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U.S. FOOD & DRUG ADMINISTRATION

US FDA and Health Canada Regional Public Consultation on the International Council for Harmonisation (ICH)

April 6, 2018

Agenda

I. Overview of the ICH
II. Update on Electronic Standards Topics and MedDRA
III. Topics recently reaching step 2 of the ICH process (draft guidance)
    - Q12
    - E9(R1)
    - S5(R3)
IV. Selected topics recently reaching step 4 of the ICH process (final guidance)
    - E17
    - E11(R1)
V. Overview of Ongoing Topics
VI. Public Comment
VII. Closing Remarks

Overview of the ICH

Theresa Mullin, PhD
Associate Director for Strategic Initiatives
FDA Center for Drug Evaluation and Research
April 6, 2018

ICH

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

- Unique harmonization project involving the regulators and research-based industries
- Begun in 1990 involving US, EU and JP
- 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**
- Accomplish through the development and implementation of harmonized Guidelines and standards

The ICH Process for Guideline Development has 5 Steps

Sampling of Major Topic Areas Addressed by ICH Guidelines

Safety

- Carcinogenicity studies
- Genotoxicity studies
- Toxicokinetics and Pharmacokinetics
- Toxicity testing
- Reproductive toxicology
- Biotechnology products
- Pharmacology studies
- Immunotoxicology studies
- Nonclinical evaluation for anticancer pharmaceuticals
- Photosafety evaluation

Efficacy

- Clinical safety
- Clinical study reports
- Dose-response studies
- Ethnic factors
- Good clinical practice
- Clinical trials
- Clinical evaluation by therapeutic cat.
- Clinical evaluation
- Pharmacogenomics
- Multi-regional clinical trials

Quality

- Stability
- Analytical validation
- Impurities
- Pharmacopoeias
- Quality of biotechnology products
- Specifications
- Good manufacturing practice
- Pharmaceutical development
- Quality risk management
- Pharmaceutical quality system
- Development and manufacture of drug substances

Multidisciplinary

- MedDRA terminology
- Electronic standards
- Nonclinical safety studies
- CTD and eCTD
- Data elements and standards for drug dictionaries
- Gene therapy
- Genotoxic impurities

ICH Work Products

- Over 60 Guidelines on technical requirements on:
  - Quality
  - Safety
  - Efficacy
  - Multidisciplinary (including for electronic submissions)
- Electronic Standards for the Transfer of Regulatory Information (ESTRI, E2B)
- MedDRA (standardized medical terminology)

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 regulators 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

Goals of the ICH Reform

- Better prepare ICH to face the challenges of global pharmaceutical development and regulation
- Expand ICH beyond the current Members
- More involvement from regulators around the world and wider inclusion of global industry sectors affected by ICH harmonization
- Focus global pharmaceutical regulatory harmonization work in one venue
- Continue to harmonize and streamline the global drug development process for the benefit of patients around the world
- Maintain efficient and well-managed operations and harmonization work processes

Governance of new ICH Association

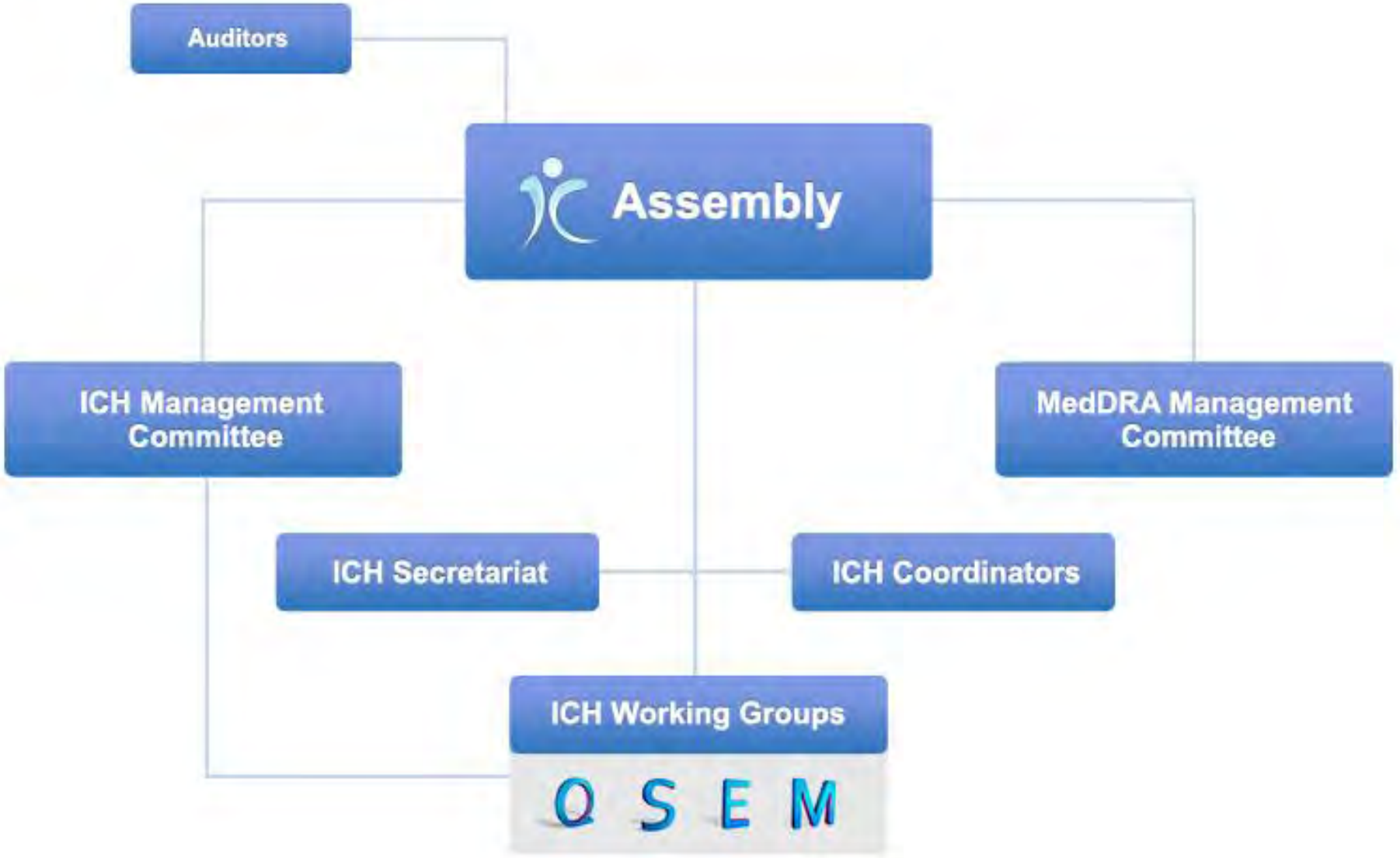
Assembly

- 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 Management Committee representatives, Guideline work plan, Adoption of ICH guidelines, Approval of budget, etc.
- **Includes all ICH Members**

Management Committee

- 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, during a transition period, ensure funding of ICH operations.
- **Includes Permanent and Standing Members, and Elected Members**

ICH Governance



Membership in the Assembly—Eligibility Criteria for Regulators

Recognized Authority

- Has a legal personality
- Responsible for the regulation of pharmaceutical products for human use

Engagement in the ICH Process

- Past regular attendance in at least 3 ICH meetings during the previous 2 consecutive years
- Past appointment of experts in at least 2 Working Groups

Application of ICH Guidelines

- Implementation of the following ICH Guidelines at minimum, upon application for membership:
  - Q1: Stability Testing guidelines
  - Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
  - E6: Good Clinical Practice Guideline

Membership in the Assembly—
Eligibility Criteria for Industry

Recognized Authority

- Has a legal personality
- Represents members from several countries in at least three continents
- Is regulated by all of some of the ICH Guidelines

Engagement in the ICH Process

- Has participated in ICH as an Observer
- Past appointment of experts in at least 2 Working Groups

ICH Members Have a Vote in the Assembly

- All ICH Members have a voice and may vote in the Assembly on decisions related to[1]:
  - Selection and nomination of new topics for harmonization
  - Approval of the annual and multi-annual strategic plan
  - Adoption, amendment, or withdrawal of ICH Guidelines
  - Approval or rejection of membership/observer admission

1 See ICH Articles of Association for more details:
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 can Propose New Topics for Harmonization

Annual topic submission and review process:

- Each ICH Member can propose topics for harmonization
- The ICH Management Committee provides a recommendation to the Assembly on selection of new topics
- The ICH Assembly makes a decision at each June meeting on new topics for harmonization

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
- EAC
- GHC
- PANDRH
- SADC
- APIC
- BMGF
- CIOMS
- EDQM
- IPEC
- PIC/S
- USP

**As of April 2018*

Summary

- ICH has achieved international harmonization of technical guidelines, with engagement of regulators and industry
- ICH uses a science- and consensus-based process following 5 transparent steps in the ICH process for Guideline development
- ICH has clear governance and increasingly global membership following ICH reform
- Recent reforms have expanded global participation in regulatory harmonization

Thank You

ICH Electronic Standards Overview and Update of Activities

Mary Ann Slack

FDA/CDER Office of Strategic Programs

April 6, 2018

Topics

- **E2B (R3) – ICH next-gen Individual Case Safety Report**
- **M8 eCTD v4.0 – ICH next-gen electronic Common Technical Document**
- **M2 and ESTRI – ICH electronic standards Activities**
- **MedDRA and MedDRA Points to Consider**

ICH E2B R3 Updates

Recent Accomplishments

- **ESTRI Update**
  - Memo documenting decision to use EDQM Dose Forms and Routes of Administration has been created
- **SOP to extract and post EDQM DF and RoA terms**
  - SOP for periodic extraction and posting of EDQM DF and RoA terms is drafted

At the Kobe Meeting

- **DF and RoA updates**
  - Evaluate and develop business requirement for dynamic refresh of EDQM DF and RoA lists
  - Develop RoA mapping table to support compatibility between R2 and R3
- **Business rule and data element template**
  - Add ICH core data elements and their business rules to the template for regional use
- **Update Backward Forward Compatibility document**
  - Address discrepancies in R2-R3 conversion rules
  - Update the compatibility document and element mapping spreadsheet to reflect adoption of EDQM DF and RoA terms

FDA E2B R3 Implementation Update

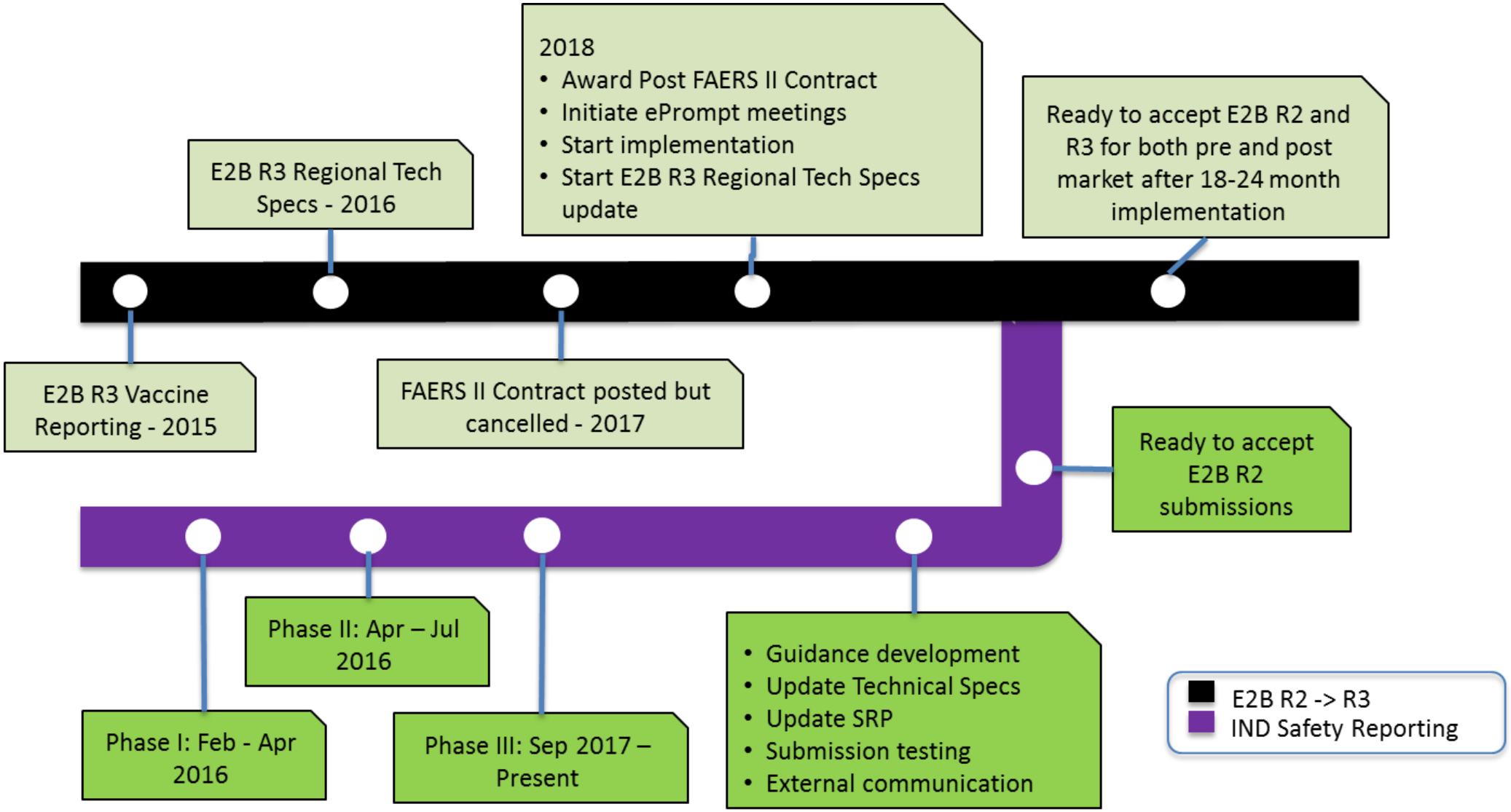
2015
- Implementation of E2B (R3) for vaccine safety reporting

2016
- E2B (R3) FDA Regional Technical Specification published

2017
- FAERS II contract posted (includes E2B (R3) implementation)
- Award cancelled

2018
- FAERS II contract to be posted (includes E2B (R3) implementation)
- Approx. 18 – 24 months implementation of FAERS II after award

FDA E2B R2 to R3 Road Map



ICH M8 (eCTD v4.0) Status Update

- Current ICH eCTD v4.0 Implementation Package (v1.2)

Document	Version	Format
eCTD v4.0 Implementation Guide	1.2	PDF
eCTD v4.0 Controlled Vocabularies	1.2	Spreadsheet
eCTD v3.2.2 Transition Mapping Message Controlled Vocabularies	1.2	Spreadsheet
Genericode Files	-	Folder and files
Schema Files	-	Folder and files
Package History	-	PDF

- Updated Implementation Package (v1.3) planned for ICH June Meeting
  - General update with additional functionality

FDA eCTD v4 Implementation Status

- US FDA Module 1 Implementation Package v1.1 Under Revision
  - Updates to be in alignment with ICH changes
- eCTD v4.0 Technical Conformance Guide
  - Includes information on submitting an eCTD v4.0 message to the FDA
    - New features
    - New processes (e.g., two-way communication)

M2 Milestones Anticipated for ICH June Meeting

Milestones
Concept proposal for electronic Common Clinical Trial Submission (eCCTS) is finalized and delivered for MC review
Project opportunity proposals (non-consensus) including e-Trial Master File metadata harmonization (eTMF) are delivered for MC review
Aggregate assessment results of existing ICH topics for technical opportunities
Revised ESTRI recommendation on secure information exchange over the Internet is drafted
Revised terminology list maintenance process and service level agreement established with other IWGs for terminology list maintenance

ESTRI Web Pages Hold Technical Standards and Recommendations

M2 Recommendations & Technical References

ESTRI Home

The M2 EWG has provided valuable functionality to the diverse international information exchange needs identified by the members of the ICH regions and observers. The M2 EWG Recommendations provide a well-defined approach for the evaluation and recommendation of standards. The M2 tasks have led to the recommendation of various open international standards that allow for the international transmission of information regardless of the technical infrastructure.

The recommendations have been endorsed by the ICH Steering Committee at their different meetings. The Recommendations are categorized as follows:

- General
- File Format
- Information Transfer
- File Integrity

Current M2 Recommendations

Category	Title	Version	Date Endorsed	Implemented				
				EU	JP	US	CA	CH
General	Procedure	3.0	June, 2015	Yes	Yes	Yes	Yes	Yes
General	ESTRI Gateway	3.0	June, 2015	Yes	Yes	Yes	Yes	Yes
File Format	PDF	2.0	April, 2011	Yes	Yes	Yes	Yes	Yes
File Format	XML	1.0	November, 2005	Yes	Yes	Yes	Yes	Yes
File Format	PDF/A	1.0	June, 2014	Yes	Pending	Yes	Yes	Yes
File Format	DOCX	1.0	June, 2015	Yes **	Pending	Yes **	Yes **	Pending
Information Transfer	Genericode	1.0	June, 2015	Yes	Pending	Yes	Pending	Pending
Information Transfer	EDIINT AS1/AS2	2.2	June, 2010	Yes	Yes	Yes	Yes	Yes
File Integrity	MD5	1.0	June, 2010	Yes	Yes	Yes	Yes	Yes
File Integrity	SHA-256	1.0	June, 2015	Pending	Pending	Yes	Pending	Pending

** Check with regulator for specifics

ICH MedDRA

- MedDRA (Medical Dictionary for Regulatory Activities): standardized medical terminology developed by ICH to facilitate sharing of regulatory information internationally for drugs, vaccines and drug-device combination products
- MedDRA Management Committee: governance body providing technical and financial oversight of the MedDRA terminology and the MedDRA maintenance organization. Under the governance of the ICH MedDRA Management Committee, MedDRA is continuously enhanced to meet the evolving needs of regulators and industry around the world.
- ICH MedDRA Points to Consider Working Group: develops guides for harmonized MedDRA usage (coding and retrieval guidelines)
- MSSO (Maintenance and Support Services Organization): contracted by ICH to maintain, develop and distribute MedDRA. The terminology is free for all regulators worldwide, academics, and health care providers while paid subscriptions are on a sliding scale linked to annual turnover of companies

MedDRA Updates

- Subscription rates have been lowered for 2018
- MedDRA is now subscribed to by over 5000 organizations in 110 countries
- The MSSO will be commencing local support in several additional areas – Central America and Republic of Korea in 2018, China in 2019; in addition to local support, this will enable training to be provided in the local languages.
- Korean and Russian MedDRA translations are planned bringing the portfolio of translations to 13
- The MedDRA MC and MSSO are collaborating with WHO to support countries transitioning from WHO-ART to MedDRA for pharmacovigilance activities

ICH MedDRA Points to Consider working group (M1 PtC)

- Author and update *Points to Consider (PtC)* documents for consistent use of MedDRA:
  - *MedDRA Term Selection (MTS:PtC), MedDRA Data Retrieval and Presentation (DRP:PtC)*
  - Update released in March 2018 for MedDRA version 21.0
- Developed *Condensed version* of PtC documents to be released in 9 MedDRA languages in 2018: Chinese, Czech, Dutch, French, German, Hungarian, Italian, Portuguese and Spanish (English and Japanese remain in full)
- Developed *Companion document* to be released in 2018, initial topics:
  - Data quality
  - Medication errors

Thank You!

Any Questions?

ICH Q12
Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

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US FDA and Health Canada
Regional Public Consultation on ICH

April 6, 2018

Disclaimer

- The views presented do not necessarily represent the views of ICH.

Outline

- ICH Q12 Step 2 Document
  - Why Q12
  - Scope
  - Key Sections
    - Established Conditions
    - Post-approval Change Management Protocol
    - Product Lifecycle Management
    - Pharmaceutical Quality System and Change management
    - Relationship Between Regulatory Assessment and Inspection
    - Post-Approval Changes for Marketed Products
- Next Steps
- Acknowledgements

Why ICH Q12?

- ICH Q8-Q11 focus mostly on premarket stage of the product lifecycle
- Lack of harmonized requirements for lifecycle management are a disincentive to manufacturers to make improvements to increase process robustness
  - One post-approval change can take 3-5 years to implement across all regions, resulting in additional costs and potential supply disruption due to need for multiple inventories
- Opportunities for “operational flexibility” offered by the science- and risk-based approaches in ICH Q8-Q11 have not been fully realized

Q12 Objectives (from the Q12 concept paper)

- …**Harmonize change management**…in a more transparent and efficient manner…across ICH regions
- …Facilitate **risk-based** regulatory **oversight**…
- Emphasize…**control strategy** as a key component of the…dossier
- Enhance use of regulatory tools for **prospective change management**…enabling **strategic** management of **post-approval changes**…

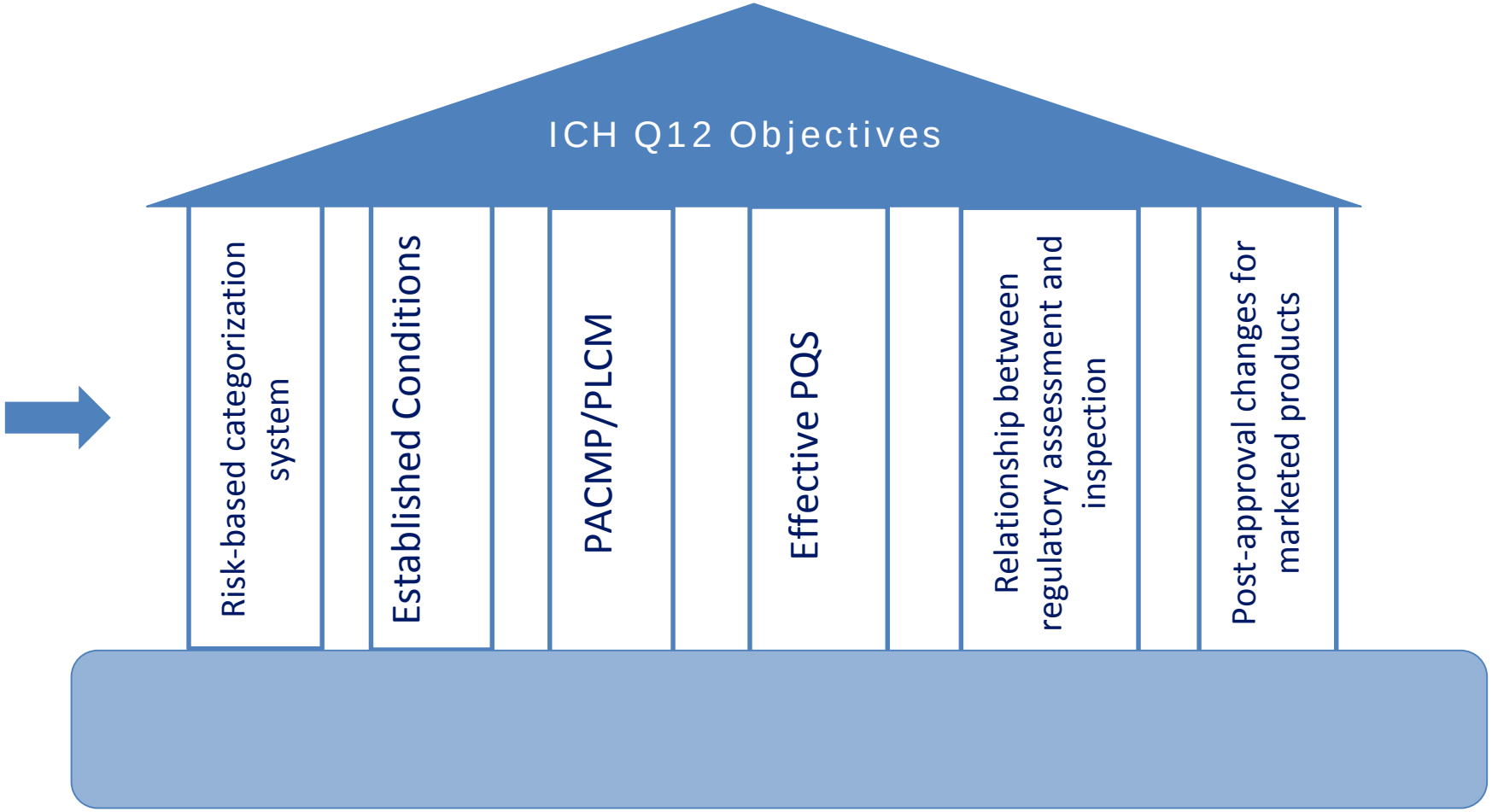
Potential Benefits

- Reduce unnecessary cost and time burdens on industry and regulators, while assuring that patients reliably have access to high quality therapies
- Support continual improvement…which can result in decreased product variability and increased manufacturing efficiency
- Help to mitigate drug shortages related to manufacturing and quality issues
- Facilitate the introduction of innovations in manufacturing…
- Support access to breakthrough drugs while ensuring quality

Scope

- Pharmaceutical drug substances (i.e., active pharmaceutical ingredients) and pharmaceutical drug products
  - Includes marketed chemical and biotechnological/biological products
- Drug-device combination products that meet the definition of a pharmaceutical or biotechnological/biological product
- Does not include changes needed to comply with Pharmacopeial monographs

ICH Q12 Regulatory Tools and Enablers



Categorization of Changes

Key Sections of Q12 Step 2 document – Chapter 2

Convergence toward risk-based categorization of post-approval changes is encouraged as an important step toward achieving the objectives of Q12

- **Prior-approval**: Changes with sufficient risk to require regulatory authority review and approval prior to implementation
- **Notification**: Moderate- to low-risk changes that do not require prior approval and generally require less information to support the change
  - These changes are communicated to the regulatory authority as a formal notification that takes place within a defined period of time before or after implementation, according to regional requirements.
- In addition, the **lowest risk changes** are only managed and documented within the PQS and not reported to regulators, but may be verified on routine inspection

Established Conditions

Key Sections of Q12 Step 2 document – Chapter 3

- ECs are legally binding information (or approved matters) considered necessary to assure product quality
  - As a consequence, any change to ECs necessitates a submission to the regulatory authority
  - All regulatory submissions contain a combination of ECs and supportive information
    - Supportive information is not considered to be ECs, but is provided to share with regulators the development and manufacturing information at an appropriate level of detail, and to justify the initial selection of ECs and their reporting category

Established Conditions

- ECs in a submission are either **implicit or explicit**:
  - Implicit ECs are elements that are not specifically proposed by the MAH but are derived from and revised according to regional regulation or guidance related to post-approval changes.
  - Explicit ECs are specifically identified and proposed by the MAH together with their proposed reporting category as part of a regulatory submission
    - Appropriate when either the proposed EC or reporting category is different than regional guidance or regulation – not required, but if proposed, should be justified

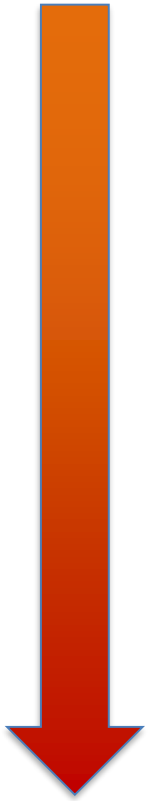
Identifying ECs and the Role of Risk

- The extent (number and how narrowly defined) of ECs will vary based on a number of factors, including:
  - product and process understanding
  - characterization
  - the firm's development approach, and
  - potential risk to product quality

Identifying ECs for Manufacturing Processes

- Unit operation and the sequence of steps
- Considering the overall control strategy, those **inputs** (e.g., process parameters, material attributes) and **outputs** (may include in-process controls) necessary to assure product quality
  - critical process parameters (CPPs, as defined in ICH Q8(R2))
  - key process parameters (KPPs)
    - parameters of the manufacturing process that may not be directly linked to critical product quality attributes, but need to be tightly controlled to assure process consistency as it relates to product quality.

Identifying ECs for Manufacturing Processes and the Development Approach



- A **parameter based approach**, in which product development prior to regulatory submission provides a limited understanding of the relationship between inputs and resulting quality attributes, will include a large number of inputs (e.g., process parameters and material attributes) along with outputs (including in-process controls).
- An **enhanced approach** with increased understanding of interaction between inputs and product quality attributes together with a corresponding control strategy can lead to identification of ECs that are focused on the most important input parameters along with outputs, as appropriate.
- In certain cases, applying knowledge from a data-rich environment enables a **performance based approach** in which ECs could be primarily focused on control of unit operation outputs rather than process inputs (e.g., process parameters and material attributes).

Proposed Reporting Category

- After identifying ECs, MAH proposes reporting category for post-approval changes
- Follow existing regional regulations and guidance or propose alternate reporting category
- Reporting category is dependent on the potential risk to quality
  - Risk assessment activities should follow approaches described in ICH Q9
  - Consider the overall control strategy and any possible concurrent changes

Post-Approval Change Management Protocol

Key Sections of Q12 Step 2 document – Chapter 4

- A PACMP provides predictability and transparency in terms of the requirements and studies needed to implement a change
- Can address one or more changes for a single product, or may address one or more changes to be applied to multiple products
- PACMP may be submitted with the original Market Authorization Application or subsequently as a stand-alone submission

Post-Approval Change Management Protocol

Step 1

- Submission of a written protocol
  - proposed change(s) with rationale(s)
  - risk management activities
  - proposed studies and acceptance criteria to assess the impact of the change(s)
  - other conditions to be met
  - the proposed reporting category
  - any other supportive information
- Approved by regulator in advance of execution

Step 2

- Carry out tests and studies outlined in the protocol
- If results/data generated meet the acceptance criteria in the protocol and any other conditions are met, submit this information to the regulatory authority according to the category in the approved protocol
- Depending on the reporting category, approval by the regulatory authority may or may not be required prior to implementation of the change.

PACMP – Implementation and the PQS

- PACMP should confirm ongoing verification will be performed under the PQS to ensure no adverse effect of the change(s) on product quality
- In cases where monitoring of the impact on product quality following implementation of the change(s) is required, a summary of the quality risk management activities should be provided to support the proposed PACMP
  - If multiple changes are to be implemented, these activities should address the potential risk from the cumulative effect of multiple changes and how they are linked

Product Lifecycle Management (PLCM)

Key Sections of Q12 Step 2 document – Chapter 5 (I)

Product Lifecycle Management (PLCM) document

- Serves as a central repository of the ECs, reporting category for making changes to approved ECs, PACMPs, and post-approval CMC commitments
- Provides a high level summary of product control strategy to clarify and highlight which elements of the control strategy should be considered ECs.
- Facilitates and encourages a more strategic approach to lifecycle management
- Enables transparency and facilitates continuous improvement

Product Lifecycle Management (PLCM)

Key Sections of Q12 Step 2 document – Chapter 5 (II, III, IV)

Submitting the PLCM document

- The initial PLCM document is submitted with the original Market Authorization Application, or
- with a supplement/variation for marketed products where defining ECs may facilitate regulatory change management.

Maintenance of the PLCM Document

- An updated PLCM document should be included in post-approval submissions for CMC changes.
- The MAH should follow regional expectations for maintaining a revision history for the PLCM document.

Format and Location of PLCM Document

- A tabular format is recommended, but not mandatory.
- The location is based on regional recommendations.

Pharmaceutical Quality System (PQS) and Change Management

Key Sections of Q12 Step 2 document – Chapter 6

- ICH Q10 describes principles for the effective management of CMC changes under the PQS
- This section articulates the importance of timely communication across multiple sites (outsourced or not), and between the MAH and the regulators on manufacturing changes
- Appendix 2 elaborates on Q10 principles and describes how the PQS can be utilized effectively in the application of Q12 concepts

Relationship Between Regulatory Assessment and Inspection

Key Sections of Q12 Step 2 document – Chapter 7

- Encourages communication between assessors and inspectors to facilitate implementation of Q12

Post-Approval Changes for Marketed Products

Key Sections of Q12 Step 2 document – Chapter 8

- Q12 regulatory tools/enablers are applicable to marketed products
- Describes a strategy for a structured approach for frequent CMC changes (e.g., analytical methods) and data requirements for CMC changes (e.g., stability)

If this approach is followed and all criteria are met, the analytical procedure change can be made with immediate or other post-implementation notification, as appropriate, to the relevant regulatory authorities.

Structured Approach for Analytical Procedure Changes

Out of Scope

- Procedure where the specification does not adequately reflect the complex information provided by the method. For example:
  - Procedures for which only a subset of the peaks are identified and specified (e.g., assay for identity by peptide map)
  - The specification acceptance criteria include a general comparison to a reference standards beyond specified peaks (e.g., "comparable to reference standard")
- Change(s) to a test method based on a biological/immunological/immunochemical principle or a method using a biological reagent (e.g., bioassay, binding assay, ELISA, testing for viral adventitious agents).
- Changes to predictive models used with multivariate methods.

All other methods are in scope including those used for biotechnological/ biological products.

The flexibility provided by the "structured approach" may not be available in all regions and in all situations; some specific changes may require prior approval as defined in regional guidance.

Structured Approach for Analytical Procedure Changes (2)

Pre-requisites:

- In order to use the "Structured Approach," a set of principles should be met.

Principles:

- The high level description of the "new" and "old" methods should be same (e.g., chromatograph with spectroscopic detection)
- Demonstrate equivalency or better through validation studies
- System suitability requirements should be established for the revised method
- No change on specifications (unless allowed by regional regulation)
- This approach may not be used if toxicological or clinical data are required as a result of the method change

Next Steps

- Public Consultation extended for one year
  - Regional review of comments Q1-4, 2018
  - Next Q12 EWG F2F Meeting not yet determined
  - Step 4 Targeted for 2019
- Training
  - Development of a comprehensive training program and supporting documentation sponsored by ICH is highly recommended to ensure the proper interpretation and effective utilization and implementation by industry and regulators
  - Important for both ICH and non-ICH regions

ACKNOWLEDGEMENTS

Moheb Nasr, Rapporteur through Step 2b

ICH Q12 EWG representing regulators (FDA, EC, MHLW/PMDA, HC, Swissmedic, ANVISA, MFDS, HSA, WHO, TFDA) and industry (PhRMA, EfPIA, JPMA, IGBA, BIO, APIC, WSMI)

U.S. FOOD & DRUG ADMINISTRATION

E9(R1): Statistical Principles for Clinical Trials

Addendum: Estimands and Sensitivity Analysis in Clinical Trials

Thomas Permutt, FDA Topic Leader

Status

- E9: Step 5 1998
- Revision: Step 3 2017
- Comments (US) until 30 April 2018
- E9(R1) is E9 + Addendum
  - No changes or deletions, only addition
  - Understanding continues to evolve

Addendum

- Estimands
- Sensitivity analysis

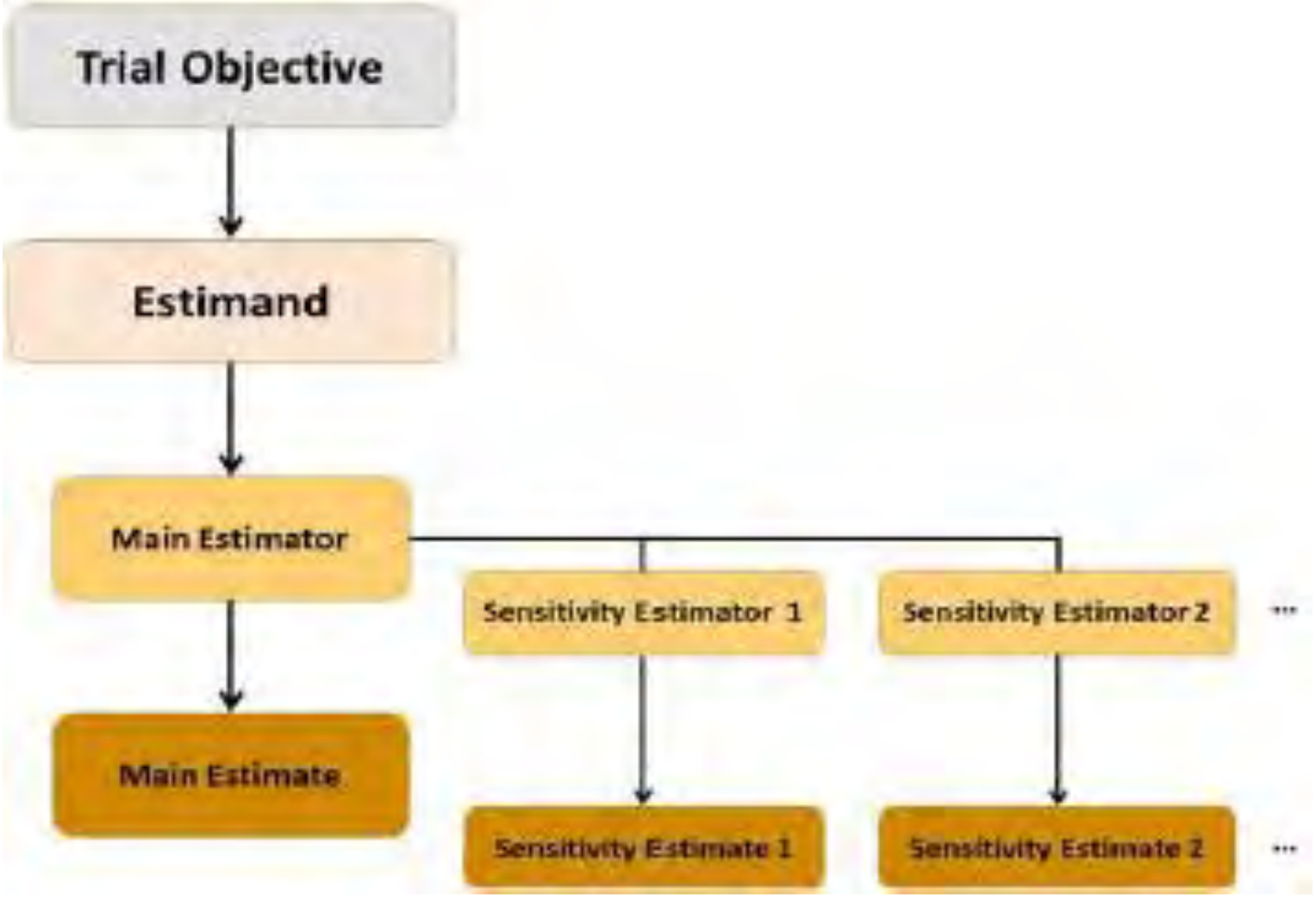
Sensitivity Analysis

- Analyses
  - A pile
  - Predates *primary*
  - Type II multiplicity
  - Joint interpretation difficult
    - One assumes A, B, C
    - Another assumes B, F, G
    - Different because A false?
    - Different because F false?
    - Both wrong because B false?
- Analysis
  - Primary assumes A
  - Sensitivity analysis assumes A + Δ
  - Discuss plausible Δ
  - If fewer assumptions, then less sensitivity analysis needed

Estimands

- Framework
- Strategies

Framework


Trial Objective
Estimand
Main Estimator
Main Estimate
Sensitivity Estimator 1
Sensitivity Estimator 2
...
Sensitivity Estimate 1
Sensitivity Estimate 2
...

“Attributes” of Estimands

A. the population, that is, the patients targeted by the scientific question

B. the variable (or endpoint), to be obtained for each patient, that is required to address the scientific question

C. the specification of how to account for intercurrent events to reflect the scientific question of interest

D. the population-level summary for the variable which provides, as required, a basis for a comparison between treatment conditions

Strategies: Defining Treatment Effects

- Abigail
  - If placebo, 15
  - If test, 17
  - What is treatment effect?

Defining Treatment Effects

- Abigail
  - If placebo, 15
  - If test, 17
  - What is treatment effect?
- Treatment effect is 2

Defining Treatment Effects

- Bert
  - If placebo, discontinue for lack of efficacy
  - If test, 18
  - What is treatment effect?

Defining Treatment Effects

- Bert
  - If placebo, discontinue for lack of efficacy
  - If test, 18
  - What is treatment effect?
- Treatment effect is to keep Bert in study (with outcome 18)

Defining Treatment Effects

- Carmen
  - If placebo, 14
  - If test, drop out for adverse event
  - What is treatment effect?
- Treatment effect is to make Carmen drop out

Defining Treatment Effects

- Donald
  - Drops out in either group
  - What is treatment effect?
- Treatment effect is zero (maybe)

Strategies

- Count everybody
  - Actual value at endpoint
  - Composite value at endpoint
  - Average value during treatment
  - Hypothetical value
- Count only A and B (or only A)

Treatment Policy Strategy

- Actual value at endpoint
- Need to get it!
- Already standard in outcome studies
- Not standard in symptom studies

Composite Strategy

- Good outcome is, alive *and* good blood pressure
- Only way to deal with treatment-related death
- Sometimes good way to deal with treatment-related dropout

While-on-Treatment Strategy

- Palliation in terminal condition
  - No pain while alive is a good outcome
- Smoking cessation
  - No cigarettes while wearing patch is not a good outcome …
  - Unless wear patch to end of study

Hypothetical Strategy

- If no rescue
  - Good idea, not easy
  - Analogous to hypothetical placebo in noninferiority
- If no adverse event or dropout
  - Bad idea

Principal Stratification Strategy

- Abigail, Bert, Carmen, Donald represent 4 principal strata
- “Efficacy” is effect in Abigails and Berts
- Hard to distinguish Abigails from Carmens in control group (because they both complete)
- Do not try to do “efficacy” with hypotheticals
  - No easier
  - Isn’t what you want, anyway

Summary

- Sensitivity analysis: Adjustment but win/win
  - Reduce Type II multiplicity
  - Encourage robust primary methods
- Framework
  - Better communication, but this leads to …
  - Different methods sometimes
- Strategies for defining treatment effects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S5(R3) Revision on Detection of Toxicity to Reproduction for Human Pharmaceuticals

Ronald Wange, PhD
FDA Topic Lead for ICH S5(R3)
Associate Director for Pharm/Tox (Acting)
Office of New Drugs, CDER, FDA

Outline

- Timeline
- Purpose of the Guidance
- Objectives of Guidance Revision
- Public Comments
- Summary

Timeline

- Concept Paper endorsed (Spring 2015)
- Step 2 draft endorsed (Spring 2017)
- Federal Register Notice published (13 Nov 2017)
- FDA public comment period closed (12 Feb 2018)
- FDA collation of public comments (completed)
- FDA Internal discussion and proposed responses (ongoing)
- Regional discussion of proposed responses (April-May 2018)
- Full EWG discussion of proposed responses (June 2018)
- Step 3 Signoff/Step 4 adoption of final guidance (Nov 2019)

Purpose of ICH S5 Guidance

- Provide harmonized guidance on approaches that can be used for assessing the reproductive and embryofetal development risk associated with exposure to a given (bio)pharmaceutical agent or vaccine.

Objectives of Revision (1)

- Align with other ICH guidances (e.g., M3(R2), S6(R1), S9)
- Establish alternative dose selection endpoints (beyond MTD)
  - for example, 25-fold AUC
- Emphasize the use of existing data
  - for example, pharmacological class
- Provide approaches to defer definitive DART studies
  - “enhanced” preliminary embryofetal development study
  - reduction in animal use due to attrition of clinical candidate compounds prior to Phase 3 testing

Objectives of Revision (2)

- Integrate testing strategies for assessing reproductive toxicity across treatment modalities (drugs, biologics & vaccines)
- Provide guidance on alternative assays:
  - Necessary performance criteria
  - Qualification for context of use
  - Scenarios where alternative assays could be appropriate
  - Integration in risk assessment
- Focus of EFD risk assessment on teratogenicity and embryo/fetal lethality
- Reduce unnecessary animal use

Objectives of Revision (3)

- The revised ICH S5 Guideline is intended to provide human safety assurance at least equivalent to that provided by current testing paradigms.

-from explanatory slides accompanying draft guideline on ICH website

Organizations Providing Comment

- Bristol-Myers Squibb (BMS)
- Shire
- Lori Dostal Consulting
- Gilead
- Aclairo
- The International Council on Animal Protection in Pharmaceutical Programs (ICAPPP)
- PhRMA
- GlaxoSmithKline (GSK)
- IQ Consortium

Comments

- More than 400 external comments
- Cover most aspects of the document

Overview of Comments (1)

- General support (from industry) for the idea of increased flexibility in approaches to DART assessment
- General consensus that the draft guidance is too long and poorly organized
- Draft guidance is not aligned with other ICH guidances
- Draft guidance is frequently unclear as to whether approaches being discussed are appropriate for small molecule drugs, biologics or both
- Discordant comments regarding the appropriate level of prominence that should be given to alternative assays vs. the current testing paradigm

Overview of Comments (2)

- Concern regarding how alternative assay drug concentrations can be related to in vivo exposures--proposal to relate to Cmax overly simplistic
  - How can risk assessment (rather than hazard ID) be conducted without such knowledge
- Imprecise usage of “hazard” and “risk” throughout
- Concern that certain concepts introduced in the draft guidance are not adequately supported with data
  - Suitability of enhanced pEFD to support EFD study deferral
  - Focus of risk assessment exclusively on TEFL

Overview of Comments (3)

- Concern that the proposed criteria for qualifying an alternative assay are overly prescriptive, with an unclear scientific basis, and outside of the scope of the guidance
- Discordant views regarding a standard of “qualification” of alternative assays for context of use, rather than applying a standard of “validation,” with public access to data supporting validation
- Discordant views expressed regarding the suitability of current in vitro assays for assessment of DART endpoints

Overview of Comments (4)

- Concern that the pathway for submission of alternative assay qualification dossiers to regulatory authorities is unclear, and is not harmonized
- Unclear how results from alternative assays can be meaningfully used in labeling to inform the doctor and patient of risk, or permit PLLR-compliant labeling
- Favor prospect of reduced animal use (assuming no reduction in rigor of human safety assessment)

Summary

- A large number of substantive comments have been received by FDA
- FDA is currently in the process of discussing the comments received, and how they should be addressed
- From the volume and scope of issues raised in the public comments, it should be anticipated that the guidance will require substantial revision prior to Step 4 signoff in November 2019


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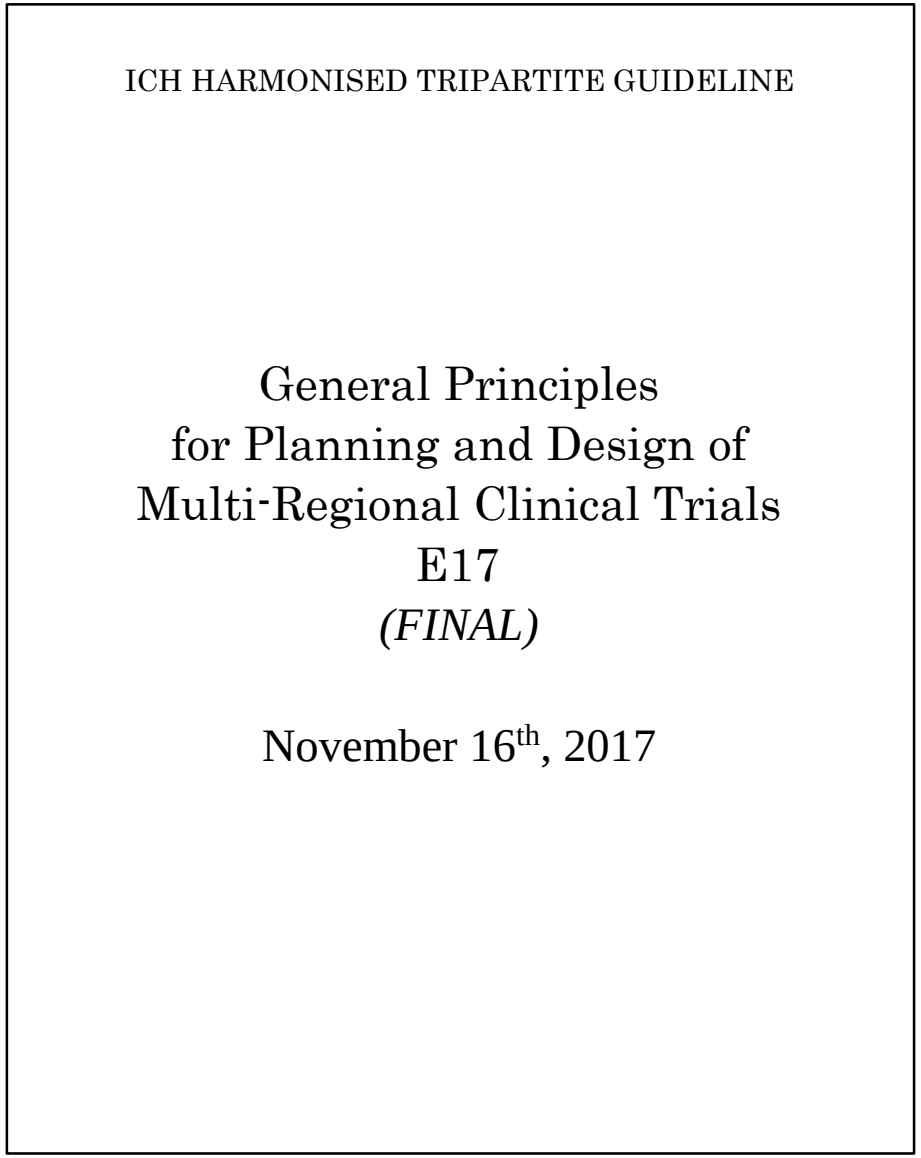
ICH E17

General Principles for Planning and Design of Multi-Regional Clinical Trials

ICH Public Meeting April 6 , 2018

Douglas Pratt MD

Associate Director for Medical Affairs
Division of Vaccines and Related Products Applications
Office of Vaccines Research and Review
CBER/FDA



ICH E17 guideline

- Started in June 2014
- Draft in June 2016
- Finalised in November 2017

FDA

Table of Contents

1.1 Objectives of the Guideline

- With the increasing globalisation of drug development, it has become important that data from multi-regional clinical trials (MRCTs) can be accepted by regulatory authorities across regions and countries as the primary source of evidence, to support marketing approval of drugs (medicinal products).

- The purpose of this guideline is to describe general principles for the planning and design of MRCTs with the aim of increasing the acceptability of MRCTs in global regulatory submissions.

- The guideline addresses strategic programme issues as well as issues that are specific to the planning and design of confirmatory MRCTs, and it should be used together with other ICH guidelines, including E5, E6, E8, E9, E10, and E18.

FDA

1.3 Scope of the Guideline

- MRCT is defined as a clinical trial conducted in more than one region under a single protocol. In this context, a region may refer to a geographical region, country or regulatory region (see Section 3. Glossary).
- The primary focus of this guideline is on MRCTs designed to provide data that will be submitted to multiple regulatory authorities for drug approval (including approval of additional indications, new formulations and new dosing regimens) and for studies conducted to satisfy post-marketing requirements.
- Certain aspects of this guideline may also be relevant to studies conducted early in clinical development or in later phases. The present guideline mainly covers drugs, including biological products, although some sections may not be applicable to all development programmes (e.g., pharmacokinetics (PK) not used for preventive vaccine dose-finding).

FDA

The Value of MRCTs in Drug Development

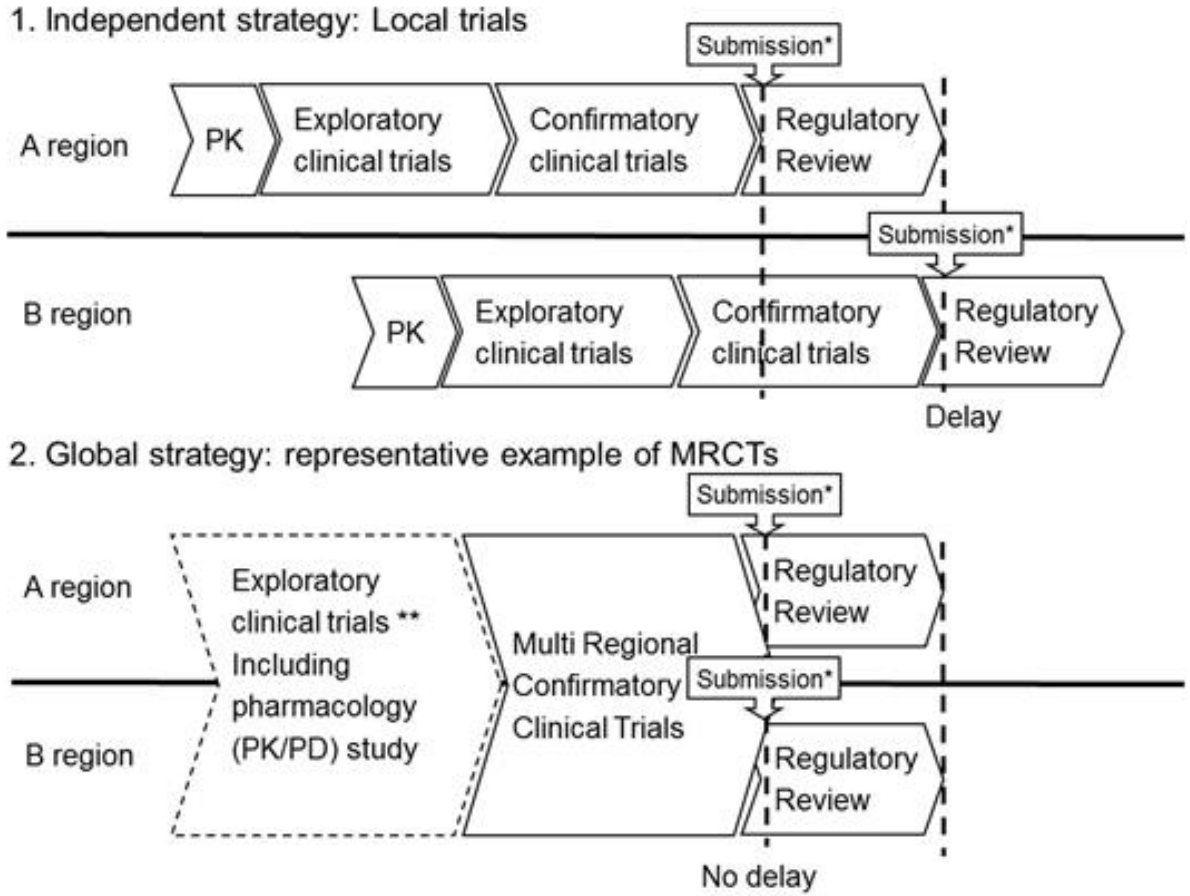


Figure 1. Illustrations of clinical drug development workflow across regions for drug submission and regulatory review in independent and global strategies

*: Marketing Authorization Application/New Drug Application

**: Could be parallel single region trials or MRCTs

FDA

1.4 Basic Principles

1.4 Basic Principles (1)

1. Strategic use of MRCTs in drug development programs can increase efficiency of drug development. MRCTs may enable simultaneous submission of marketing authorisation applications and support regulatory decision-making in multiple regions, allowing earlier access to new drugs worldwide.

2. The potential for regional differences to impact the interpretability of study results should be carefully considered. Intrinsic and extrinsic factors important to the drug development programme, should be identified early. The potential impact of these factors could be examined in the exploratory phases before the design of confirmatory MRCTs. Information about them should also be collected during the confirmatory trial for evaluation of their impact on treatment effects.

FDA

1.4 Basic Principles (2)

3. MRCTs are planned under the assumption that the treatment effect applies to the entire target population, particularly to the regions included in the trial. Strategic allocation of the sample size to regions allows an evaluation of the extent to which this assumption holds.

4. Pre-specified pooling of regions or subpopulations, based on established knowledge about similarities, may help provide flexibility in sample size allocation to regions, facilitate the assessment of consistency in treatment effects across regions, and support regulatory decision-making.

5. A single primary analysis approach for hypothesis testing and estimation of the overall treatment effect should be planned so that it will be acceptable to all concerned regulatory authorities. A structured exploration to examine the consistency of treatment effects across regions and subpopulations should be planned.

FDA

1.4 Basic Principles (3)

6. In light of diverse regional practices, ensuring high quality of study design and conduct in accordance with ICH E6 in all regions is of paramount importance to ensure the study results are interpretable. Careful attention to quality during trial planning, investigator training, and trial monitoring will help achieve consistently high trial quality required for a successful MRCT.

7. Efficient communication among sponsors and regulatory authorities is encouraged at the planning stage of MRCTs, with the goal of obtaining acceptance of a global approach to study design across the different regulatory regions.

FDA

Major points described in Section 2

2.2.2 Subject Selection

- In MRCTs, subject selection should be carefully considered to better understand and possibly mitigate potential sources of regional variability and their impact on trial results.
- Clear and specific inclusion and exclusion criteria, that are acceptable and can be applied across regions, should be included in the protocol.
- To harmonise subject selection, uniform classification and criteria for diagnosis of the disease, or definition of the at-risk population, should be implemented, such as the use of relevant guidelines for disease definitions.

FDA

2.2.3 Selection of Doses for Use in Confirmatory MRCTs

- It is important to execute well-planned early development programmes that include PK and/or PK-PD studies of applicable parameters, in order to identify regional differences which may impact dose selection
- The dose regimens in confirmatory MRCTs (based on data from studies mentioned above) should in principle be the same in all participating ethnic population
- If earlier trial data show a clear difference in dose-response and/or exposure-response relationships for an ethnic population, it may be appropriate to use a different dosing regimen, provided that the regimen is expected to produce similar therapeutic effects with an acceptable safety margin, and provided it is scientifically justified in the study protocol. Prospective careful planning of assessment strategies where different doses are used should be tailored to each case and described in the analysis plans.

FDA

2.2.4 Choice of Endpoints

- The primary endpoint should be relevant to the target population. In MRCTs, this relevance needs to be considered for all regions in the trial and with respect to the various drug, disease and population characteristics represented in those regions
- An ideal clinical trial endpoint is one that is clinically relevant, accepted in medical practice and sufficiently specific and sensitive to detect the anticipated effect of the treatment
- The primary endpoint, whether efficacy or safety, should satisfy these criteria, as well as being acceptable to all concerned regulatory authorities, to ensure that interpretation of the success or failure of the MRCT is consistent across regions and among regulatory authorities
- The primary endpoint of MRCTs should be one for which experience is already available in the participating regions.

FDA

2.2.6 Collecting and Handling of Efficacy and Safety Information

- Adherence to GCP is critical for any clinical trial to meet its stated objectives and is particularly important in an MRCT, because of the coordination required to conduct a trial in diverse geographic regions.
- Methods of collecting and handling efficacy and safety information should be standardised across participating regions.
- It is also important to provide standardised training for investigators and study personnel in each region before initiating the trial in that region to ensure that the trial objectives are met through standardised implementation of the study protocol.

FDA

2.2.8. Selection of Comparators

- The choice of control groups should be considered in the context of the available standard therapies, the adequacy of the evidence to support the chosen design, and ethical considerations.
- Comparators in MRCTs should in principle be the same in all participating regions.
- The justification (including safety considerations) for the use of an unapproved drug should therefore be described in the protocol based on scientific information, treatment guidelines and other relevant documents.

FDA

2.2.9. Handling Concomitant Medications

- In general, drugs used concomitantly with the investigational drug should be the same throughout the regions to the extent possible, but there may be some differences in the drugs and/or doses actually used due to variations in medical practices. This could be acceptable if not expected to substantially impact trial results.
- In circumstances where approved drugs are combined with an investigational drug, the same dosage regimen in all regions should generally be applied.
- If required by protocol, concomitant medications that are not approved in a region should have their use justified based on scientific information, treatment guidelines and other relevant documents.

FDA

Impacts of E17 guideline

- Earlier access to innovative therapies
  - Synchronize clinical drug development across different regions
- Avoid duplication
  - Reduce the need for region specific studies and bridging studies
- Promote international harmonization
  - A globally harmonized approach to drug development should be considered first
- Provide better evidence for drug approval in each region
  - Incorporate latest knowledge and experience from regions into one trial
- Develop an infrastructure for global drug development
  - Conducting high quality MRCTs is a valuable investment in modern drug development

FDA

3.0 Glossary

- **Consistency of treatment effect**: A lack of clinically relevant differences between treatment effects in different regions or subpopulations of an MRCT
- **Multi-Regional Clinical Trial, MRCT**: A clinical trial conducted in more than one region under a single protocol.
- **Region**: A geographical region, country or regulatory region
- **Regulatory Region**: A region comprised of countries for which a common set of regulatory requirements applies for drug approval (e.g., EU).
- **Pooled regions**: Pooling some geographical regions, countries or regulatory regions at the planning stage, if subjects in those regions are thought to be similar enough with respect to intrinsic and/or extrinsic factors relevant to the disease and/or drug under study.
- **Pooled subpopulations**: Pooling a subset of the subjects from a particular region with similarly defined subsets from other regions whose members share one or more intrinsic or extrinsic factors important for the drug development program at the planning stage. Pooled subpopulation is assumed as ethnicity-related subgroup particular important in the MRCT setting.

General Principles for Planning and Design of Multi-regional Clinical Trials (MRCTs) - ICH E17

Statistical Principles

Aloka Chakravarty, Ph.D.
Director (Acting)
Office of Biostatistics
CDER, FDA

Co-authors: Yoshi Uyama and William Wang

ICH Public Meeting April 6 2018

ICH E17 guideline

- Started in June 2014
- Draft in June 2016
- Finalized in November 2017

ICH HARMONISED TRIPARTITE GUIDELINE

General Principles
for Planning and Design of
Multi-Regional Clinical Trials
E17
(FINAL)

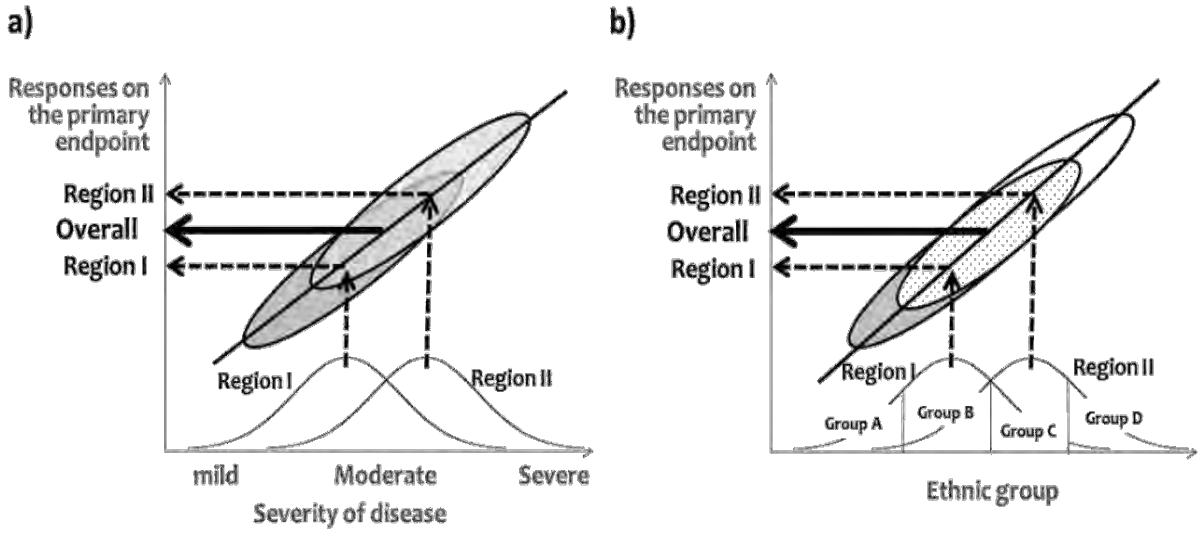
November 16th, 2017

E17 EWG, Geneva in November 2017

Major Statistical Principles Described in Section 2

2.2.1 Pre-consideration of Regional Variability and its Potential Impact on Efficacy and Safety

- At the planning stage, regional variability, the extent to which it can be explained by intrinsic and extrinsic factors, and its potential to influence the study results, should be carefully considered in determining the role MRCTs can play in the drug development strategy.
- The intrinsic and extrinsic factors important to the drug development program should be identified during the planning stage of an MRCT- disease severity (Figure a) or ethnicity (Figure b) may manifest as regional differences in treatment response.



2.2.4 Choice of Endpoints

- The primary endpoint should be relevant to the target population
  - this relevance needs to be considered for all regions in the trial and with respect to the various drug, disease and population characteristics represented in those regions
- An ideal clinical trial endpoint is one that is clinically relevant, accepted in medical practice (e.g., by regulatory guidance or professional society guidelines) and sufficiently sensitive and specific to detect the anticipated effect of the treatment
- The primary endpoint should be acceptable to all concerned regulatory authorities
  - ensures that interpretation of the success or failure of the MRCT is consistent across regions and among regulatory authorities
- The primary endpoint of MRCTs should be one for which experience is already available in the participating regions.

2.2.5 Sample Size Planning

- The key consideration for sample size planning, is ensuring sufficient sample size to be able to evaluate the overall treatment effect
  - under the assumption that the treatment effect applies to the entire target population, particularly to the regions included in the trial.
- Two additional factors are particularly important in the MRCT setting
  - the size of the treatment effect that is considered clinically relevant to all regions in the trial
  - the expected variability of the primary outcome variables based on combining data across regions.

2.2.5 Sample Size Planning

- The MRCT should be planned to include an evaluation of the consistency of treatment effects among regions,
  - consistency is defined as a lack of clinically relevant differences.
- If clinically relevant differences among regions are observed, then the MRCT provides a unique opportunity for additional learning about the factors that may explain these differences.
- Regional allocation should have a scientific basis (rather than arbitrary targets)
  - should support the evaluation of consistency
  - should provide the information needed to support regulatory decisions

2.2.5 Sample Size Planning
Pooled Region and Pooled Subpopulation

- Science based strategic pooling can bring efficiency and knowledge to enable regulatory decision making

Pooled Region	• Pooling subjects across geographical regions, countries or regulatory regions based on a commonality of extrinsic and/or intrinsic factors (e.g., North America, EU+UK, Asia tripartite, regions with tropical weather)
Pooled Subpopulation	• Pooling subsets of the subjects across geographical regions and regulatory jurisdictions, who share one or more key intrinsic or extrinsic factors (e.g., Caucasian in EU& US, patients of Asian origin (e.g. ISEL trial), Biomarker + (e.g. EGFR+))

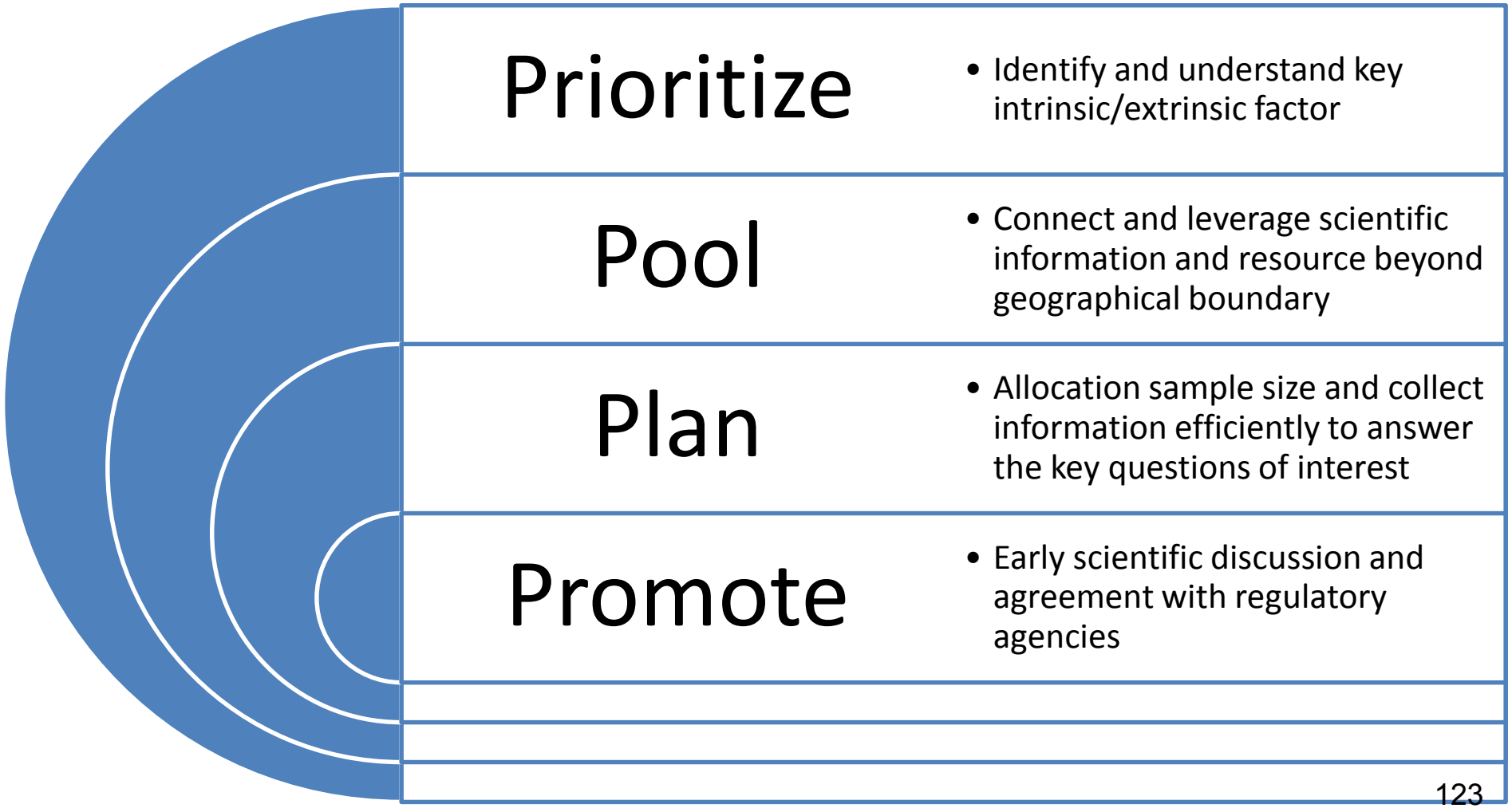
2.2.5 Sample Size Planning

Pooled Regions and Subpopulations

- Pre-specified pooling of regions or subpopulations may help provide flexibility in sample size allocation to regions, facilitate the assessment of consistency in treatment effects across regions, and support regulatory decision-making.
- The pooling strategy should be justified based on the distribution of the intrinsic and extrinsic factors known to affect the treatment response, and the disease under investigation and similarity of those factors across regions.
  - For example, pooling Canada and the United States into a North American region is often justified because of similar medical practices and similar use of concomitant medications.
- Pooling strategies should be specified in the study protocol and statistical analysis plan, if applicable.

Value of Pooled Region and Pooled Subpopulation Concepts

- Not just analysis concepts, important as design concepts



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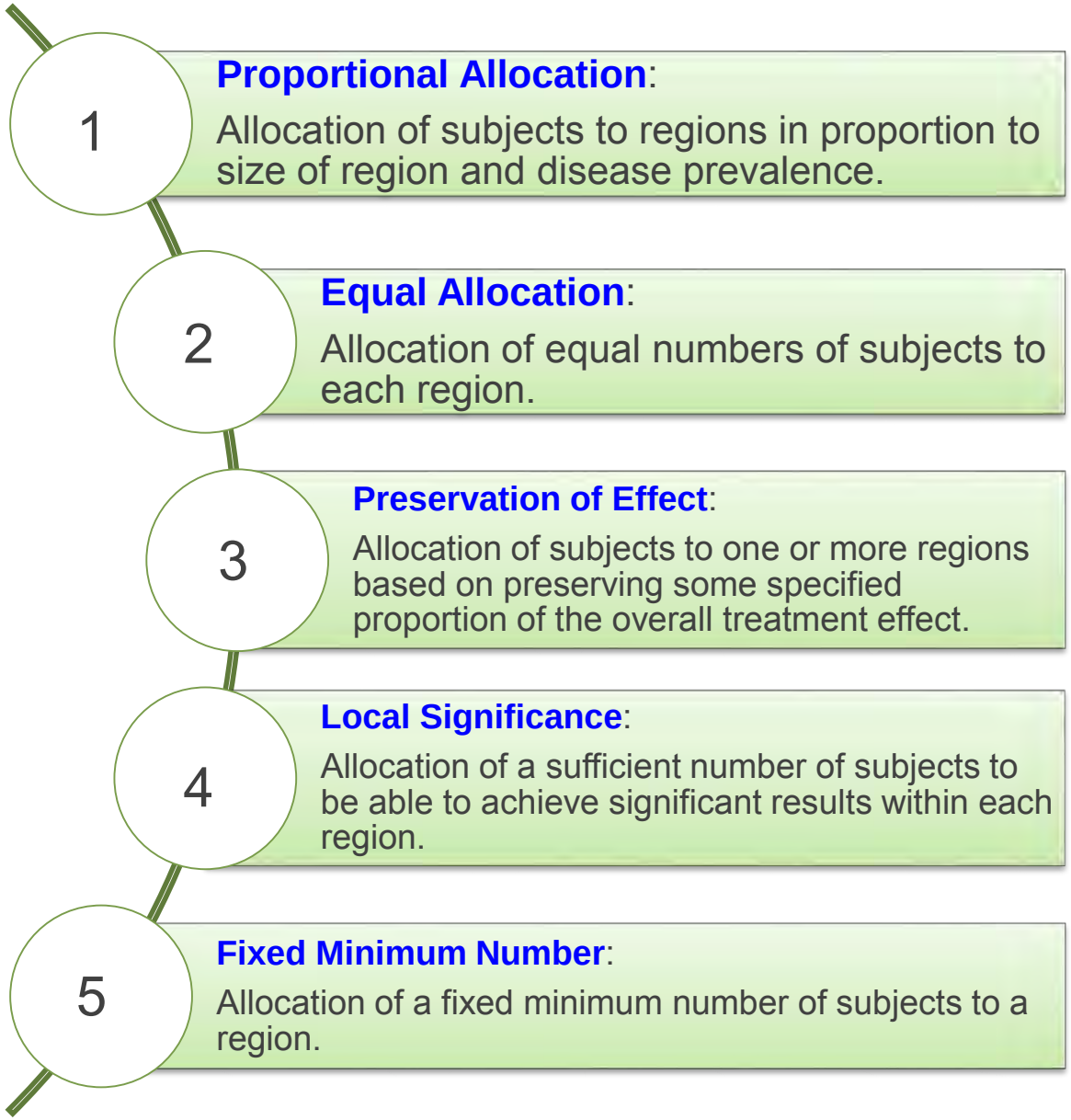
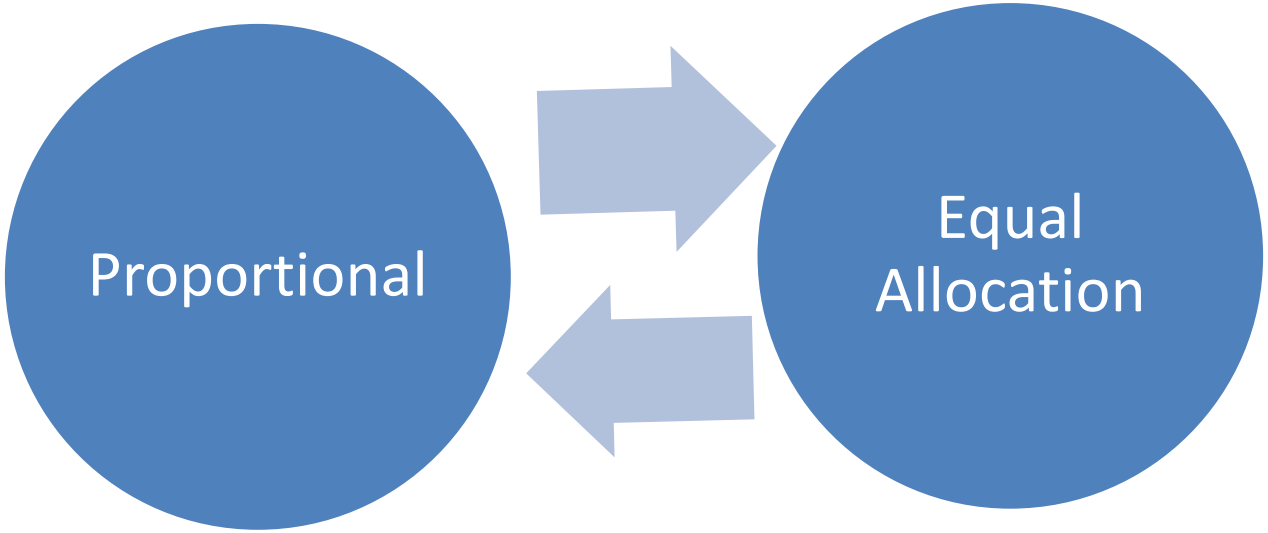


Five examples for sample size allocation to region

- A balance between #1 and #2 is recommended to ensure that recruitment is feasible and able to be completed in a timely fashion, but also to provide sufficient information to evaluate the drug in its regional context.

Sample Size Allocation to Region (cont.)

A balanced approach is recommended



- Caveat:
  - Preservation is not practical if many regions have this requirement.
  - Local significance of regional treatment effects is not practical, as this strategy may inflate the total sample size
  - A fixed minimum sample size for regions is not recommended, if there is no scientific justification for the minimum.

Key Statistical Considerations: Primary Analyses

- The analysis strategy should be planned to enable the qualitative and/or quantitative evaluation of benefit/risk across regions or important subpopulations represented in the MRCT

- If randomization is stratified by region, the primary analysis should adjust for regions, using appropriate statistical methods

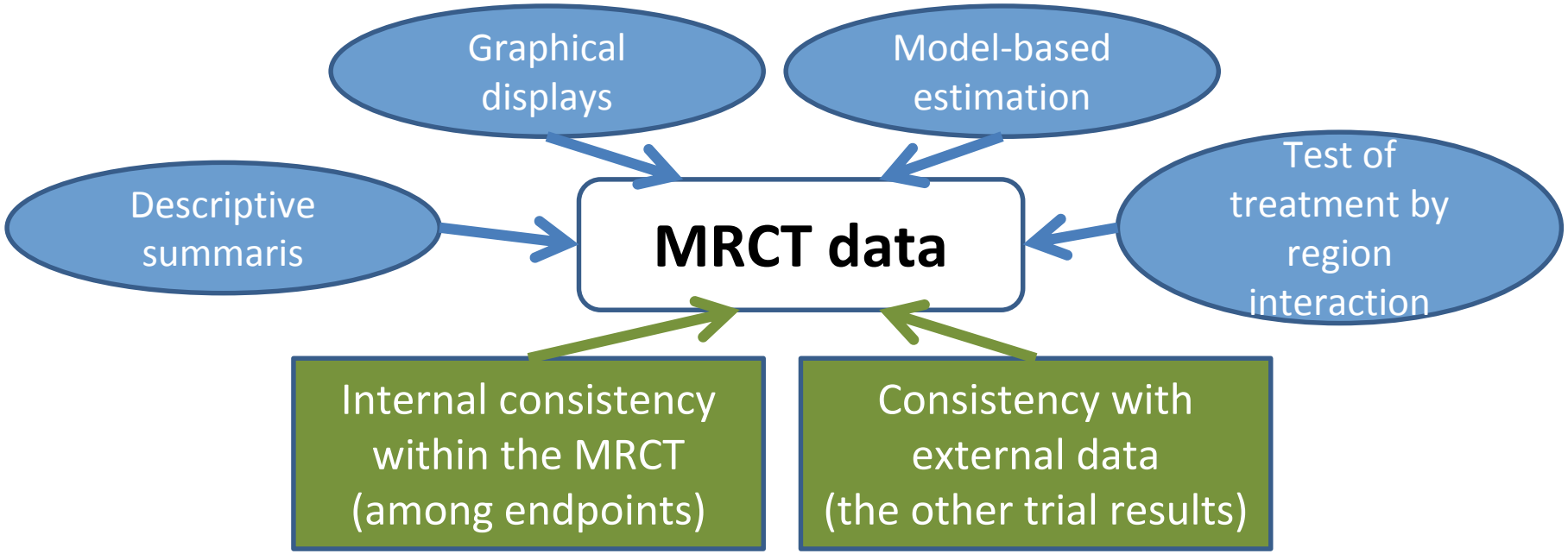
- If some regions were pooled based on intrinsic and/or extrinsic factors, or if pooled subpopulations were defined for stratification purposes during trial planning, then this pooling should be reflected in the analysis

2.2.7. Statistical Analysis Planning

- The analysis strategy should be planned to enable the qualitative and/or quantitative evaluation of benefit/risk across regions or important subpopulations represented in the MRCT.
- In planning an MRCT, the primary analysis strategy should carefully consider
  - the target population
  - the endpoints/variables of primary interest
  - the relevant intrinsic and extrinsic factors in the multi-regional, multi-subpopulation context
  - the population-level summary of data required to describe the treatment effect.
- For most MRCTs, the primary analysis will correspond to a test of the hypothesis about the treatment effect and the estimation of that effect, considering data from all regions and subpopulations included in the trial.

2.2.7. Statistical Analysis Planning

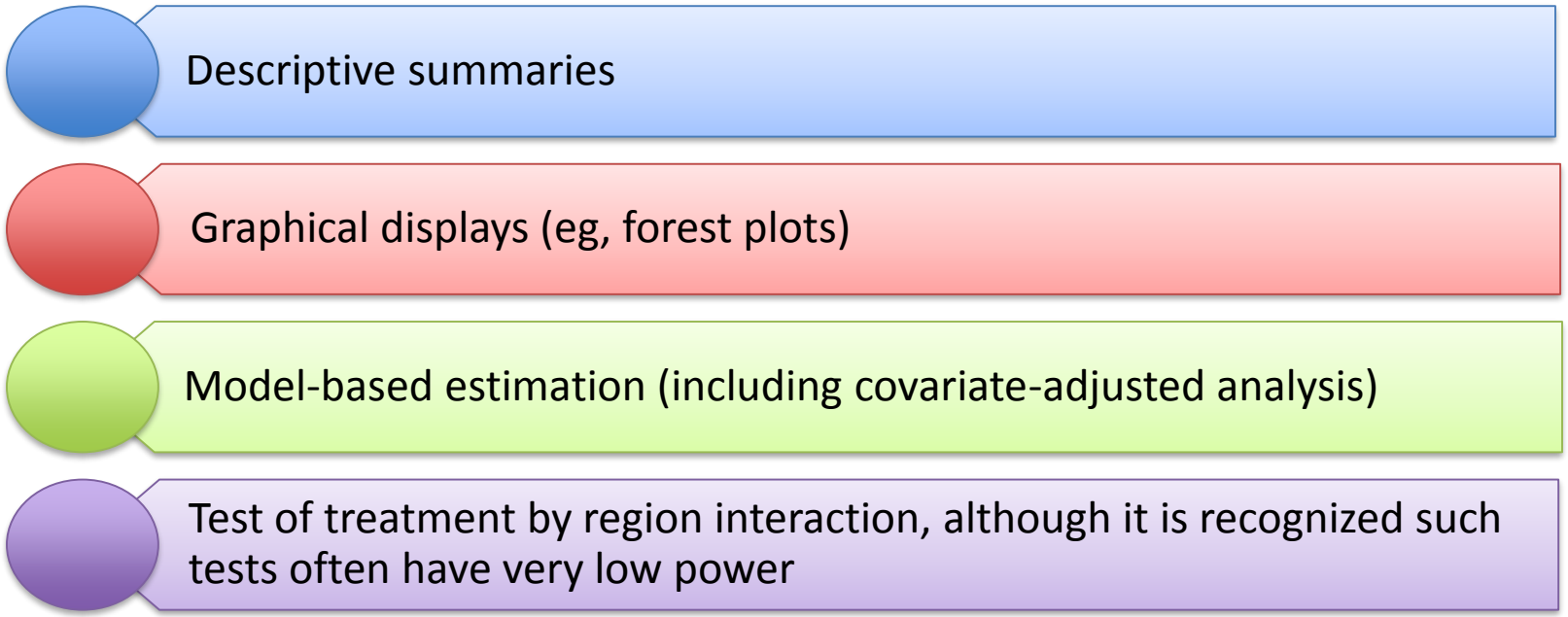
The statistical analysis strategy should include the evaluation of the consistency of treatment effects across regions and subpopulations.



The evaluation of regional consistency is not considered a confirmatory exercise but rather a gateway for further exploration

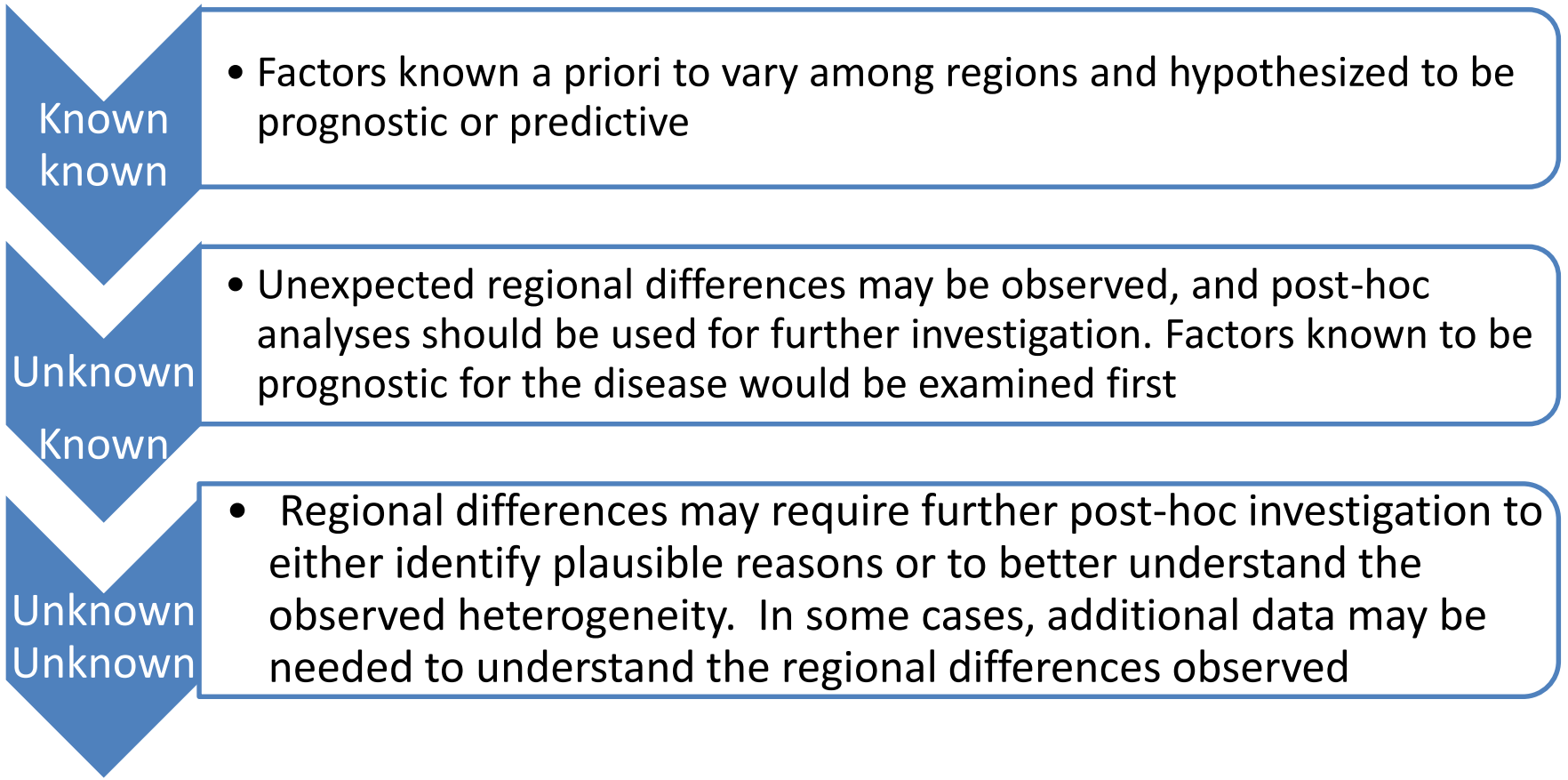
Examination of Regional Consistency

- The statistical analysis plan should include strategy for evaluating consistency of treatment effects across regions
- Various analytical approaches, possibly used in combination, include:



Examination of Regional Consistency (cont.)

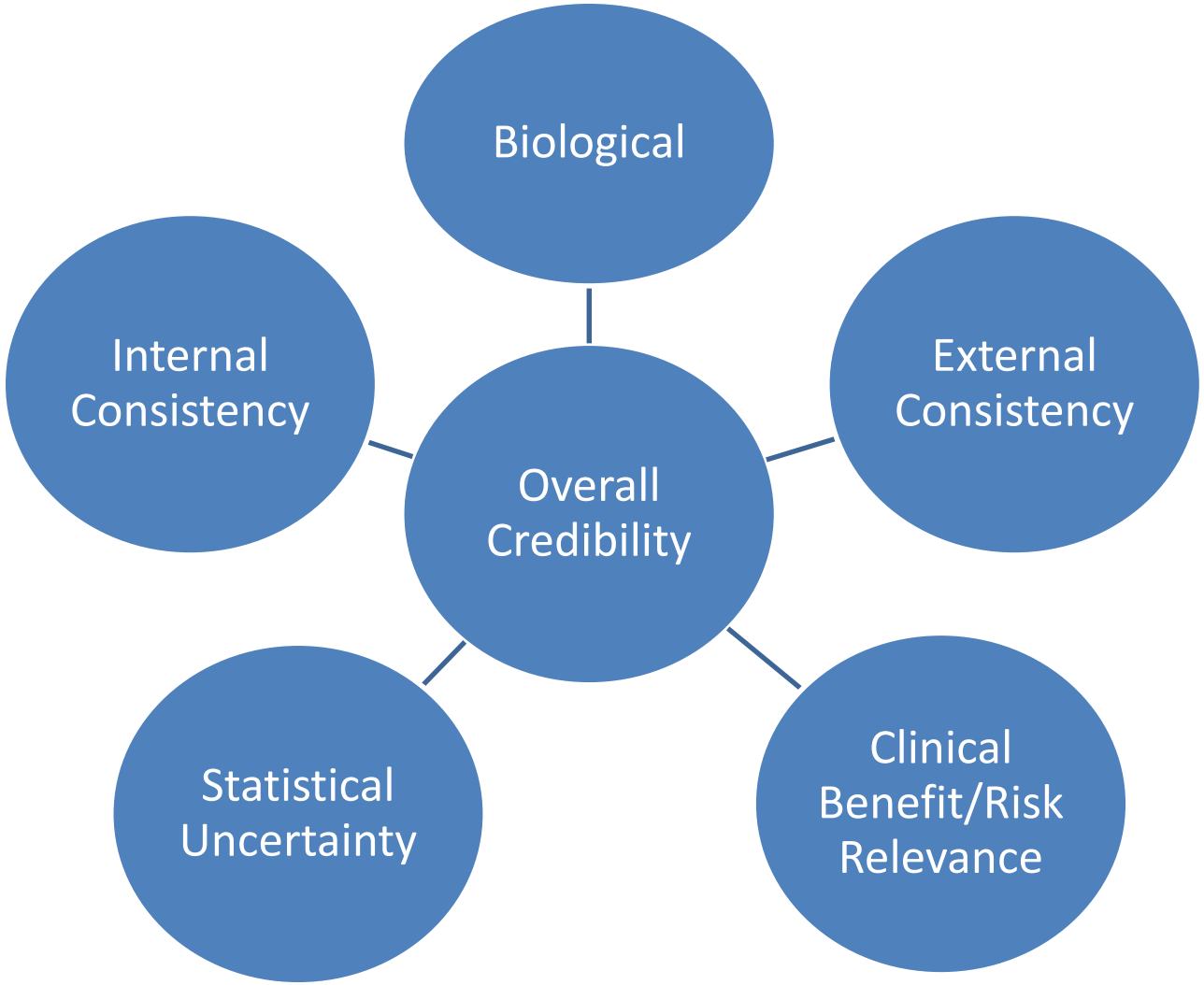
A structured exploration of regional differences should be planned



These eventualities should be carefully considered at the planning stage

Examination of Regional Consistency (cont.)

A structured exploration of regional differences should be planned



Impacts of E17 guideline

- Earlier access to innovative therapies
  - Synchronize clinical drug development across different regions
- Avoid duplication
  - Reduce the need for region specific studies and bridging studies
- Promote international harmonization
  - A globally harmonized approach to drug development should be considered first
- Provide better evidences for drug approval in each region
  - Incorporate latest knowledge and experience from regions into one trial
- Develop an infrastructure for global drug development
  - Conducting high quality MRCTs is a valuable investment in modern drug development

ICH E17 Future Work Plan
(Based on discussion at the Geneva Meeting)

- Form an E17 Implementation Working Group (IWG)
- Training materials describing practical cases for which E17 guideline apply will facilitate the understanding of contents and promote harmonized implementation of this guideline
- In the process of finalization of the training materials, the necessity of formal Q&As will be discussed.

E11(R1): ADDENDUM TO ICH E11 (CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION):

Lynne P. Yao, M.D.
Director, Division of Pediatric and Maternal Health
US FDA
April 6, 2018

Pediatric Drug Development

- Children first described as the therapeutic orphan in 1963 by Harry Shirkey, M.D.
- “By an odd twist of fate, infants and children are becoming therapeutic or pharmaceutical orphans.” Conference of Professional and Scientific Societies, Commission on Drug Safety. 1963.
- Principles Stated in Original ICH E11 Guideline:
  - Pediatric patients should have access to products that have been appropriately evaluated
  - Product development programs should include pediatric studies when pediatric use is anticipated

U.S. Pediatric Drug Development Legislation

- Best Pharmaceuticals for Children Act (BPCA)
  - Section 505A of the Federal Food, Drug , and Cosmetic Act
  - Provides a financial incentive to companies to voluntarily conduct pediatric studies
- Pediatric Research Equity Act (PREA)
  - Section 505B of the Federal Food, Drug , and Cosmetic Act
  - Requires companies to assess safety and effectiveness of certain products in pediatric patients
  - Applies to any product application for new indication, new active ingredient, new dosage form, new dosing regimen, or new route of administration

Canadian Pediatric Drug Legislation

- Health Canada has incentive provision for pediatric studies
  - Six month extension of data protection under Food and Drug Regulations
  - No specific requirements to conduct pediatric studies under current Food and Drug Regulations
  - No PIP/PSP equivalent in Canada
- Considering its stewardship role in both protecting Canadians and facilitating the provision of products vital to their health and well-being, Health Canada recognizes the importance of developing safe and effective medicines specifically for children
- Health Canada supports international harmonization efforts aimed at improving drug development for children and facilitating the conduct of studies that will permit appropriate labelling and use of medicinal products in the pediatric population
- Applying clinically and scientifically sound methodologies to the conduct of studies is expected to provide the evidence necessary to ensure that this important patient group has access to the full benefits of therapies available to adults

European Union Pediatric Drug Development Legislation

- Pediatric Regulation entered into force in 2007
  - (EC No 1901/2006)
  - Pediatric development obligatory in EU for new products, new indications, new routes of administration or new pharmaceutical forms protected by a Supplementary Protection Certificate (SPC) or a patent that qualifies
  - Fulfillment of requirements qualifies the product for incentive under this regulation

Global Pediatric Product Development

- Advances in understanding of pediatric product development
  - Advancements in scientific and clinical knowledge of pediatric diseases and therapeutics
  - Increased understanding in design and conduct of pediatric clinical trials
  - Changes in regulatory requirements for pediatric product development
  - Better understanding of complexities related to pediatric product development

- **The purpose of this addendum is to complement and provide clarification and current regulatory perspective on topics in pediatric drug development**

ICH E11 Expert Working Group (EWG)

- Representatives from Global Regulatory Authorities and Industry
  - FDA, EMA, PMDA, HC, FPIA, PhRMA, JPMA, WHO, Swiss Medic, ANVISA, EFTA, TGA
- To Step 2:
  - Joanne Palmisano, M.D., Boehringer Ingelheim, Rapporteur
  - Masakazu Hirata, M.D., MHLW/PMDA, Regulatory Chair
- After Step 2:
  - Masakazu Hirata, M.D., MHLW/PMDA, Rapporteur
  - Lynne Yao, M.D., FDA, Regulatory Chair

ICH E11 Addendum-Consensus Topics

- Scope and Objectives of the Addendum
- Ethical Considerations
- Age Classification and Pediatric Subgroups, including Neonates
- Commonality of Scientific Approach for Pediatric Drug Development Programs
- Approaches to Optimize Pediatric Drug Development
- Use of Existing Data in Pediatric Drug Development
- Use of Extrapolation in Pediatric Drug Development
- Use of Modeling & Simulation in Pediatric Drug Development
- Practicalities in the Design and Execution of Pediatric Clinical Trials
- Pediatric Formulations

Ethical Issues and Age Classification

- Ethical issues related to conduct of research
  - Children should not be enrolled in a clinical study unless necessary to achieve an important pediatric public health need
  - Fundamental principles of informed consent and assent
- Advances in understanding of complexities of clinical trial design
  - Regulatory definitions of “age classifications” may vary according to region
  - Increased understanding that chronologic age may not always be the best biomarker to evaluate changes during development

Commonality of Scientific Approach

- Regulatory and statutory requirements differ across regions related to some aspects of pediatric product development
- Despite these differences, there is much commonality and convergence that exists
- Common scientific and clinical principles exist that are foundational to pediatric therapeutic development

Common scientific approach

- What is the medical need in one or more pediatric populations that the drug could address?
- Who are the appropriate pediatric populations or subgroups that could be considered?
- What are the key issues in the drug development program that need to be addressed based on the intended pediatric use of the drug?
- Based on the existing knowledge, including developmental physiology, disease pathophysiology, nonclinical data, data in adult or pediatric populations, or data from related compounds, what are the knowledge gaps that should be addressed to establish the safe and effective use of the drug?
- What specific nonclinical studies could be considered?
- What clinical studies and/or methodological approaches could be considered?
- What pediatric-specific clinical study design elements could be considered?
- What practical and operational issues should be considered?
- Are there different formulations/dosage forms or delivery devices that will be needed for specific pediatric subgroups, both to facilitate an optimal dose-finding strategy, and for treatment of pediatric patients in different subgroups?

Approaches to Optimize Pediatric Drug Development

- Use of Existing Data in Pediatric Drug Development
  - Use of Extrapolation in Pediatric Drug Development
  - Use of Modeling & Simulation in Pediatric Drug Development

Pediatric Extrapolation

- “Pediatric extrapolation” is defined as an approach to providing evidence in support of effective and safe use of drugs in the pediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric and reference (adult or other pediatric) population.
- Addendum provides an overview and question based framework development

Pediatric Extrapolation

- What evidence supports a common pathophysiology of disease, natural history, and similarity of the disease course between the reference and pediatric population(s)?
- What is the strength of the evidence of efficacy in the reference populations?
- Is there a biomarker or surrogate endpoint in the reference populations that is relevant in the pediatric population?
- What evidence supports a similar exposure-response between the reference and intended populations?
- What uncertainties and/or limitations do the existing data (e.g., clinical or historical data and published literature) have, and what uncertainties about the pediatric population remain?
- If uncertainties remain, what additional information should be generated (e.g., information from M&S, animal, adult, pediatric subgroup studies) in order to inform the acceptability of the extrapolation approach?

Use of Modeling & Simulation in Pediatric Drug Development

- Modeling and Simulation can help quantify available information and assist in defining the design of pediatric clinical studies and/or the dosing strategy
- The usefulness of M&S in pediatric drug development includes
  - Clinical trial simulation
  - Dose selection
  - Choice and optimization of study design, endpoint selection, and pediatric extrapolation
- Development of an acceptable model
  - Context of use of the model
  - Quality and the extent of the existing data
  - Assumptions made
- Important to refine the model as new information becomes available
- Important to assess the risks of the model in decision-making during drug development

Practicalities in the Design and Execution of Pediatric Clinical Trials

- Feasibility
  - Pediatric clinical trials generally have small number of eligible children for clinical research
  - Limited pediatric specific resources at research centers
  - Scarcity of dedicated pediatric trial networks
- Outcome assessments
  - Outcome assessments often differ based on age and developmental stage
  - Need standardized measurement, collection, analysis, and reporting of outcome assessments
- Long-term Clinical Aspects

Pediatric Formulations

- Optimize efficacy and reduce the risk for medication and dosing errors
  - Age-appropriate dosage forms
  - Ease of preparations and instructions for use for caregivers
  - Acceptability (e.g., palatability, tablet size), choice and Amount of excipients
  - Alternative delivery systems and appropriate packaging
- Special considerations related to Neonates

Summary

- Addendum represents significant advancement that accounts for increased knowledge and experience in pediatric therapeutic development since the first guideline was published
- Clearly a need to provide more detailed guidance regarding specific areas including
  - Pediatric Extrapolation
  - Modeling and Simulation
  - Pediatric Formulations
- Global regulatory and industry representatives on the EWG have worked diligently to develop the addendum
- Words are important!

Overview of Ongoing ICH Topics

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April 6, 2018

Topics for Discussion

Efficacy Topics:

- E19 Optimization of Safety Data Collection
- E8(R1) Revision on General Considerations for Clinical Trials
- E11A Pediatric Extrapolation
- E14/S7B Discussion Group on Clinical and non-Clinical Evaluation of QT/QTc Interval Prolongation

Multidisciplinary Topics:

- M9 Biopharmaceutics Classification System-based Biowaivers
- M10 Bioanalytical Method Validation

Safety Topics:

- S1(R1) Revision on Rodent Carcinogenicity Studies for Human Pharmaceuticals
- S5(R3) Revision on Detection of Toxicity to Reproduction for Human Pharmaceuticals
- S9 Q&A on Nonclinical Evaluation for Anticancer Pharmaceuticals
- S11 Nonclinical Safety Testing in Support of Development of Pediatric Medicines

Quality Topics:

- Q3C(R7) Impurities: Guideline for Residual Solvents
- Q3D(R1) Guideline on Elemental Impurities

E19 Optimization of Safety Data Collection

Perceived Problem:

- During later stage of drug development, common side effects are well-understood and documented, some of the data routinely collected in clinical studies provides limited additional knowledge
- Unnecessary data collection can be burdensome to patients and serve as a disincentive to participation in clinical research
- A more targeted approach to safety data collection may be more appropriate

Objective:

- Provide internationally harmonized guidance on when it is appropriate to use a targeted approach to safety data collection in some late-stage pre-marketing or post-marketing studies, and how such an approach would be implemented
- Decrease burden to patients and promote larger number of informative clinical studies to be carried out with greater efficiency

Timeline for Development:

- Guideline initiated in 2017
- Draft guideline anticipated November 2018
- Final guideline anticipated June 2020

E8(R1) Revision on General Considerations for Clinical Trials

Perceived Problem:

- ICH E8 General Considerations for Clinical Trials was adopted in 1997 and has not undergone revision since
- Over the years, clinical trial design and conduct have become more complex
- 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
- E8 includes a very high level description of trial objectives and design but it doesn't address design or planning considerations for data quality

Objective:

- Enhance the reliability of trial results through attention to trial quality:
  - Identify a basic set of critical-to-quality factors (e.g. eligibility criteria, masking, types of controls, outcome ascertainment, site feasibility, safety monitoring, statistical analysis, and investigational product handling and administration) 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 comprehensive guide to, or cross-referencing of, all other relevant ICH guidelines that inform the design, planning and conduct of clinical research, without reproducing the detailed material found in those guidelines

Timeline for Development:

- Guideline initiated in 2017
- Draft guideline anticipated November 2018
- Final guideline anticipated June 2020

E11A Pediatric Extrapolation

Perceived Problem:	Objective:	Timeline for Development:
• In many cases, there is a long gap (between 7-10 years) between the initial adult approval and the inclusion of pediatric-specific information in product labeling • The use of pediatric extrapolation has advanced substantially as an approach to improve the efficiency and success of pediatric drug development. However, there is variability in the interpretation and application of extrapolation across regulatory authorities.	• Harmonize methodologies and strategies to incorporate pediatric extrapolation into overall drug development plans • Improve the speed of access to new drugs for pediatric patients while limiting the number of children required for enrollment in clinical trails	• Guideline proposed by FDA and PhRMA and initiated in October 2017 • Draft guideline anticipated November 2020

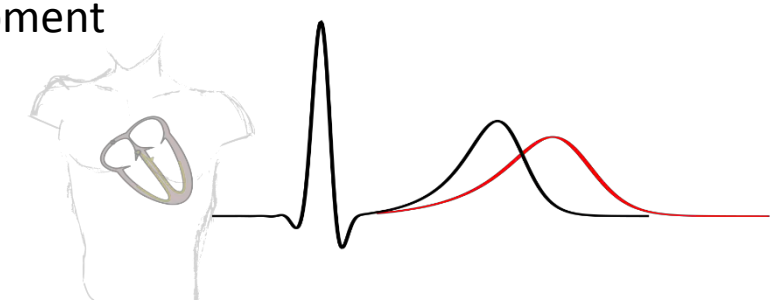
E14/S7B Discussion Group on Clinical and non-Clinical Evaluation of QT/QTc Interval Prolongation

Objective:

- The E14/S7B Discussion Group was created to assess advances in the science and methods related to the clinical assessment of QT prolongation and to continue its discussion of the Comprehensive in vitro Proarrhythmia Assessment (CiPA)
- The goal of the CiPA initiative is to develop a new in vitro paradigm for cardiac safety evaluations of new drugs that provides a more accurate and comprehensive mechanistic-based assessment of proarrhythmic potential
- The Assessment seeks to define drug effects on multiple human cardiac currents, characterize integrated electrical responses using in silico reconstructions of human ventricular electrophysiology, and verify effects on human stem-cell derived ventricular myocytes.
- The WG is currently looking at whether these new technologies can be applied with the current S7B and E14 frameworks
- The goal is to streamline clinical development for drugs that prolong the QT interval but are found to have low proarrhythmic risk and result in few products being dropped from development

Timeline for Development:

- Work initiated in 2015
- Recommendation for any revision or Q&A is anticipated by June 2018



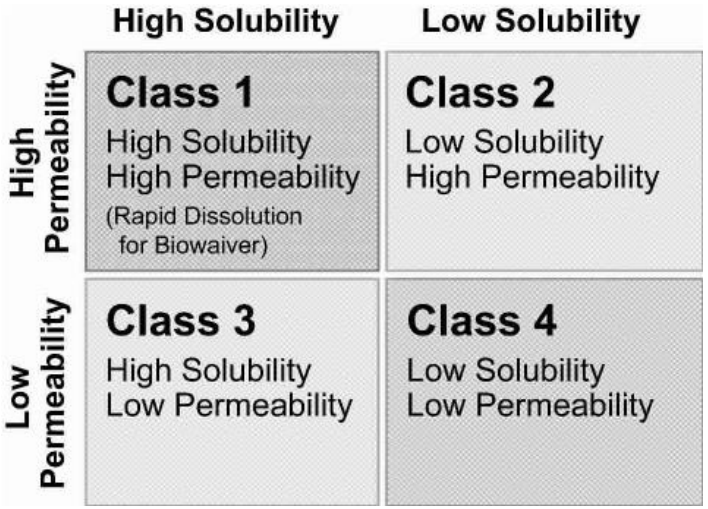
M9 Biopharmaceutics Classification System-based Biowaivers

Perceived Problem:

- The Biopharmaceutics Classification System (BCS) is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability
- BCS can be used to request waiver of bioequivalence study requirement
- Biopharmaceutics Classification System (BCS)-based biowaivers may be applicable to BCS Class I (high solubility – high permeability) and Class III (high solubility – low permeability) drugs; however, BCS-based biowaivers for these two classes are not recognized worldwide

Objective:

- Provide recommendations to support:
  - Biopharmaceutics classification of medicinal products
  - Waiver of bioequivalence studies
- Harmonize current regional guidelines/guidance and supporting streamlined global drug development
- Prevent unnecessary exposure of mostly healthy volunteers to medicinal products
- Reduce the costs and time for pharmaceutical development when in vivo studies to prove the biopharmaceutical quality of the medicinal product are unneeded



Timeline for Development:

- Guideline initiated in 2016
- Draft guideline anticipated June 2018
- Final guideline anticipated 2019

M10 Bioanalytical Method Validation

Perceived Problem:

- During pharmaceutical development, bioanalytical methods are used in non-clinical and clinical studies to describe the exposure to the drugs and their metabolites
- Bioanalytical methods must be well characterized to establish their validity and reliability
- Regional requirements for method validation and study sample analysis vary resulting in challenges in use of bioanalytical data in global drug development

Objective:

- Provide recommendations on the scientific regulatory requirements for bioanalysis conducted during the development of drugs of both chemical and biological origins
- Address issues on method validation by considering the characteristics of the analytical methods used in bioanalysis, e.g., chromatographic assay and ligand binding assay and study sample analysis by establishing requirements for ensuring the validity of each analytical run
- Establish the recommended documentation of validation and study sample analysis reports

Timeline for Development:

- Guideline initiation in 2016
- Draft guideline anticipated November 2018
- Final guideline anticipated June 2020

S1 Rodent Carcinogenicity Studies for Human Pharmaceuticals

Background:

- Prospective evaluation study is being conducted where sponsors voluntarily submit Carcinogenicity Assessment Documents (CADs) to regulatory authorities - announced in August 2012
- Carcinogenicity Assessment Documents (CADs) address carcinogenic potential of investigational pharmaceutical using WOE approach
- CADs accepted until Dec 2017
- Regional drug regulatory authorities review CADs and rationale for sponsors assessment
- As 2 year rat studies are completed, the results are submitted to the regulatory authorities – the study outcome is then checked against the WOE assessment in the respective CAD
- Results on accuracy of the prospective assessments and degree of agreement among regulatory parties will be used to determine whether a WOE approach can be used to characterize carcinogenicity risks without conducting a 2-year rat carcinogenicity study

Objective:

- This may result in a change to the current S1 Guideline on rodent carcinogenicity testing to introduce a more comprehensive and integrated approach to addressing the risk of human carcinogenicity of pharmaceuticals
- Expected to clarify and update, without compromising safety, the criteria for deciding whether the conduct of a two-year rodent carcinogenicity study of a given pharmaceutical would add value to this risk assessment
- Benefits may include:
  - Reduction in 2-year rat carcinogenicity studies where there is regulator and sponsor agreement that a product presents a low risk or likely risk of human carcinogenicity
  - Reduction in animal use

S5(R3) Revision of S5 Guideline on Detection of Toxicity to Reproduction for Human Pharmaceuticals

Perceived Problem:

- The S5(R2) Guideline on Reproductive Toxicity was finalized in 2000. Since then , experience has been gained:
  - With the testing of pharmaceuticals using the current and novel testing paradigms
  - Scientific, technological and regulatory knowledge has also significantly evolved
- Opportunities exist for modernizing testing paradigms to enhance human risk assessment, while also potentially reducing animal use
- There are areas in which the guideline could be revised or amended for greater clarity or usefulness as well as to align more fully with other guidelines, e.g. ICH M3(R2), ICH S6(R1) as well as ICH S9

Objective:

Harmonize guidance on:

- Appropriate multiples above human exposure and other endpoints that could be used for dose selection in reproductive toxicity studies
- Criteria for species selection taking into account relevance to humans
- Basic principles for possible regulatory acceptance of in vitro, ex vivo, and non-mammalian in vivo Embryo Fetal Development (EFD) assays
- Design of optional integrated testing strategies involving an in vivo mammalian EFD assessment and in vitro, ex vivo and non-mammalian in vivo EFD assays

Timeline for Development:

- Topic endorsed in March 2015
- Draft guideline was finalized in August 2017
- Final guideline anticipated November 2019

S9 Q&A on Nonclinical Evaluation for Anticancer Pharmaceuticals

Perceived Problem:

- Following implementation of the ICH S9 guidance a need was identified to provide clarity and more specificity around the scope and interpretation and implementation of the guideline

Objective:

- Clarify the scope of the document and other technical areas:
  - Clarify what studies are needed for antibody drug conjugate
  - When supportive care is acceptable
- Progress in 3Rs (replacement, reduction, and refinement)
- Facilitate a harmonized approach to the implementation of the guideline

Timeline for Development:

- Guideline initiated October 2014
- Draft guideline published June 2016
- Final guideline anticipated in 2018

S11 Nonclinical Safety Testing in Support of Development of Pediatric Medicines

Perceived Problem:

- Regional regulatory authorities differ in their recommendations on major aspects of the nonclinical development program to support pediatric clinical trials
- Defining a single nonclinical development plan that satisfies all regulatory regions is challenging and can result in unnecessary delay in delivering safe medicines to pediatric patients
- Variability also exists in the nonclinical plans proposed by companies

Objective:

- Provide clarity in determining the situations where non-clinical safety studies are important to support pediatric development
- Harmonize guidance to support:
  - Determination of whether prior animal data and human safety data are sufficient to avoid pediatric studies
  - Aspects of the design of juvenile animal studies, when appropriate
  - Describe studies needed to support a pediatric-only development (i.e. no indication in adults)

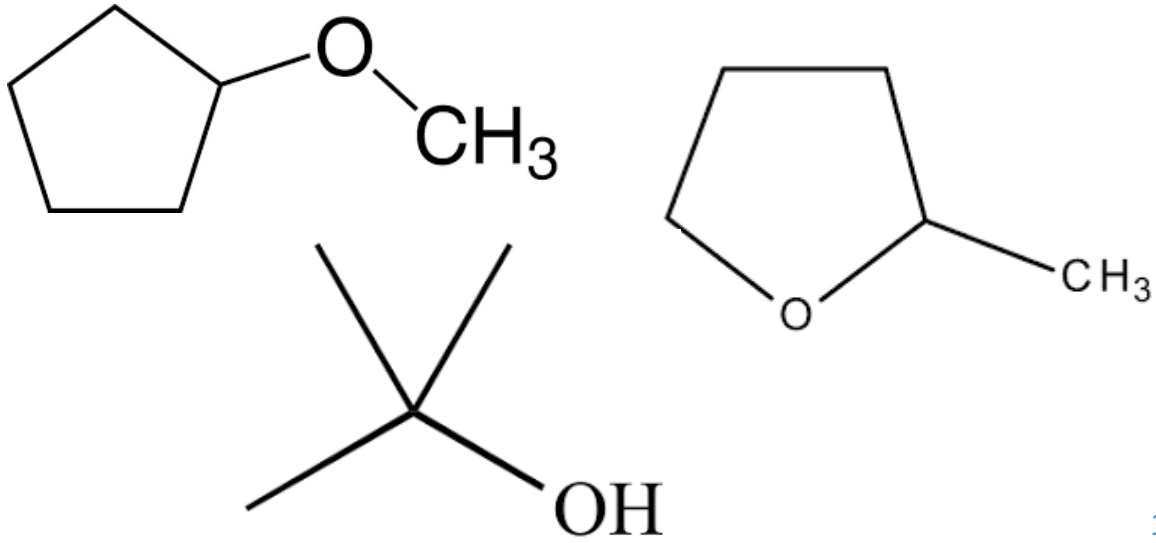
Timeline for Development:

- Guideline initiated in November 2014
- Draft guideline anticipated June 2018
- Final guideline anticipated June 2020

Q3C(R7) Impurities: Guideline for Residual Solvents

Objective:

- Q3C sets pharmaceutical limits for residual solvents in drug products called “Permitted daily exposure” (PDE) and recommends the use of less toxic solvents in the manufacture of drug substances and dosage forms
- Originally finalized in 1997, a maintenance procedure was developed for this guideline in 1999 to add PDEs for new solvents and to revise existing PDEs as new toxicological data for solvents become available
- In 2017, the ICH Assembly approved development of Permitted Daily Exposures for three new solvents:
  - 2-methyltetrahydrofuran
  - cyclo pentyl methyl ether
  - tert-butanol



Timeline for Development:

- Work on the three solvents began in early 2017
- Draft guideline anticipated June 2018

Q3D(R1) Guide for Elemental Impurities

Objective:

- Establish a global policy to limit metal impurities in drug products and ingredients
- Q3D establishes Permitted Daily Exposures (PDEs) for 24 Elemental Impurities for drugs administered by the oral, parenteral and inhalation routes of administration
- PDEs for new elemental impurities are added as new toxicological data becomes available
- Work is currently ongoing to include PDEs for the subcutaneous and transdermal route of administration

Timeline for Development:

- Guideline initiated in 2017
- Draft guideline anticipated December 2018

Timeline for Finalization of Final ICH Guidelines

Guideline	Current Status	Topic Endorsed by ICH Assembly	Step 1	Step 2	Step 3	Step 4
S9 IWG Q&As on Nonclinical Evaluation for Anticancer Pharmaceuticals	Step 3b: Comments	Oct 2014	Jun 2016	June 2016	Mar 2018	*June 2018*
E9(R1) EWG Addendum: Statistical Principles for Clinical Trials	Step 3a: Public Consultation	Oct 2014	June 2017	Aug 2017	*2019*	*2019*
S5(R3) EWG Revision on Detection of Toxicity to Reproduction for Human Pharmaceuticals	Step 3b: Comments	Mar 2015	June 2017	Aug 2017	*Nov 2019*	*Nov 2019*
Q12 EWG: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management	Step 3a: Public Consultation	Sept 2014	June 2017	Nov 2017		*Jun 2019*

E9(R1) - FDA deadline for comments – April 30th

Timeline for Finalization of Draft ICH Guidelines

Guideline	Current Status	Topic Endorsed by ICH Assembly	Step 1	Step 2	Step 3	Step 4
M9 EWG: Biopharmaceutics Classification System-based Biowaivers	Pre-Step 1	June 2016	*June 2018*	*June 2018*	*June 2019*	*June 2019*
Q3C(R7) Maintenance EWG: Maintenance of the Guideline for Residual Solvents	Pre-Step 1	Feb 2017	*June 2018*	*June 2018*	*2019*	*2019*
Q3D(R1) Maintenance EWG: Maintenance of the Guideline for Elemental Impurities	Pre-Step 1	June 2017	*June 2018*	*June 2018*	*2019*	*2019*
E8(R1) EWG Revision on General Considerations for Clinical Trials	Pre-Step 1	June 2017	*Nov 2018*	*Nov 2018*	*June 2020*	*June 2020*
S11 EWG: Nonclinical Safety Testing in Support of Development of Paediatric Medicines	Pre-Step 1	Nov 2014	*June 2018*	*June 2018*	*June 2020*	*June 2020*
E19 EWG Optimization of Safety Data Collection	Pre-Step 1	Sept 2016	*Nov 2018*	*Nov 2018*	*June 2020*	*June 2020*
M10 EWG: Bioanalytical Method Validation	Pre-Step 1	June 2016	*Nov 2018*	*Nov 2018*	*June 2020*	*June 2020*
E11A EWG Paediatric Extrapolation	Pre-Step 1	June 2017	*Nov 2020*	*Nov 2020*	*TBD*	*TBD*

U.S. FOOD & DRUG ADMINISTRATION

Questions?

U.S. FOOD & DRUG ADMINISTRATION

Public Comment

U.S. FOOD & DRUG ADMINISTRATION

Thank you for attending!

The public docket will remain open until April 30, 2018:
https://www.regulations.gov/document?D=FDA-2016-N-1112-0007

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