U.S. FOOD & DRUG ADMINISTRATION

Opportunities and Rewards of Reform

ICH Updates Including GCP Renovation

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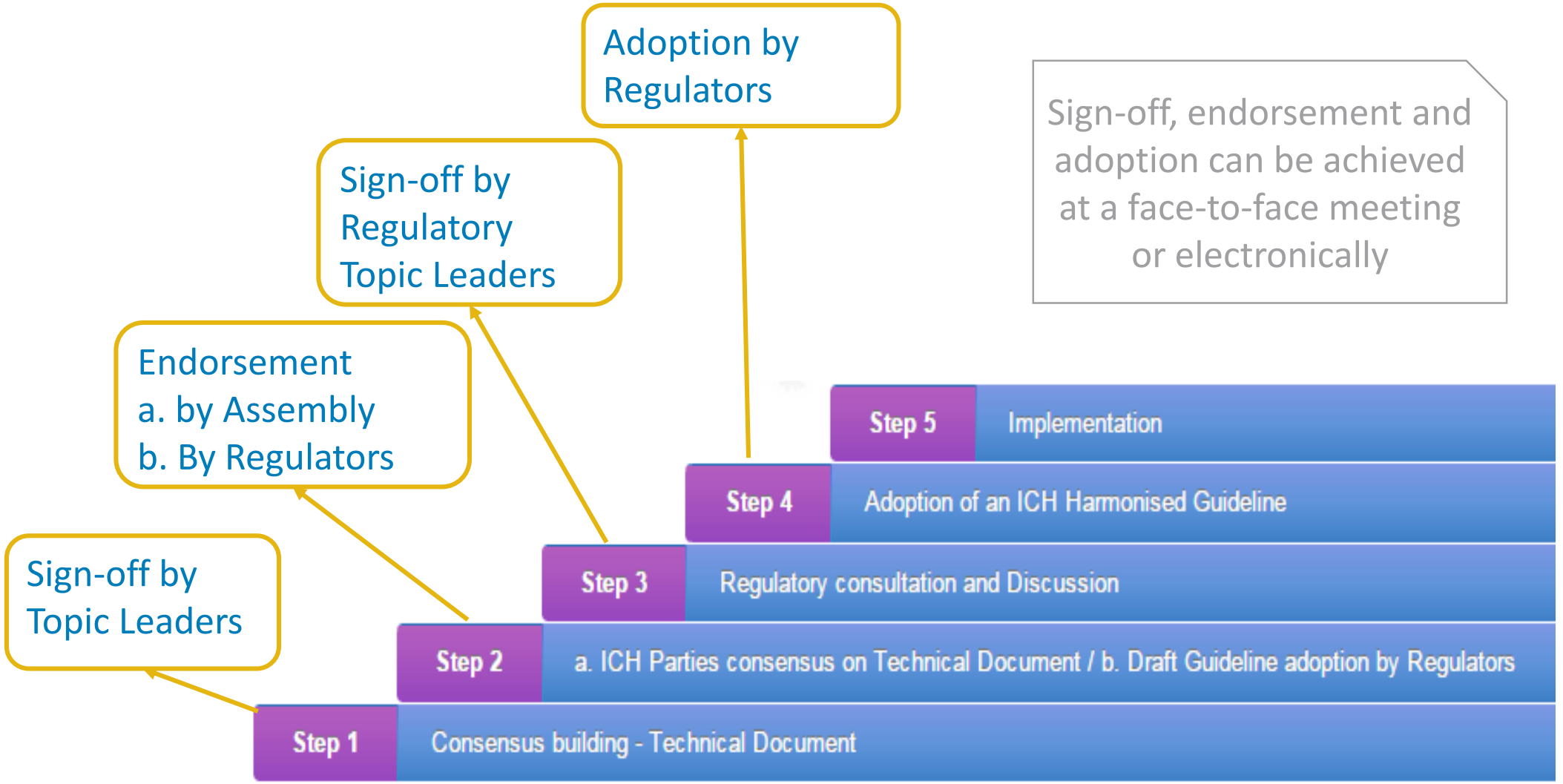
International Council for Harmonisation Of Technical Requirements For Pharmaceuticals for Human Use (ICH)

ICH Background

- Since 1990, a unique harmonisation effort to:
  - Improve efficiency of new drug development and registration process
  - Prevent duplication of clinical trials in humans and minimize use of animal testing ---without compromising safety and effectiveness
- Accomplished through the development and implementation of harmonised technical regulatory Guidelines

- Keys to success:
  - Involvement of both regulators and industry
  - Science-based, well-managed, consensus driven
  - Limited number of players with comparable regulatory and technical expertise/capability
  - Commitment of regulators to implement products of harmonisation

Steps in the ICH Process



Sign-off, endorsement and adoption can be achieved at a face-to-face meeting or electronically

ICH Finalised Guidelines

Safety, Total = 14

- S1A – S1C: Carcinogenicity studies (3)
- S2: Genotoxicity studies (1)
- S3A – S3B: Toxicokinetics and Pharmacokinetics (2)
- S4: Toxicity Testing (1)
- S5: Reproductive toxicology (1)
- S6: Biotechnology products (1)
- S7A – S7B: Pharmacology studies (2)
- S8: Immunotoxicology studies (1)
- S9: Nonclinical evaluation for anticancer pharmaceuticals (1)
- S10: Photosafety evaluation (1)

Quality, Total = 23

- Q1A – Q1E: Stability (5)
- Q2: Analytical validation (1)
- Q3A – Q3D: Impurities (4)
- Q4 – Q4B: Pharmacopoeias (1)
- Q5A – Q5E: Quality of biotechnology products (5)
- Q6A – Q6B: Specifications (2)
- Q7: Good Manufacturing Practice (1)
- Q8: Pharmaceutical development (1)
- Q9: Quality risk management (1)
- Q10: Pharmaceutical quality system (1)
- Q11: Development and manufacture of drug substances (1)

Efficacy, Total = 21

- E1: Clinical safety (1)
- E2A – E2F: Pharmacovigilance (5)
- E3: Clinical study reports (1)
- E4: Dose-response studies (1)
- E5: Ethnic factors (1)
- E6: Good Clinical Practice (1)
- E7, E8, E9, E10, E11-E11A: Clinical Trials (5)
- E12: Clinical evaluation by therapeutic category (1)
- E14: Clinical evaluation (1)
- E15: Definitions in Pharmacogenomics (1)
- E16: Qualification of Genomic Biomarkers (1)
- E17: Multi-Regional Clinical Trials (1)
- E18: Genomic Sampling (1)

Multidisciplinary, Total = 6

- M3: Nonclinical safety studies (1)
- M4, M4Q, M4S, M4E: CTD (4)
- M7: Genotoxic impurities (1)

ICH Other Products

Other products include electronic standards, a standardized Medical dictionary, and Q&As.

Examples:

Safety	
▪ S3A : Toxicokinetics and Pharmacokinetics (Q&As)	▪ S9: Nonclinical evaluation for anticancer pharmaceuticals (Q&As)

Quality	
▪ Q3D: Impurities (Training) ▪ Q6A : Specifications (Decision Trees)	▪ Q7: Good Manufacturing Practice (Q&As) ▪ Q8, Q9, Q10 - Q&As ▪ Q11: Development and manufacture of drug substances (Q&As)

Efficacy	
▪ E2B, E2C : Pharmacovigilance (Q&As, Specifications and related files, ESTRI) ▪ E3: Clinical study reports (Q&As) ▪ E5: Ethnic factors (Q&As)	▪ E7: CT in Geriatric Population (Q&As) ▪ E14: Clinical evaluation (Q&As)

Multidisciplinary	
▪ M1: MedDRA terminology & PtC ▪ M2: Electronic standards (Recommendations - ESTRI) ▪ M3: Nonclinical safety studies (Q&As)	▪ M6: Gene Therapy (Considerations) ▪ M8: eCTD

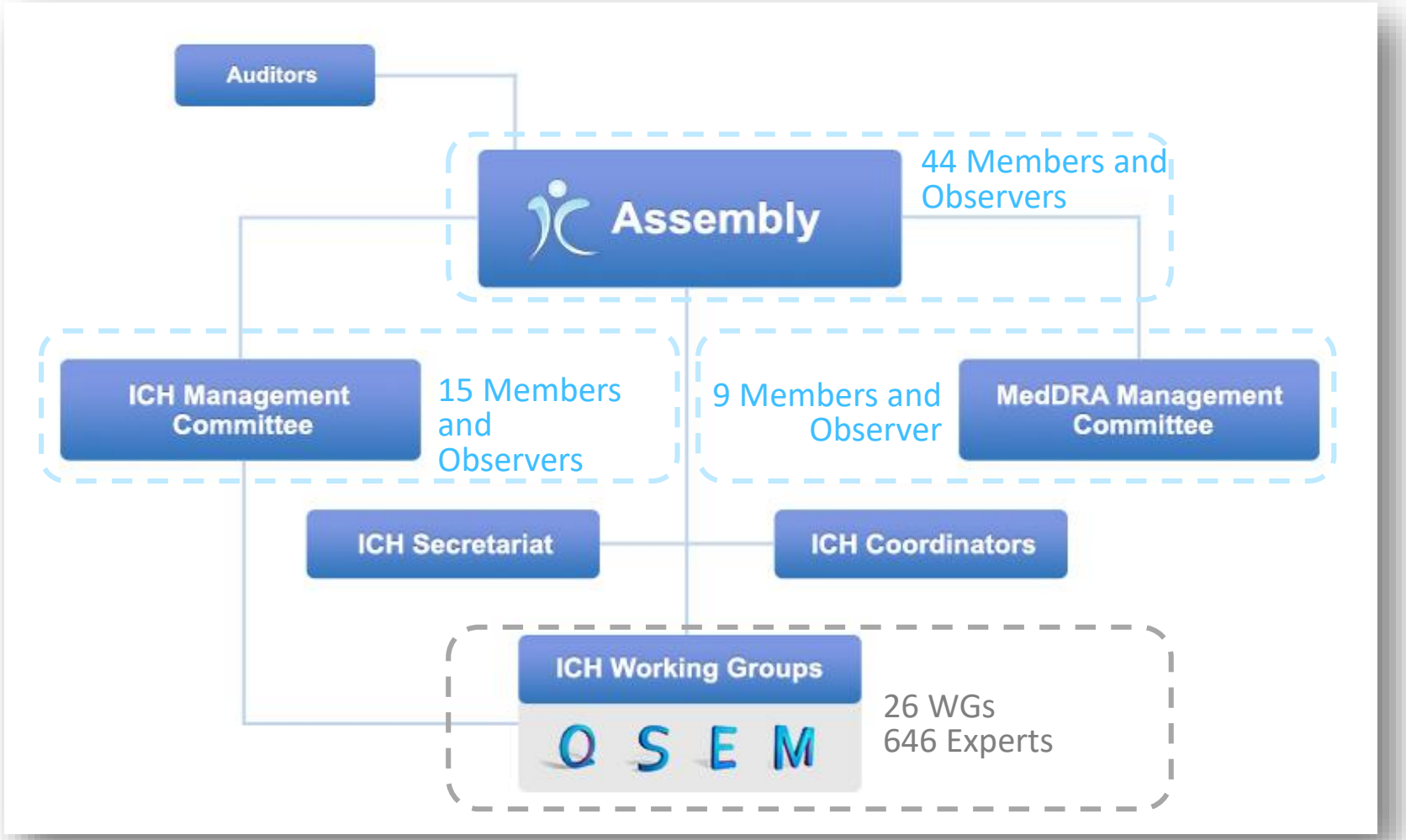
ICH Reform

Goals for Reform

1. Focus global pharmaceutical regulatory harmonisation work in **one venue.**
2. Create a venue that gives to all key pharmaceutical regulatory authorities and industry stakeholders the **opportunity to be more actively involved** in pharmaceutical harmonisation work.
3. **Maintain efficient and well-managed operations** and harmonisation work processes.

The ICH Association, established in October 2015, is a non-profit legal entity under Swiss law with the aim to focus global pharmaceutical regulatory harmonisation work in one venue. http://www.ich.org/about/articles-procedures.html

ICH Organization and Governance



http://www.ich.org/about/organisation-of-ich.html

Governance of ICH Association

Assembly

The overarching body of the Association that makes decisions regarding the Articles of Association and its Rules of Procedures, admission of new Members, election of Elected MC representatives, annual work plan, adoption of ICH Guidelines, approval of budget, etc.

Management Committee (MC)

The body that oversees operational aspects on behalf of all Members of the Association, including administrative and financial matters and oversight of WG operations. Financial responsibilities include preparation of the ICH budget and ensuring funding of ICH operations.

Opening up of Membership in the ICH Association

- Any eligible party can apply for Membership/Observership.
- Decisions on Membership/Observership admission by the Assembly become effective on the date of the decision

Opportunities and Rewards of ICH Reform

1. Enabling growth in the number and diversity of participants
    - Encouraging participation and expanding portfolio (e.g., generic drugs)
2. Preserving the technical expertise and efficiency
    - Recent enhancements to manage size of Expert Working Groups
3. Increasing ICH focus on strategy
    - More formal structure and approach enables longer planning horizon and management continuity
    - Reflection papers help identify opportunities, e.g., **GCP Renovation**

ICH Members and Observers October 2015

Founding Regulatory Members

- EC, Europe
- FDA, United States
- MHLW/PMDA, Japan

Founding Industry Members

- EFPIA
- JPMA
- PhRMA

Standing Members

- Health Canada, Canada
- Swissmedic, Switzerland

Observers

- IFPMA
- WHO

ICH Members and Observers May 2019

MEMBERS
Click here for the list

Founding Regulatory Members
- EC, Europe
- FDA, United States
- MHLW/PMDA, Japan

Founding Industry Members
- EFPIA
- JPMA
- PhRMA

Standing Regulatory Members
- Health Canada, Canada
- Swissmedic, Switzerland

Regulatory Members
- ANVISA, Brazil
- MFDS, Republic of Korea
- HSA, Singapore
- NMPA, China
- TFDA, Chinese Taipei

Industry Members
- BIO
- IGBA
- WSMI

OBSERVERS
Click here for the list

Standing Observers
- IFPMA
- WHO

Legislative or Administrative Authorities
- CDSCO, India
- CECMED, Cuba
- COFEPRIS, Mexico
- INVIMA, Colombia
- MMDA, Moldova
- National Center, Kazakhstan
- NPRA, Malaysia
- NRA, Iran
- Roszdravnadzor, Russia
- SAHPRA, South Africa
- SCDMTE, Armenia
- TGA, Australia
- TITCK, Turkey

Regional Harmonisation Initiatives (RHIs)
- APEC
- ASEAN
- EAC
- GHC
- PANDRH
- SADC

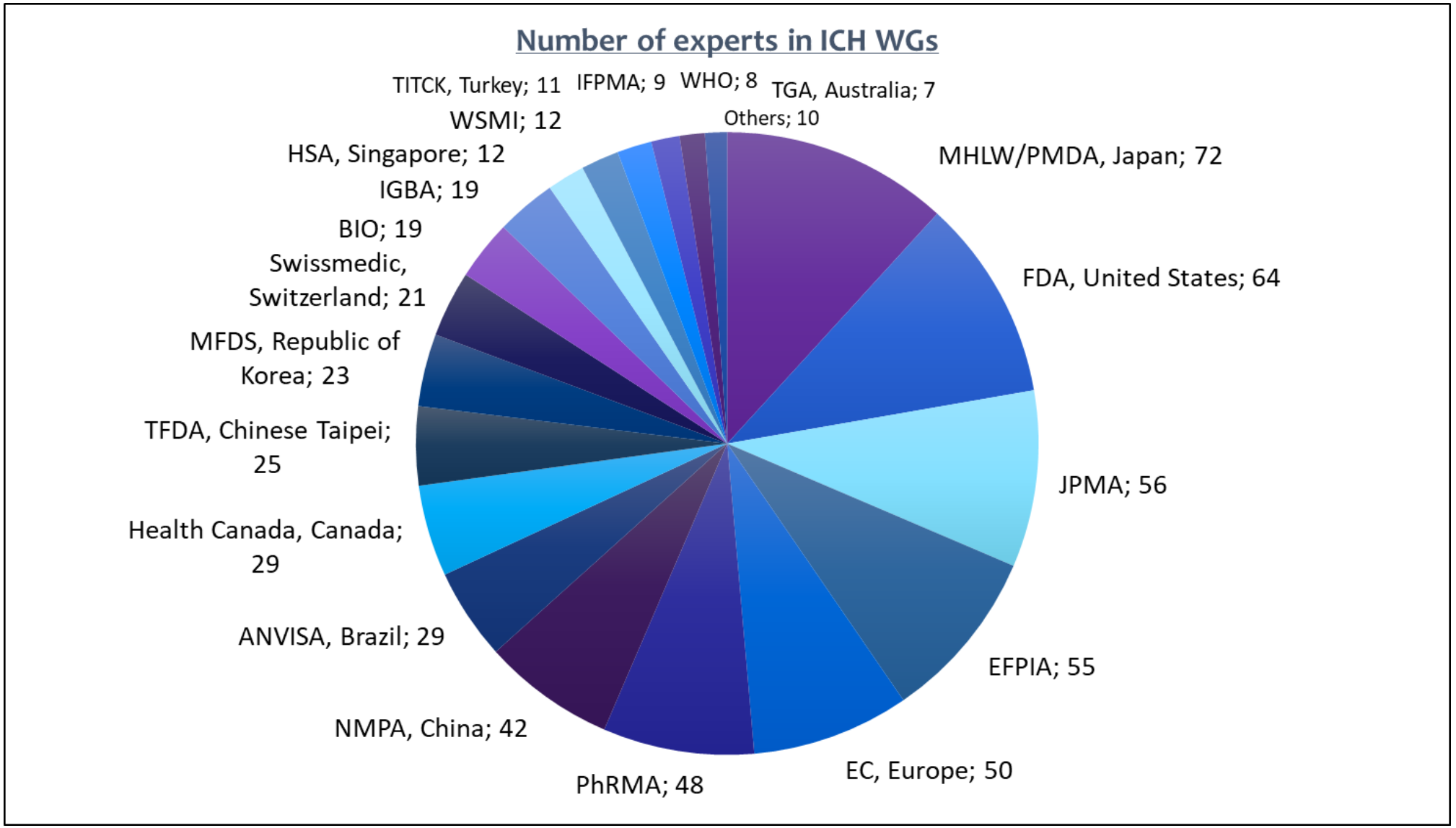
International Pharmaceutical Industry Organisation
- APIC

International Organisation regulated or affected by ICH Guideline(s)
- Bill & Melinda Gates Foundation
- CIOMS
- EDQM
- IPEC
- PIC/S
- USP

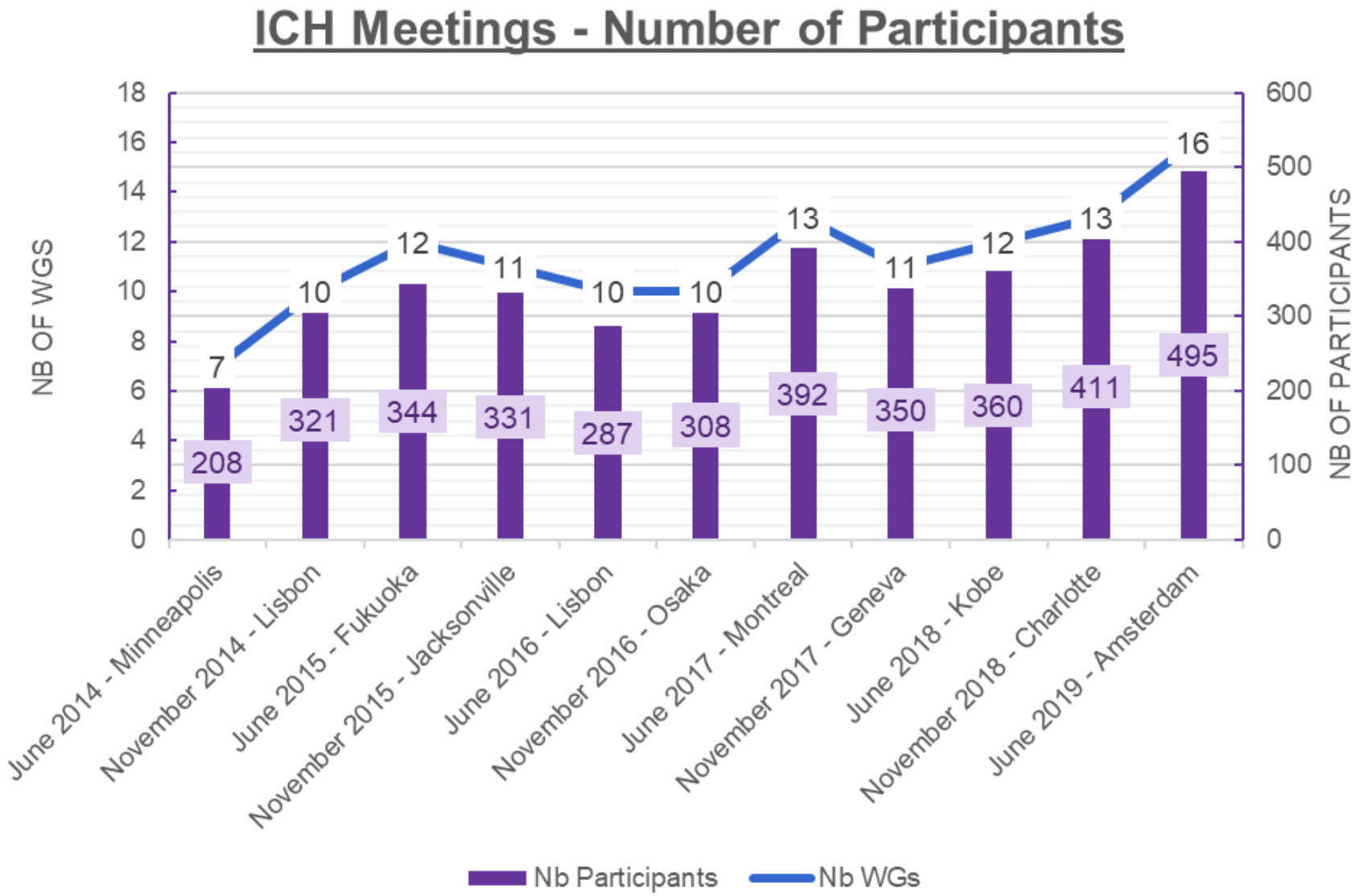
ICH – as of 20 May 2019

- ICH comprises of 44 Members and Observers:
  - 16 Members
  - 28 Observers
- ICH comprises of 26 WGs
- ICH involves 856 persons:
  - **96** Representatives of Members/Observers in the ICH Assembly, ICH MC, MedDRA MC
  - **646** Experts in WGs
  - **128** persons are serving in support roles.

646 Experts in 26 WGs– as of 20 May 2019



Growth in Size of ICH Biannual Meeting



Evolution – May 2018 to May 2019

In one year:

- Increase in ICH Membership/Observership**: +16%**

  (+1 new Member and 5 new Observers)

- Increase in number of WGs: **+13%** (+3 new WGs)

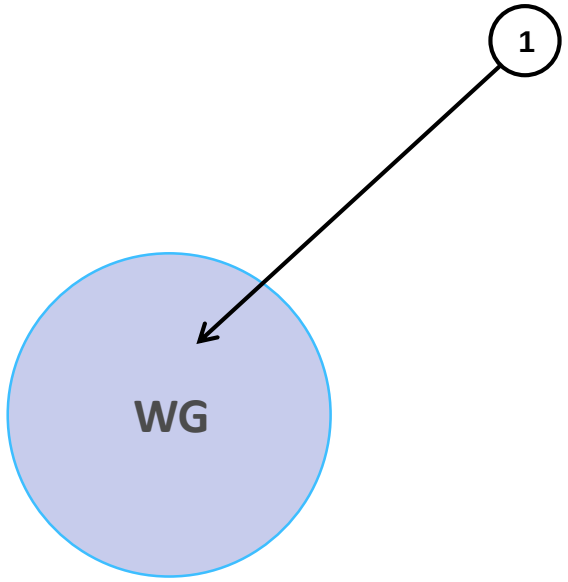
  [not counting E20 & M12 postponed to start in June/July 2019]

- Increase in number of experts: +**23%** (+121 new experts) in new and pre-existing WGs:
  - +15% (+53) Founding and Standing Members
  - +34% (+46) Members (non-Founding, non-Standing)
  - +42 % (+5) Standing Observers
  - +55% (+17) for Observers

Recent enhancements to manage size of Expert Working Groups (WG)

- Due to the expansion of ICH (i.e. increasing number of Members / Observers) the demand to nominate experts to Working Groups (WGs) has continued to increase, resulting in increasingly larger WGs
- The difficulty in managing the size of WGs within the earlier operating procedures prompted the MC to put forward a new approach to ensure:
  - WG size is **small enough** to be efficient such that Guideline development work is done in a timely manner
  - WG membership is **expert enough** to produce Guidelines that are clear, correct, reflecting latest accepted science and technical understanding
  - WG **harmonization work is accessible enough** to other ICH Members to enable good understanding, support for adoption, and later implementation
  - **Administrative burden** of implementation **is minimal**

Recent enhancements to manage size of Expert Working Groups (WG)

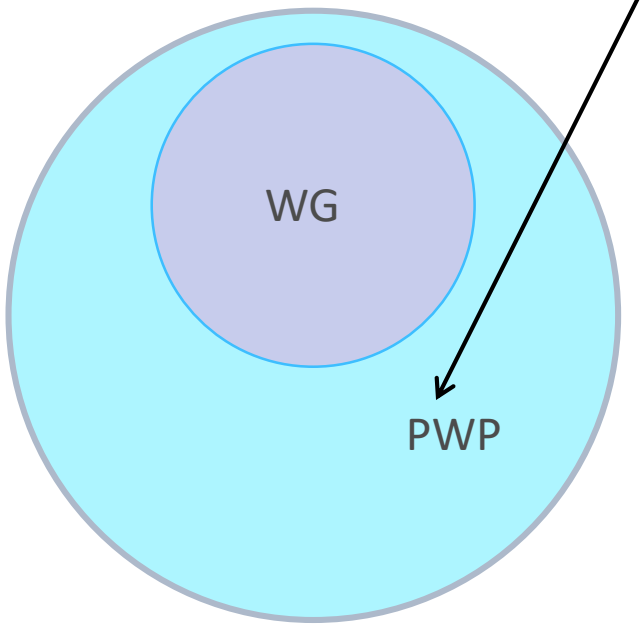


Changes impacting Working Groups (WG)

New approach:

- WG size is capped at 30
- Founding Regulatory Members may nominate up to 2 experts (Topic Lead and Deputy Topic Lead)
- Founding Industry Members, Standing Regulatory Members, Regulatory Members and Industry Members may nominate one Topic Leader, and one alternate expert.
- Industry Members and IFPMA as Standing Observer, as a group, may nominate up to three additional industry experts.
- Any request for additional expertise should come from the WG and is processed on an ad-hoc basis.
- Requests to nominate experts from Members/Observers not represented in the group are reviewed by the MC twice year.

Recent enhancements to manage size of Expert WGs (cont.)



Included in New Approach: Plenary Working Party (PWP)

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- For Members / Observers who want to follow the progress of a WG but who are unable to either:
  - participate to a WG due to size limitations,
  - devote the necessary level of effort to participate actively in the WG activities.

→ Such Members /Observers may appoint one expert to the PWP.

→ PWP are established based on interest and need:
  - For WGs established prior to June 2019: MC approval required
  - For WGs established after June 2019:
    - Prior to *Step 2a/b*: Automatically established (based on interest and need)
    - After *Step 2a/b*: MC approval required

- The PWP is involved in:
  - *Step 1*:
    - Ahead of Step 1 sign-off, PWP experts are provided 1 month to review Step 1 document and provide input;
    - At Step 1, PWP experts are invited to sign-off the Step 1 document.
  - *Step 3*:
    - Ahead of *Step 3* sign-off, PWP experts are provided 1 month to review *Step 3* document and provide input;
    - At *Step* 3, PWP experts are invited to sign-off the *Step 3* document.
  - Workshops with Industry Stakeholders.

Increasing ICH focus on strategy (example: GLs)

- Shift from thinking only about individual new topic proposals to thinking about needed **new topic areas**
  - Prior to ICH Reform: focus on "*where is there an existing g*ap?"
  - Post-ICH Reform: focus on "*what are the emerging needs/opportunities?" PLUS "where are existing gaps?"*
- Multiple guidelines (GLs) may be needed to address the opportunities—a new format was needed to communicate both the strategic context and the more comprehensive proposal for harmonization work that could be needed: **"Strategic Reflection Paper"**
- Examples
  - Enabling development innovative new therapies, delivery systems, modern manufacturing technology –and-- avoiding shortages of older (often critical) first line therapies -- (Quality modernization)
  - Enabling appropriate use of new data sources and new types of studies as more types of digital health data and technologies become available **(GCP Renovation)***

* http://www.ich.org/products/gcp-renovation.html

Background: Following regional comment on E6 (R2), ICH received direct Stakeholder input on ICH approach to GCP

- Following the regional comment on ICH E6(R2), ICH received direct public stakeholder comments related to E6 (R2) (in June 2016) with a request for further enhancement to address additional issues related to good clinical practice
- The comments to ICH recognized the importance of:
  - The 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
  - The most recent E6 (R2) has made major steps in this direction clarifying the flexibility; use of a quality management system approach, key responsibilities of investigators versus sponsors, and essential documents
- However, public stakeholders from clinical research community and others cited <u>further opportunities</u> to modernize ICH GCP-related GLs:
  - More explicit attention to quality of study / study design
  - More flexibility to better fit diverse range of studies and data sources
  - A sense of urgency for these needs to be addressed

ICH Conducted Follow-up to the Public Stakeholder Input: Developing a Reflection Paper (RP) on GCP Renovation

- **RP developed by September 2016 and endorsed by ICH Assembly in November 2016**: Update ICH guidelines to both address study quality and provide further flexibility to address the increasing diversity of clinical trial designs and data sources
  - 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, and 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 subsidiary use cases/annexes addressing specific types of studies/ data sources
- To communicate to public stakeholders about ICH response to their 2016 comments, ICH posted its Reflection Paper in January 2017 to seek further public comment.
  - Comment period closed in March 2017.
  - Public input cited a number of suggestions and general support for the RP approach

GCP Renovation: Attention to study quality and increasing diversity of potential study types and data sources

- **GCP Renovation begins with revision of ICH E8 General Considerations for Clinical Trials**
  - ICH E8 was issued in 1997 as high level guidance providing general roadmap to other ICH Guidelines concerning CTs.
  - Provided high-level descriptions of trial objectives and design; but did not address design or planning considerations affecting *quality of the study* that generates, and determines the quality of, the data.
  - Did not explicitly address targets or metrics for data quality parameters that are essential to successful conduct of the trial , and then design and plan trial conduct, based on an assessment of risk, in order to achieve these targets.
- **ICH E8 revision further addresses fundamental issue of study quality** *(now at Step 3)*
  - Enhance E8 treatment of principles of study design and planning-- to achieve an appropriate level of data quality and ability to meet stated study objectives.
  - Identify basic set of critical-to-quality (CTQ) factors --generally relevant to the integrity and reliability of study conclusions and patient safety --that sponsors should consider, to determine which factors stand out as critical and need to be explicitly addressed in a risk-based management and monitoring plan.
  - This type of prospective planning feeds directly into ICH E6, where the procedures implemented and followed should flow from the prospective identification of the desired data quality parameters for various types of data.

GCP Renovation (Cont.)

- **GCP Renovations will continue with further revision to ICH E6 Good Clinical Practices**
  - Since ICH E6 was first drafted clinical trial conduct has evolved, calling for a more flexible risk-based approach to oversight and ICH E6(R2) made important steps in this direction
  - New emerging trial designs and environment–not explicitly addressed in E6—also play increasingly important role (e.g., real-world data (RWD), such as electronic health records, patient disease registries, etc.) and these could inform regulatory decision-making
- **Planned ICH E6 (R3) will:** *(New topic approved by ICH Assembly in June 2019)*
  - Create a new "general principles" document (including key elements of human subject protection and study integrity, using a risk-based approach to study oversight and monitoring)
  - "General principles" document will later be augmented by series of annexes addressing the principles in the context of different types of studies and data sources, e.g.:
    - Traditional Interventional Trials of investigational unapproved or approved drugs – including trials of unapproved drugs or of approved drugs for a new indication or use in a controlled setting with prospective collection of trial data
    - Non-Traditional Interventional Trials and/or data sources. including pragmatic clinical trials and decentralized clinical trials including use of RWD sources in these and other study designs to supplement or possibly replace new data collection within the trial itself

Opportunities and Rewards of ICH Reform: Summary

1. Growth in the number and diversity of participants has energized and challenged ICH to better:
    - Plan and manage operations *(Biannual and interim meetings, t-cons, etc.)*
    - Orient new ICH participants and train on the ICH guidelines
2. Continued policy and procedure enhancements will enable ICH to:
    - Continually improve Guideline WG operations and preserve technical expertise and efficiency
3. More formal structure and approach post-reform has enabled longer planning horizon and management continuity
    - Supporting more strategic approach to managing and expanding the guideline portfolio

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Thank you!