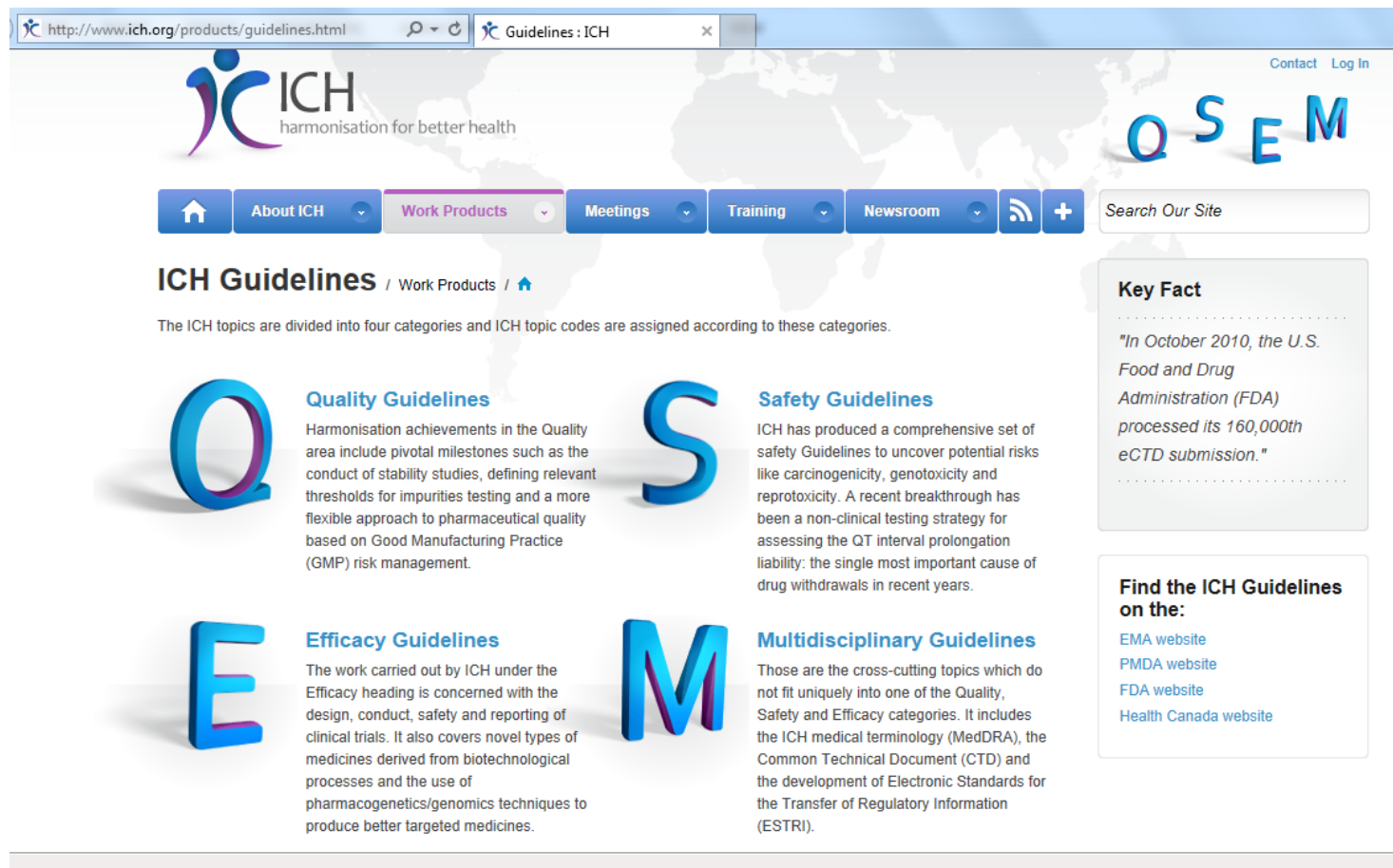


# ICH E8 R1

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# There is more to ICH than GCP

# ICH Guidelines



http://www.ich.org/products/guidelines.html Guidelines : ICH

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## ICH Guidelines / Work Products / Home

The ICH topics are divided into four categories and ICH topic codes are assigned according to these categories.

### Q Quality Guidelines

Harmonisation achievements in the Quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.

### S Safety Guidelines

ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity. A recent breakthrough has been a non-clinical testing strategy for assessing the QT interval prolongation liability: the single most important cause of drug withdrawals in recent years.

### E Efficacy Guidelines

The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/genomics techniques to produce better targeted medicines.

### M Multidisciplinary Guidelines

Those are the cross-cutting topics which do not fit uniquely into one of the Quality, Safety and Efficacy categories. It includes the ICH medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI).

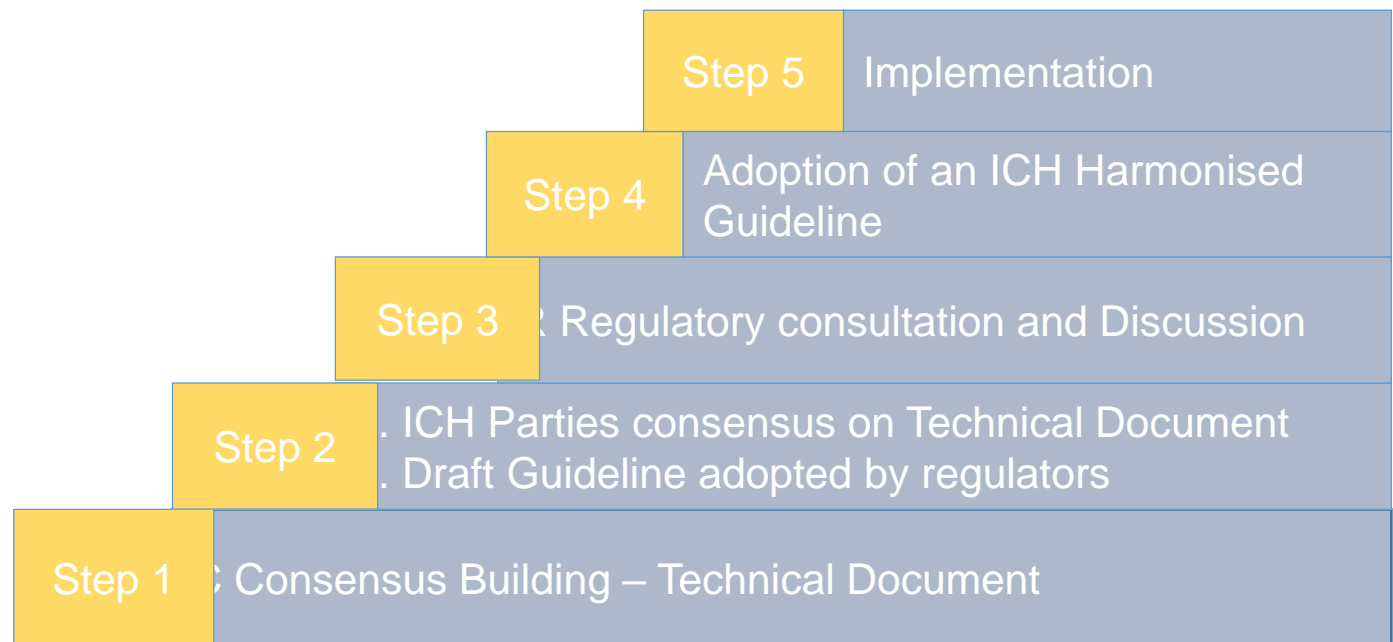
### Key Fact

*"In October 2010, the U.S. Food and Drug Administration (FDA) processed its 160,000th eCTD submission."*

### Find the ICH Guidelines on the:

- [EMA website](#)
- [PMDA website](#)
- [FDA website](#)
- [Health Canada website](#)

# ICH Development Process



# ICH Reflection Paper – upcoming E8 & E6 changes

**Reflection Paper Released 12<sup>th</sup> January 2017**

**E8**

- Not updated since 2007
- Data Quality Considerations not included
- High Level Guidance - Roadmap to applicable other ICH Guidance
- Plan to identify **Critical To Quality Factors [CTQF]** for Risk Based Management
- Status: Step 3 Consultation closes October 2019 – Stakeholder meeting 31<sup>st</sup> Oct 2019
- Step 4 anticipated June 2020

# ICH Reflection Paper – upcoming E8 & E6 changes

E6 – E6R2 released November 2016

- Focused on RCT for Regulatory Submissions – to be updated to reflect alternative research designs and purposes [e.g. Non Interventional; Real World; Health Care Economic.
- Currently much of this research is outside of the regulations
- Retain & Strengthen Risk Based Guidance

Overarching Principles Document & 3 Annexes  
proposed

# ICH Reflection Paper – upcoming E8 & E6 changes

## **E6 Overarching Principles**

- Risk Based Approach
- Reference to E8 and CTQFs
- Trial design & Objectives strongly influence CTQFs
- Time Line: start once E8 is at step 2b [Oct 2019]

## **Annex 1 - Traditional Interventional Trials**

- Risk Based Approach
- include E6R2 updates and additional clarifications

Time Line: once E6 overarching principles is at step  
2b [? 2020]

# ICH Reflection Paper – upcoming E8 & E6 changes

## **Annex 2 - Non Traditional interventional Trials and or Data Sources**

- e.g. Pragmatic Clinical Trials and Real World Data sources to supplement or replace data collection within the trial.
- Objectives may be for regulatory purposes or broader research
- Time Line: once E6 Annex 1 is at step 2b [? 2020/2021]

## **Annex 3 - Non Interventional Trials**

- Observational studies; Registries
- Use of alternative data sources e.g. EHR & Claims Data
- Data for practice & policy but may also be used for post marketing safety
- Protocol compliance and monitoring expectations to reflect use of marketed products with better known safety
- Time Line: once E6 Annex 2 is at step 2b [? Late 2021]



# ICH Efficacy Guidelines

- The ICH Efficacy guidelines cover the design, conduct, analysis and reporting of clinical studies. The guidelines should be used in an integrated manner rather than one or other guideline or subsection being focussed on in isolation of the others.
- E8(R1) provides an overall introduction to clinical development, designing quality into clinical studies and focusing on those factors critical to the quality of the studies.

## Considerations

# ICH E family of guidelines – need to be read together

### E8 General Considerations for Clinical Trials

#### Design and analysis:

E4 Dose-Response Studies  
E9 Statistical Principles for Clinical Trials  
E10 Choice of Control Group in Clinical Trials  
E17 Multi-Regional Clinical Trials

#### Conduct and reporting:

E3 Clinical Study Reports  
E6 Good Clinical Practice

#### Safety reporting:

E1 Clinical Safety for Drugs used in Long-Term Treatment  
E2A - E2F Pharmacovigilance  
E14 Clinical Evaluation of QT  
E19 Safety Data Collection

#### Populations:

E5 Ethnic Factors  
E7 Clinical Trials in Geriatric Population  
E11 - E11A Clinical Trials in Pediatric Population  
E12 Clinical Evaluation by Therapeutic Category

#### Genetics/genomics:

E15 Definitions in Pharmacogenetics / Pharmacogenomics  
E16 Qualification of Genomic Biomarkers  
E18 Genomic Sampling

# So what is planned for E8

- Incorporation of most current concepts for achieving **fit-for-purpose data** quality as one of the essential considerations for all clinical trials.
- Identification of a basic set of **critical-to-quality factors** that can be adapted to different types of trials to support the meaningfulness and reliability of trial results and to protect human subjects
- Address a broader range of trial designs and data sources
- Provide an updated cross-referencing of all other relevant ICH Guidelines that should be referred to when planning clinical studies.

# Guideline Objectives

- Describe internationally agreed upon principles and practices to facilitate regulatory acceptance.
- Provide a guide to all of the ICH Efficacy Guidelines.
- Provide guidance on the consideration of quality in the design and conduct of clinical studies, including:
  - Identification of factors critical to the quality of the study.
  - Management of risks to those factors during study conduct.
- Provide an overview of the types of clinical studies performed during the product lifecycle, including:
  - Study design aspects that support the determination of quality factors critical to ensuring the protection of study subjects and ability to meet the study objectives.

# Key Principles

- Protection of clinical study subjects is a shared responsibility (investigators, sponsors, IRB/IECs).
- Clinical studies should be designed, conducted, and analysed according to sound scientific principles and reported appropriately.
- Consulting with patients and/or patient organisations in the design, planning and conduct of clinical studies helps to ensure that all perspectives are captured.

## 6.1.4 Access to Interim Data

- Inappropriate access to data during the conduct of the study may compromise study integrity.
- In studies with planned interim analyses, special attention should be given to which individuals have access to the data and results.
- Even in studies without planned interim analyses, special attention should be paid to any ongoing monitoring of data to avoid inappropriate access.

# Development Plan

- Across the product lifecycle, different types of studies will be conducted with different objectives and designs.
- Depending on the study objectives and the position of the study in the overall development plan, the data sources may vary.
- For purposes of this guideline, the development plan is considered to cover the entire product lifecycle and include non-clinical, clinical, and post-approval studies.

# Logical Development

- The cardinal logic behind serially conducted studies is that the results of prior studies should inform the plan of later studies.
- Emerging data will frequently prompt a modification of the development strategy.
- For example, results of a confirmatory study may suggest a need for additional human pharmacology studies.



# Move away from Phase I-IV Descriptors

## Reminders

The phase concept is a description, not a set of requirements

Temporal phases do not imply a fixed order

Descriptors more based on study objectives

- Human Pharmacology
- Exploratory
- Confirmatory
- Post Approval

# Clinical Studies require

- Clear pre-defined study objectives that address the primary scientific question(s)
- Selection of appropriate subjects that have the disease, condition, or molecular/genetic profile that is being studied
- Methods to minimize bias such as randomisation, blinding or masking, and/or control of confounding factors
- Endpoints that are well-defined and measurable, and methods of assessment of those endpoints that are accurate and able to be implemented with minimal reporting or measurement bias.
- Clear understanding of the feasibility of the study
- Selection of suitable investigator sites,
- Quality of specialised analytical and testing facilities and procedures
- Processes that ensure data integrity.

## 2.3 Patient Input into Study Design

- Consulting with patients and/or patient organisations in the design, planning and conduct of clinical studies helps to ensure that all perspectives are captured.
- Patients' views can be requested on all phases of drug development.
- Involving patients at the early stage of study design is likely to increase trust in the study, facilitate recruitment, and promote adherence.
- Patients also provide their perspective of living with a condition, which contributes to the determination of endpoints that are meaningful to patients, selection of the right population, duration of the study, and use of the right comparators.
- This ultimately supports the development of medicines that are better tailored to patients' needs.

# Quality by Design of Clinical Studies

- Quality of a clinical study is fitness for purpose.
- The quality of the information generated should be sufficient to support good decision making.
- The quality of a study is driven proactively by designing quality into the study protocol and processes.
- Critical to quality factors should be determined for each study.
- Risks that threaten the integrity of the critical to quality factors should be identified and managed in a proportionate manner.

# Critical to Quality Factors

- A basic set of factors relevant to ensuring study quality should be identified for each study.
- These critical to quality factors are attributes of a study whose integrity is fundamental to the protection of study subjects, the reliability and interpretability of the study results, and the decisions made based on the study results.
- These quality factors are considered to be critical because, if their integrity were to be undermined by errors of design or conduct, the reliability or ethics of decision-making would also be undermined.

ICH E8(R1) Guideline

ANNEX 3: SELECTED EXAMPLES OF CRITICAL TO QUALITY FACTORS

Selected Examples of Critical to Quality Factors	E1	E2A-E2F	E3	E4	E5	E6	E7	E8	E9	E10	E11	E12	E14	E15	E16	E17	E18
<b>Protocol Design</b>																	
Eligibility Criteria						√	√	√	√		√	√	√	√		√	
Randomisation				√		√		√	√	√		√	√			√	
Blinding/Masking						√		√	√	√							
Types of Controls	√			√				√		√			√			√	
Data Quality	√						√	√	√					√			
Endpoints				√	√			√	√	√	√	√					√
Procedures Supporting Study Endpoints and Data Integrity					√	√		√	√	√	√	√				√	
Investigational Product (IP) Handling and Administration						√							√				
<b>Feasibility</b>																	
Study and Site Feasibility																√	√
Accrual									√		√		√				
<b>Patient Safety</b>																	
Informed Consent						√					√						√
Withdrawal Criteria and Trial Participant Retention			√			√					√		√				

## ICH E8(R1) Guideline

Selected Examples of Critical to Quality Factors	E1	E2A-E2F	E3	E4	E5	E6	E7	E8	E9	E10	E11	E12	E14	E15	E16	E17	E18
<b>Signal Detection and Safety Reporting</b>		√ (B)	√			√						√	√				
<b>Data Monitoring Committee (DMC)/Stopping Rules</b>						√			√	√			√				
<b>Study Conduct</b>																	
<b>Training</b>						√							√			√	√
<b>Data Recording and Reporting</b>		√ (B,C,F)	√	√					√		√		√		√	√	√
<b>Data Monitoring and Management</b>		√ (A,B,D)	√						√						√	√	√
<b>Statistical Analysis</b>			√	√	√				√				√			√	
<b>Study Reporting</b>																	
<b>Dissemination of Study Results</b>		√ (D,F)															√
<b>Third-Party Engagement</b>																	
<b>Delegation of Sponsor Responsibilities</b>						√											
<b>Collaborations</b>						√											

\*This chart will be updated as ICH guidelines are finalized or updated.

# Focus and Tailor

- Discourage inflexible “one size fits all” approaches that undermine creation of specific strategies and actions intended to effectively and efficiently support quality in a given study.
- Consider whether nonessential activities may be eliminated from the study to simplify conduct, improve study efficiency, and target resources to critical areas.
- Rigorously evaluate the study design to verify that planned activities and choice of data to be collected are essential.
- Deploy resources to identify and prevent or control errors that matter.



# Perfection?

- Perfection in every aspect of an activity is rarely achievable or can only be achieved by use of resources that are out of proportion to the benefit obtained.
- The quality factors should be prioritized to identify those that are critical to the study, at the time of the study design
- Study procedures should be proportionate to the risks inherent in the study and the importance of the information collected.
- The critical to quality factors should be clear and should not be cluttered with minor issues
  - extensive secondary objectives or processes/data
  - collection not linked to the proper protection of the study subjects and/or primary study objectives

# 3.3.1 Establishing a Culture that Supports Open Dialogue

- Create a culture that values and rewards critical thinking and open dialogue about quality and that **goes beyond sole reliance on tools and checklists.**
- Choose quality measures and performance indicators that are aligned with a proactive approach to design. For example, an **overemphasis on minimising the time to first patient enrolled may result in devoting too little time to identifying and preventing errors that matter through careful design.**