant drugs.

Health Policy Bureau

The Health Policy Bureau drafts policies aimed at achieving a high-quality, efficient healthcare supply system. Two divisions - the Economic Affairs Division and the R&D Division are closely linked to the pharmaceutical industry and their functions include the following:

- activities related to the production and trade of drugs and medical devices
- financial services and work related to fostering and promoting the production and distribution of drugs
- the enforcement of laws covering the production and distribution of drugs
- providing a forum on behalf of companies and the industry as a whole in areas related to pricing

Overview of key US regulations affecting clinical research

The key regulations affecting, but not limited to, FDA requirements are summarised below. The latest versions at the time of writing are dated April 2006. All Code of Federal Regulations may be located, by inserting the section details, via the website <www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm>

Title 21 CFR Part 11, Electronic records, electronic signatures

Part 11 outlines the regulation relating to electronic records and electronic signatures, including the circumstances under which they will be considered equivalent to handwritten signatures. This Part of the regulations has been subject to much criticism. Whilst there is now a general acceptance that many of the requirements are not workable, the predicate rules must still be followed. Part 11 describes the requirements needed to make sure that systems used to create, modify, maintain or transmit electronic records can preserve the authenticity, integrity and confidentiality of the records. Guidance has been issued by the FDA on this subject and represents the current thinking (May 2007 update). <www.fda.gov/cder/guidance/7359fnl.htm>

Title 21 CFR Part 50, Protection of human subjects

Part 50 protects human subjects participating in clinical investigations regulated by the FDA and those that support applications for research or marketing permits for products regulated by the FDA. It covers the informed consent process:

- General requirements for informed consent
- Exception from general requirements
- Exception from informed consent requirements for emergency research
- Elements of informed consent
- Documentation of informed consent
- Additional safeguards needed for research in children.

Title 21 CFR Part 56, Institutional review boards

Part 56 aims to protect the rights and welfare of human subjects involved in clinical investigations. It defines the standards for the composition, operation and responsibility of institutional review boards (IRBs) involved in reviewing research regulated by the FDA or used to support applications for research or marketing permits for products regulated by the FDA. Sections in Part 56 outline

- The circumstances in which IRB review is required
- Exemptions and waivers
- IRB membership
- IRB functions and operations
- IRB review of research
- Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research
- Criteria for IRB approval of research
- Review by institution
- Suspension or termination of IRB approval of research
- Cooperative research
- IRB records
- Administrative actions for non-compliance.

Regulations and guidelines affecting clinical research and product development in Europe

The Rules Governing Medicinal Products in the EU

Spanning 10 volumes, the complete set of The Rules Governing Medicinal Products in the European Union (EudraLex) can now be accessed online. Below we give an overview of the key content that relates to clinical drug development.

Volumes 1–3 of EudraLex cover medicinal products and Volumes 5–8 relate to veterinary products. Volumes 4 and 9 apply to both human and animal products, while Volume 10 deals exclusively with clinical trials in humans.

Volume 1: Pharmaceutical Legislation

Volume 1 provides links to the texts (in all relevant EU languages) for the current EU legislation relating to medicinal products for human use. The key Directives (with applicable amendments and corrections) are listed first, followed by the Regulations. A final section, headed “Miscellaneous”, provides links to documents such as Council Decisions, Council Directives and Council Communications going back as far as 1975.

Volume 2: Notice to Applicants

The Notice to Applicants (NTA) was first published in 1986 and has been updated regularly ever since. It has been prepared by the EC, in consultation with the Member States’ competent authorities and the European Medicines Agency (EMA), and is intended to facilitate the interpretation and application of Community pharmaceutical legislation. However, the NTA is not legally binding and, in case of doubt, refer-

Overview of key forms used in clinical research

Forms commonly used in the USA

FDA Form 1571

An Investigational New Drug Application (IND) is a request for authorisation from the FDA to administer an investigational drug or biological product to humans. Such authorisation must be secured prior to the shipment and administration of any new drug or biological product that does not have an approved New Drug Application or Biologics/Product License Application. The request for such an authorisation is made using FDA Form 1571.

www.fda.gov/opacom/morechoices/fdaforms/1571es.pdf

FDA Form 1572

Prior to taking part in a clinical study under IND regulations, an investigator must complete and sign FDA Form 1572, Statement of Investigator, to indicate that s/he will abide by the federal guidelines set forth in the Code of Federal Regulations for the use of drugs in an investigational setting.

www.fda.gov/opacom/morechoices/fdaforms/FDA-1572.pdf

FDA Form 3397

This is the Prescription Drug User Fee Act user fee cover sheet, designed to provide the minimum necessary information to determine whether a fee is required for review of an application, to determine the amount of fee required, and to help the FDA track payments.

www.fda.gov/oc/pdufa/coversheet.html

FDA Forms 3454 and 3455

When a marketing application for a drug, biological or medical device is submitted, certain information must also be submitted regarding the compensation to, and financial interests of, any clinical investigator who conducted any of the clinical studies covered in the application. Applicants must either certify to the absence of certain financial interests of clinical investigators on Financial Interest Form: Certification: Financial Interests and Arrangements of Clinical Investigations, FDA Form 3454, or disclose those financial interests on Financial Interest Form: Disclosure: Financial Interests and Arrangements of Clinical Investigators, FDA Form 3455.