Harmonization of Bioequivalence: FDA Perspective

Lei Zhang, Ph.D.

Deputy Director
Office of Research and Standards, Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

January 31, 2020
19th Regulatory and Scientific Affairs Conference
Amsterdam, Netherlands

Outline

- Brief introduction of ICH
- ICH Reflection Paper on “Further Opportunities for Harmonization of Standards for Generic Drugs”
- New developments since the publication of the ICH reflection paper
- Key take home messages

ICH: The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ich.org)

International Council for Harmonisation (ICH)

- Originally founded in 1990, ICH is a unique harmonization initiative for regulatory authorities and pharmaceutical associations
- ICH's mission is to achieve greater harmonization worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner
- Harmonization is achieved through the development of ICH Guidelines via a process of scientific consensus

International Harmonization Leads to:

- More efficient regulatory review
- More efficient exchange of information between regulatory authorities
- Reduced time to get a product to the market
- Reduced patient burden through prevention of unnecessary duplication of clinical trials and post market clinical evaluations
- Reduction of unnecessary animal testing without compromising safety and effectiveness

Reforms of ICH Association

- Reformed as a non-profit legal entity under Swiss Law on October 23, 2015
- The new association aims to focus global pharmaceutical regulatory harmonization work in one venue
- More involvement from regulators and industry around the world is welcomed and expected

ICH Members

Founding Regulatory Members (permanent Management Committee (MC) Members):

- EC, Europe; FDA, US; MHLW/PMDA, Japan

Founding Industry Members (permanent MC Members):

- EFPIA, JPMA, PhRMA

Standing Regulatory Members (permanent MC Members):

- Swissmedic, Switzerland; Health Canada, Canada

Elected MC Members:

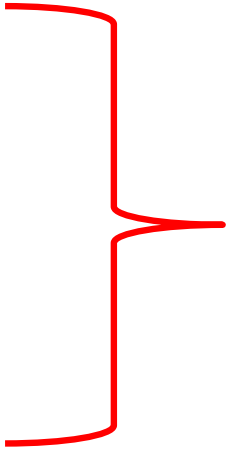
- Regulatory Members: NMPA, China; HSA, Singapore; MFDS, Korea
- Industry Members: BIO, IGBA

Regulatory Members:

- ANVISA, Brazil; TFDA, Chinese Taipei

Industry Members:

- GSCF



Pathway to Membership

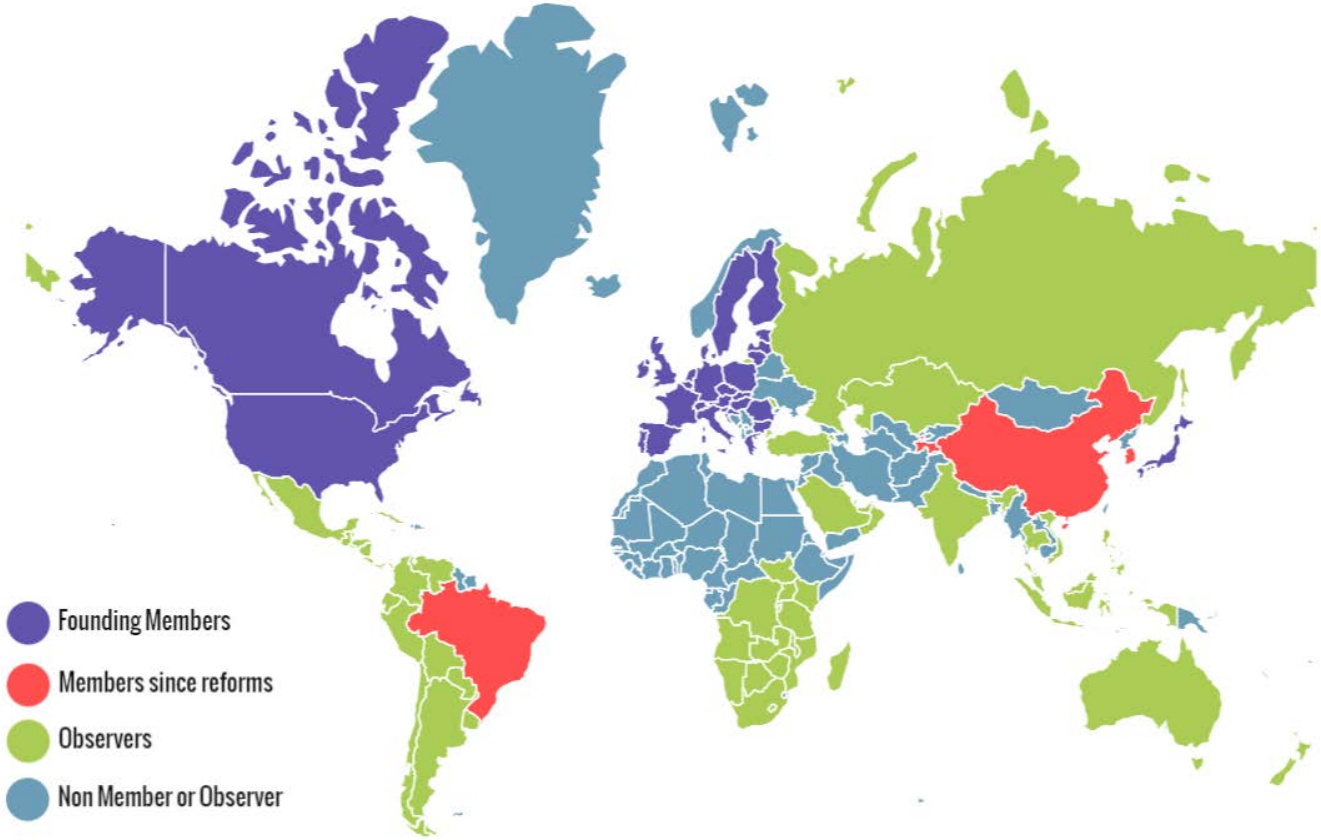
ELIGIBILITY CRITERIA FOR LEGISLATIVE OR REGULATORY MEMBER

- Legal personality
- Responsible for the regulation of pharmaceutical products for human use
- Has participated in at least 3 out of 4 Assembly 2 years
- Has appointed experts in at least two ICH Working Groups
- Has implemented the ICH Q1, Q7, and E6 Guidelines

INDUSTRY MEMBER CRITERIA

- Legal Personality
- Represents Members from several countries in at least three continents
- It or its members are regulated or affected by all or some ICH Guidelines
- Has participated in at least 3 out of 4 Assembly meetings during the past 2 years
- Has appointed experts in at least two ICH Working Groups

ICH Footprint



Global Harmonization for Generic Drugs

- Generic drugs comprise a significant portion of the pharmaceutical market
- Common standards and global development for generics can improve access to generic medicines
- ICH is uniquely positioned to develop harmonized recommendations as the global venue for harmonization of standards for pharmaceutical products
  - Regulatory members are expected to implement ICH guidelines
- Historically, ICH has focused on standards for new drugs, however, many ICH guidelines are applicable to generic drugs (e.g., ICH Quality Guidelines)

What are the strategies for developing and enhancing ICH guidelines to support the harmonization of scientific and technical standards for generic drugs?

ICH Reflection Paper on Generic Drug Harmonization

- Outlines a strategic approach for developing and enhancing ICH guidelines to support the harmonization of scientific and technical standards for generic drugs
- Proposes steps and recommendations for global harmonization of standards for generic drugs
- The reflection paper (drafted by FDA) was discussed at the November 2018 ICH Assembly Meeting and endorsed

https://admin.ich.org/sites/default/files/2019-04/ICH_ReflectionPaper_GenericDrugs_Final_2019_0130.pdf

Key Proposals in the Reflection Paper

- Develop a series of ICH guidelines on standards for demonstrating equivalence (e.g., bioequivalence) for
  - (1) non-complex dosage forms
  - (2) more complex dosage forms and products
- Establish a generic drug discussion group
  - To assist in assessing the feasibility of harmonization of standards for generic drugs
  - To prioritize work areas

Regulatory and Scientific Frameworks for Generic Drugs

- The reflection paper recognizes that different regions have different regulatory frameworks
  - Example: Tablet and Capsule
    - Not a “generic” in the U.S.
    - Possible “generic” in the EU
- The reflection paper focuses on harmonizing scientific standards for bioequivalence that can be used within the existing regulatory frameworks

Reflection Paper Outcomes

- Formed an ICH Generic Drug discussion Group (GDG) in April 2019*
  - To assist ICH in identifying recommended topic areas for harmonization
  - To survey existing ICH and WHO guidelines to assess gaps in guidances for generic drugs
  - To prioritize work areas and send proposals/make recommendations to ICH

- First ICH Topic on Bioequivalence Harmonization was endorsed by ICH Assembly in November 2019
  - ICH M13: Harmonization of BE standards for immediate-release oral dosage forms

* https://database.ich.org/sites/default/files/IGDG_Remit.pdf

Potential Future Areas

- Issues related to more complex products may be on the horizon
  - Modified-release products
  - Complex Injectables
  - Transdermal
  - Topical dermatological
  - Inhalation

Value of Scientific Harmonization

- Bioequivalence studies world-wide can be conducted according to common expectations
  - Increases efficiency of generic drug development
  - Increases quality of generic drug development
- It is the essential first step toward global development of generic products

What are the Opportunities?

- Movement toward common standards and global development for generics can improve access to generic products
  - Products with small markets may not be economically viable unless markets can be aggregated across regions
  - Investment in development of complex generics can be supported by entrance into multiple markets

What are the Challenges?

- What are the scientific data and analytical tools that provide evidence that reference product sourced in region “A” and reference product sourced in region “B” are similar enough that BE comparisons will be the same?
  - ICH expert working group
- A regulatory policy system in each region that will allow scientifically sound data to be used
  - Regulatory members

What is the Role of Industry?

- Invest resources to address regulatory and scientific challenges
- Participate in ICH expert working groups to provide useful input into ICH discussions to address challenges and lead towards harmonization in standards

Key Take Home Messages

- Generic drugs comprise a significant portion of the pharmaceutical market, and common standards and global development for generics can improve access to generic medicines
- ICH is uniquely positioned to develop harmonized recommendations as the global venue for harmonization of standards for pharmaceutical products
- ICH reflection paper on “Further Opportunities for Harmonization of Standards for Generic Drugs” lays out the strategy for global harmonization for generic drugs

ICH: The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ich.org)

Acknowledgements

- ICH GDG members
  - Nilufer Tampal, Rapporteur
  - Jan Welink, Regulatory Chair
  - Ethan Stier, FDA Deputy Topic Lead
  - Pam Eason, Rapporteur Supporter
- Amanda Roache
- Mathew Thomas
- Robert Lionberger

For more information on ICH Member and Observer eligibility criteria:

ICH Assembly Rules of Procedure:

- https://admin.ich.org/sites/default/files/2019-08/AssemblyRoP_Approved_v7-0_2019_0606.pdf

Articles of Association:

- https://admin.ich.org/sites/default/files/2019-08/ArticlesOfAssociation_Approved_v3-0_2019_0606.pdf


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Back-Up Slides

ICH Observers

Standing Observers

- International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) (MC Member)
- World Health Organization (WHO) (MC Member)

Legislative or Administrative Authorities

- Central Drugs Standard Control Organization (CDSCO, India)
- Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos (CECMED, Cuba)
- Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS, Mexico)
- Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA, Colombia)
- Medicines and Medical Devices Agency (MMDA, Moldova)
- National Center for the Expertise of Drugs, Medical Devices and Equipment (National Center, Kazakhstan)
- National Pharmaceutical Regulatory Agency (NPRA, Malaysia)
- Roszdravnadzor (Russia)
- South African Healthcare Products Regulatory Autority, (SAHPRA, South Africa)
- The Scientific Center of Drug and Medical Technology Expertise (SCDMTE, Armenia)
- Therapeutic Goods Administration (TGA, Australia)
- Turkish Medicines and Medical Devices Agency (TITCK, Tukey)

Regional Harmonization Initiatives

- Asia-Pacific Economic Cooperation (APEC)
- Association of Southeast Asian Nations (ASEAN)
- East African Community (EAC)
- Gulf Cooperation Council (GCC)
- Pan American Network for Drug Regulatory Harmonization (PANDRH)
- Southern African Development Community (SADC)

International Pharmaceutical Industry Organization

- Active Pharmaceutical Ingredients Committee (APIC)

International Organizations with an Interest in Pharmaceuticals

- Bill & Melinda Gates Foundation
- Council for International Organizations of Medical Sciences (CIOMS)
- European Directorate for the Quality of Medicines & HealthCare (EDQM)
- International Pharmaceutical Excipient Council (IPEC)
- Pharmaceutical Inspection Cooperation Scheme (PIC/S)
- United States Pharmacopeia (USP)

Source: www.ich.org

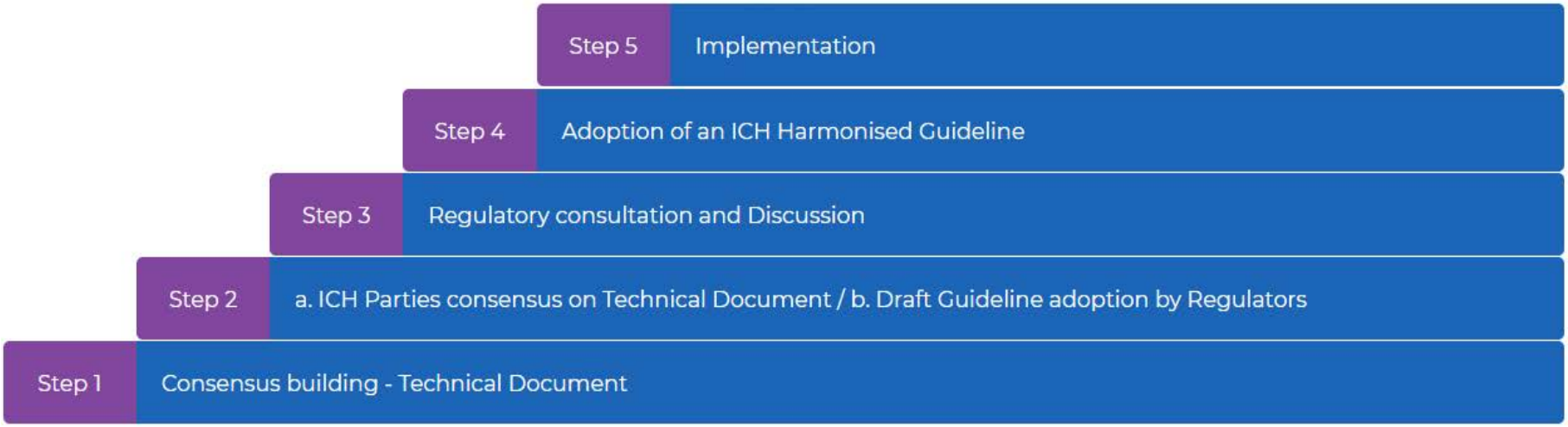
ICH Observer Criteria

- Legislative or administrative authorities and Regional Harmonization Initiatives with the responsibility for regulation of pharmaceuticals for human use
- International pharmaceutical industry organizations that are regulated by all of some of ICH guidelines
- International organizations represented at the global level who work is regulated or affected by ICH guidelines

Source: www.ich.org

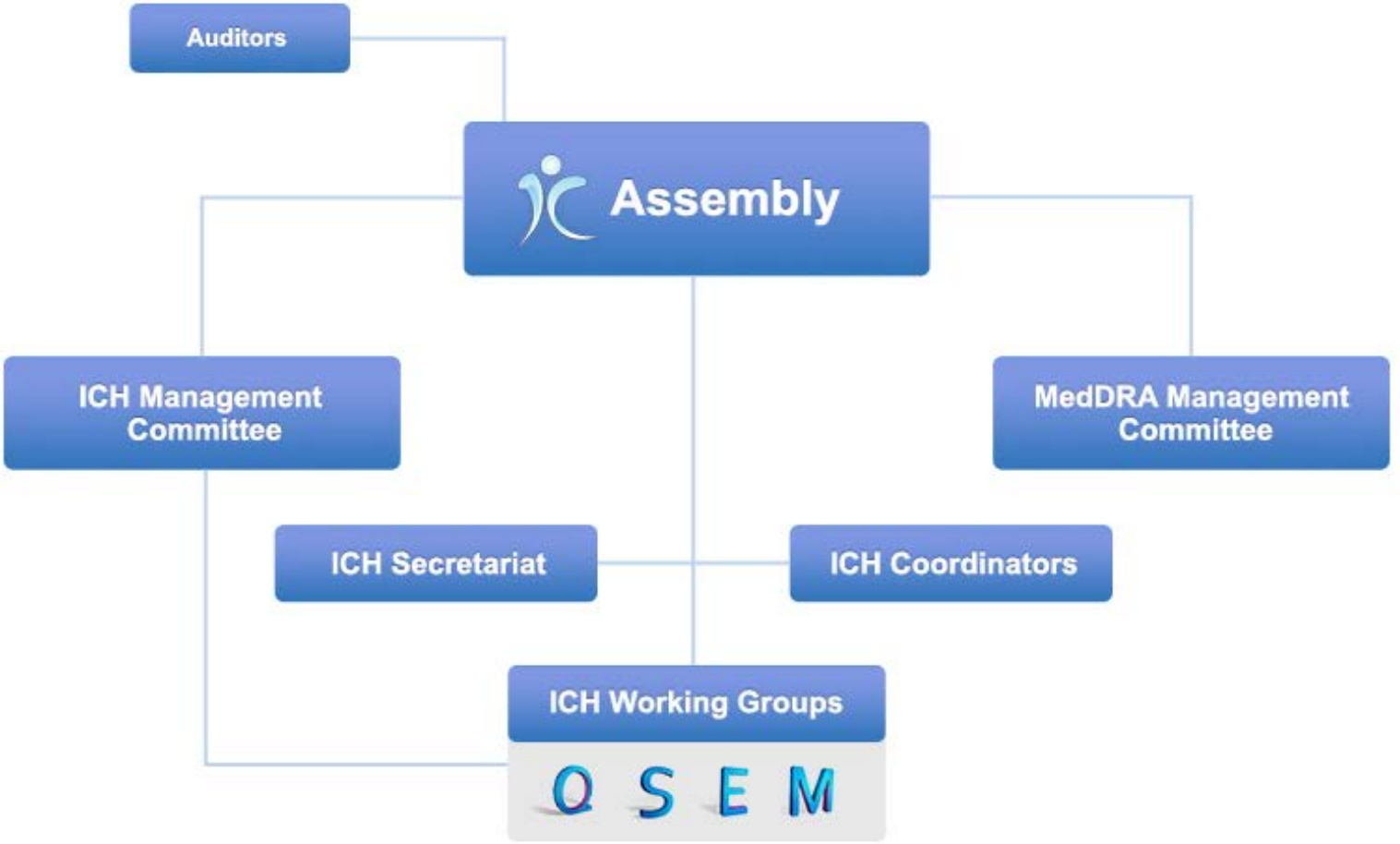
ICH Formal Procedure

- Harmonization is achieved through the development of ICH Guidelines via a 5-step process of scientific consensus



Source: www.ich.org

Governance Structure of ICH Association



Source: www.ich.org