

Changing Ecosystem— A Brief Review of ICH GCP Renovations Planned and Currently Under Way

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ICH



International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

- Provides unique harmonization venue involving drug regulatory and regulated industry experts
- Begun in 1990 involving US, EU, and Japan
- Well-defined objectives:
 - To improve efficiency of new drug development and registration processes
 - To promote public health, prevent duplication of clinical trials in humans and minimize the use of animal testing without compromising safety and effectiveness
- Accomplished through the development and implementation of harmonized Guidelines and standards

ICH Reform - Establishment of Non-Profit Association

- The new ICH Association was officially established on October 23, 2015.
- The new ICH Association is a non-profit legal entity under Swiss Law with the aim to focus global pharmaceutical regulatory harmonization work in one venue
- More involvement from drug regulators and affected industry around the world is welcomed and expected

ICH Articles of Association:

http://www.ich.org/fileadmin/Public_Web_Site/ABOUT_ICH/Organisational_changes/ICH_Articles_of_Association_Adopted_by_Founding_ICH_Members_October_23_2015_for_publication.pdf

ICH Members and Observers *



Members

- EC, Europe
- FDA, US
- MHLW/PMDA, Japan
- EFPIA
- JPMA
- PhRMA
- Health Canada, Canada
- Swissmedic, Switzerland
- ANVISA, Brazil
- CFDA, China
- HSA, Singapore
- MFDA, Republic of Korea
- BIO
- IGBA
- WSMI

Observers

- IFPMA
- WHO
- CDSCO, India
- CECMED, Cuba
- COFEPRIS, Mexico
- INVIMA, Columbia
- MCC, South Africa
- National Center, Kazakhstan
- Roszdravnadzor, Russia
- TFDA, Chinese Taipei
- TGA, Australia
- APEC
- ASEAN
- BMGF
- EAC
- GHC
- PANDRH
- SADC
- APIC
- CIOMS
- EDQM
- IPEC
- PIC/S
- USP

**As of November 2017*



ICH GCP RENOVATION -- EVOLVING WORK

Background—ICH E6 considered foundational



- Originally Developed and adopted in mid-1990s
- Focus on:
 - Clinical research performed with regulatory intent
 - Assurance of human subject protection,
 - Assurance of data quality and integrity
 - Provide standard guide to clinical researchers on what they need to do to comply with regulations and document compliance
- Content
 - Principles of ICH GCP
 - Responsibilities of institutional review boards, investigators, and sponsors
 - Clinical trial protocol and amendments
 - Investigator’s brochure
 - Essential documents

ICH E6 revision (addendum) was needed



- Since ICH E6 was adopted in 1996, clinical trials have evolved substantially - increases in globalization, study complexity, and technological capabilities
- The approach to GCP needs to modernize to keep pace with the scale and complexity of clinical trials and to ensure appropriate use of technology
- ICH E6 gave sponsors flexibility to implement innovative approaches – but it has been misinterpreted and implemented in ways that impede innovation
- ICH E6 (R2) Expert Working Group (EWG) formed to modernize ICH E6 by supplementing it with additional recommendations



E6(R2) “Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice”

- Considerations of ICH E6 (R2) EWG in 2014: Existing E6 content is relevant and flexible – but need to address:
 - Misplaced emphasis on avoiding all errors (e.g., frequent on-site monitoring)
 - Broader than originally intended application to all types of trials
 - Need to address use of technology (e.g., electronic trial master file)
- E6 (R2) Concept:
 - Keep pace with the scale and complexity of clinical trials and to ensure optimal use of technology
 - Supplement E6 with recommendations on quality risk management, risk-based monitoring, and use of technology will facilitate implementation
 - Draft E6 (R2) guideline developed
- ICH Regional Consultation on E6(R2) draft guideline in 2015-16

Future Potential Enhancement to ICH Guidelines Related to GCPs



- Public comments received in 2016 consultation on the E6(R2) draft guideline identified opportunities for further enhancement
- Comments recognized importance of:
 - Original focus of E6 on provisions to assure human subject protection and data quality and critical guidance related to training, responsibilities and expectations of investigators, sponsors, IRBs
 - Most recent E6 (R2) has made major steps in this direction clarifying flexibility; use of a quality management system approach, key responsibilities of investigators versus sponsors, and essential documents
- Stakeholders from clinical research community cited opportunity to further modernize ICH GCP-related GLs to be:
 - More explicit attention to quality of study / study design
 - More flexible—to fit diverse range of studies and data sources

Proposed Approach in ICH Reflection Paper on GCP Renovation



- Update ICH guidelines to both address study quality and provide further flexibility
- Modernize *ICH E8 General Considerations for Clinical Trials*
 - Review issues and questions most critical to study quality, e.g., “critical to quality” factors to be considered
 - Provide more comprehensive cross-reference to other ICH GLs with relevant discussions
- Further renovate *ICH E6 Good Clinical Practices* to address a broader range of study types.
 - Create umbrella document of key principles with a series of annexes to address specific types of studies and data sources
 - Proposed Annex 1: Traditional Interventional Trials of investigational unapproved or approved drugs
 - Proposed Annex 2: Non-Traditional Interventional Trials and/or data sources
 - Proposed Annex 3: Non-Traditional Trial Designs

Modernize ICH E8 General Considerations for Clinical Trials



- Adopted in 1997 and has not undergone revision.
 - Since its adoption, clinical trial design and conduct have become more complex, impacting the time and cost required to develop drugs
 - A wide range of both trial designs and data sources play a role in drug development and are not adequately addressed in the original E8 guideline.
- Approaches for optimizing trial quality which promote the reliability, efficiency, and patient focus of clinical trials are needed.
 - This involves identifying the factors that are critical to the quality of a clinical trial at the design stage and planning the trial conduct proportionate to the risks to these quality factors, thereby protecting human subjects and ensuring the reliability of trial results.

Principles of study design and planning to be addressed



- Identification of basic set of critical-to-quality (CTQ) factors that impact the meaningfulness and reliability of study conclusions and patient safety, such as:
 - eligibility criteria
 - masking
 - types of controls
 - outcome ascertainment
 - site feasibility
 - safety monitoring
 - statistical analysis, and
 - investigational product handling and administration
- General strategies and actions that could effectively and efficiently address CTQ factors

ICH E8(R1) Guideline objectives



- Enhance the reliability of trial results through attention to trial quality
- Better integrate overall design and planning with subject protection and data reliability considerations that are the focus of ICH E6, statistical considerations that are the focus of ICH E9, and other considerations addressed in other ICH Efficacy guidelines.
- Enhance the utility of the ICH Efficacy guidelines by including critical-to-quality factors as a key consideration in planning and design of clinical trials
- Promote the quality of trial design and conduct for a broad range of trial types and data sources with critical-to-quality factors aligned to the objectives of the trial

