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Health Canada – US FDA ICH Public Meeting

November 4, 2019
Sir Frederick G. Banting Research Centre
Ottawa, Ontario, Canada

Health Canada Santé Canada

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

FDA U.S. FOOD & DRUG ADMINISTRATION

Agenda

1. Welcome and Opening Remarks
2. Overview of ICH
3. Update on MedDRA
4. Topics Recently Reaching Step 3 of ICH Process
5. Topics Soon to Reach Step 4 of the ICH Process
6. Overview of Ongoing ICH Topics
7. Overview of New ICH Topics & Strategic Discussion Groups
8. Public Comment Period
9. Closing Remarks

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Overview of ICH

Nick Orphanos, ICH Coordinator, Office of Policy and International Collaboration, Biologics and Genetic Therapies Directorate, Health Canada

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ICH (*International Council for Harmonisation of Technical Requirements 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

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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)

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The 5 Step ICH Guideline Development Process

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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

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ICH Reform - Establishment of Non-Profit Association

- The **new I**CH 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:
https://admin.ich.org/sites/default/files/2019-08/ArticlesOfAssociation_Approved_v3-0_2019_0606.pdf

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Goals of the ICH Reform

- Better prepare ICH to face the challenges of global pharmaceutical development and regulation
- Expand ICH beyond the previous 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

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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**

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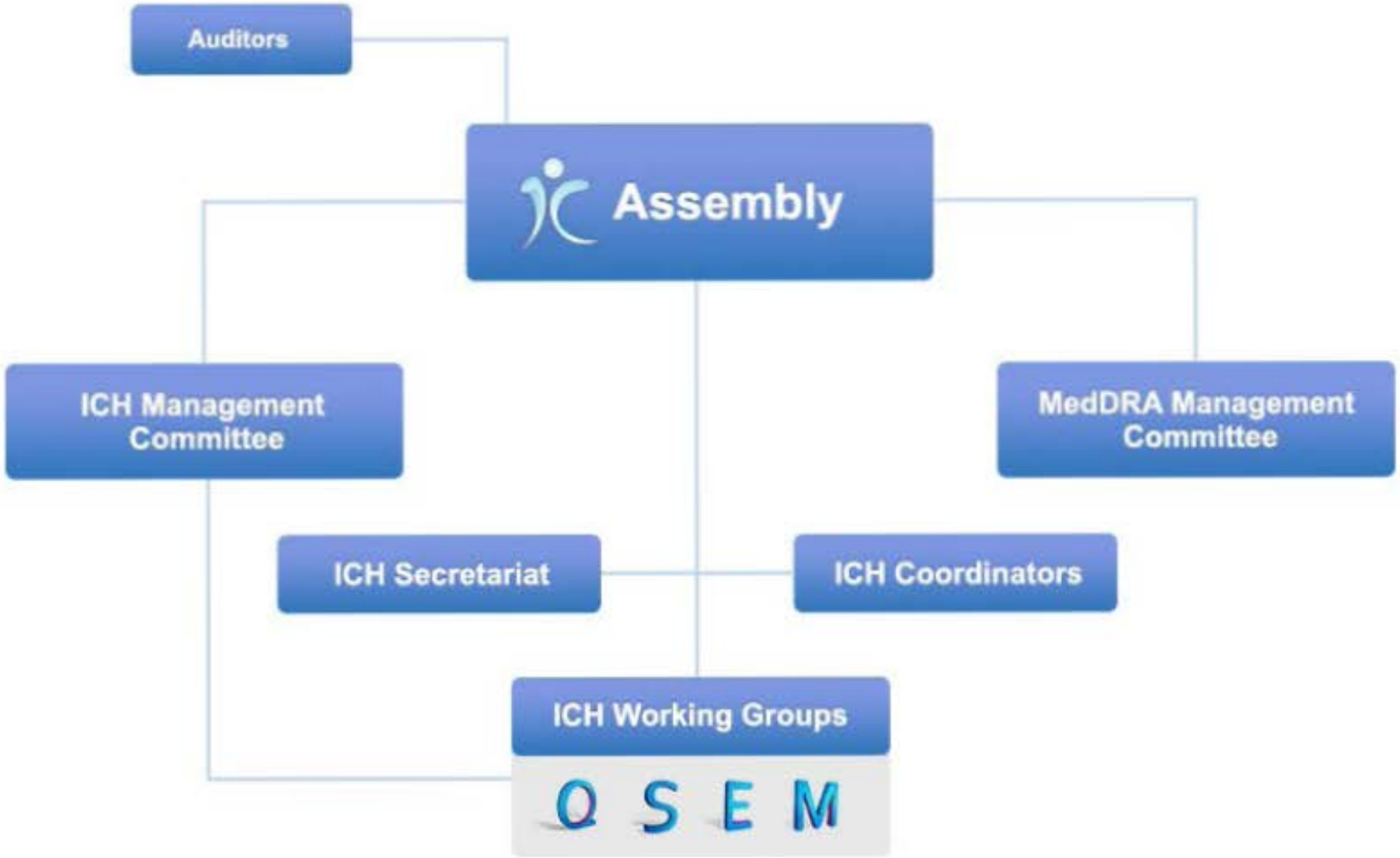
ICH Governance



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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

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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

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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

See ICH Articles of Association for more details:
https://admin.ich.org/sites/default/files/2019-08/ArticlesOfAssociation_Approved_v3-0_2019_0606.pdf

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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

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ICH Members and Observers *

Members

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

Founding Industry Members
- EFPIA
- JPMA
- PhRMA

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

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

Industry Members
- BIO
- IGBA
- WSMI

Observers

Standing Observers
- IFPMA
- WHO

Authorities
- ANMAT, Argentina
- CDSCO, India
- CECMED, Cuba
- COFEPRIS, Mexico
- CPED, Israel
- INVIMA, Columbia
- JFDA, Jordan
- MMDA, Moldova
- National Ctr, Kazakhstan
- NPRA, Malaysia
- NRA, Iran
- Roszdravnadzor, Russia
- SAHPRA, South Africa
- SCDMTE, Armenia
- SFDA, Saudi Arabia
- TGA, Australia
- TITCK, Turkey

Regional Harmonization Initiatives
- APEC
- ASEAN
- EAC
- GHC
- PANDRH
- SADC

Int'l Pharmaceutical Industry Organizations
- APIC

Int'l Orgs regulated by or affected by ICH guidelines
- BMGF
- CIOMS
- EDQM
- IPEC
- PIC/S
- USP

**As of June 2019*

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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

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Update on M1: MedDRA Terminology

Heather Morrison, Health Product Surveillance and Epidemiology Bureau, Marketed Health Products Directorate, Health Canada

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MedDRA – an ICH Product – 20th Anniversary

- MedDRA (Medical Dictionary for Regulatory Activities): Standardized medical terminology developed by ICH to facilitate sharing of regulatory information internationally for medical products used by humans – drugs, vaccines and drug-device combination products.
- MedDRA Management Committee: Appointed by ICH Assembly. Provides direction of MedDRA and oversees the activities of the MedDRA "Maintenance and Support Services Organization" (MSSO) to continuously enhance and meet the evolving needs of regulators and industry around the world
- 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 revenue
- ICH MedDRA Points to Consider Working Group: develops guides for harmonized MedDRA usage (coding and retrieval guidelines)

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MedDRA Updates

- Over 5,700 subscribers from over 125 countries using MedDRA which is available in 13 languages
- Russian translation became available as of version 22.0 released in March 2019
- Korean translation available as of version 22.1 released in September 2019.
- Bi-directional mapping between MedDRA and SNOMED CT continues with an initial subset of approximately 7000 terms to be completed by February 2020
- MedDRA Version 22.1 is available to download with the transition date of November 4, 2019.
- New Standardized MedDRA Query with Version 22.1 release – Sepsis. The addition of this modified the inclusion/exclusion criteria of the Agranulocytosis SMQ

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MedDRA Points to Consider Working Group

- Author and update with each version of MedDRA the following documents which assist with the consistent use of MedDRA
  - MedDRA Term Selection: Points to Consider
  - MedDRA Data Retrieval and Presentation: Points to Consider

- Medication errors section of the Points to Consider Companion Document will be released in Q1 of 2020

- No face-to-face meeting in Singapore in November 2018

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Topics Recently Reaching Step 3 of the ICH Process

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E8(R1): Revision to General Considerations for Clinical Trials

Dr. Carole Legare, Office of Clinical Trials, Therapeutic Products Directorate, Health Canada

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Acknowledgement

Thank you to Andreas Kirisits, EWG representative, EC, Europe, from whom most of these slides were borrowed

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Background

- ICH E8 was published in 1997 and has not been revised until now.
- ICH Reflection on “GCP Renovation”: Modernization of ICH E8 and Subsequent Renovation of ICH E6 (2017)
  - Followed expression of concerns from academic stakeholders following publication of ICH E6(R2)
  - Proposed revision of E8 as 1st step towards a broader GCP renovation
  - E8(R1) will inform the development of future guidelines

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E8 (R1) - Goals & Challenges

- Promote **fit-for-purpose clinical trials** by:
  - Introducing ‘Quality by Design’ concept and identifying ‘Critical to Quality’ (CtQ) factors
  - Upfront assessment of risks specific to development programme & study design
  - Proportionate management of these risks and respective controls
  - ➢ Facilitating a broad range of study designs and data sources

This is about doing things differently – change – don’t just add more to the status quo.

General Principles

Chapter 2

- Protection of Study Participants
  - Health risks and confidentiality
- Scientific Approach
  - On development programme & study level
  - Iterative research process
- Patient Voice
  - Patient involvement
  - To improve feasibility & promote commitment

Promoting high-quality studies

Chapter 3

- Introduces ‘Quality by Design’ concept to clinical research
- Suggests devising a specific set of factors critical to the quality of a given study (‘CtQ factors’)
- Outlines approach to identifying and managing risks to these factors

Critical to Quality Factors

Chapter 3

- Identifying attributes whose integrity is fundamental to study quality via:
  - Open dialogue, multiple stakeholders
  - Triage and focus on essential activities
  - Proactive implementation in protocol
  - Continuous review and risk-proportionate adaptations

➢ Flexibility instead of one-size-fits-all strategy

Drug development planning

Chapter 4

- Considerations at the development programme level
- From target product profiling through post-approval research
- Main focus on clinical studies, combining step-wise evidence building with flexibility in study planning
- Special populations and study feasibility addressed as additionally important issues

Types of clinical studies

Chapter 4

Study type	Example study objectives
Human pharmacology	• Initial Safety & Tolerability • Mechanism of action • Pharmacokinetics • Pharmacodynamics
Exploratory	• Dose selection • Population selection • Establish prognostic & predictive factors
Confirmatory	• Establish efficacy & safety profile in broadly representative population
Post-approval	• Broaden and refine understanding of efficacy & safety profile

Elements of study design

Chapter 5

- Key design aspects include:
  - Study population
  - Intervention
  - Control group
  - Response variable
  - Bias reduction
  - Statistical analysis

A variety of study designs may be realised to address specific research objectives.

Data sources

Chapter 5

- Broadly describes primary & secondary data generation/collection
- Acknowledges different data sources and respective methods and technologies used
- Highlights the importance of data standards

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Study conduct & Reporting

Chapter 6

- Study Conduct
  - Adequate protocol set-up, adherence and training
  - Data Management and (interim) access to study data
- Participant safety
  - Safety monitoring, data collection and stopping rules
  - Role of Data Monitoring Committees
- Study Reporting
  - Reference to ICH E3
  - Promotes transparency and public access to study data

Identifying CtQ factors

Chapter 7

- Example list of considerations for identifying CtQ factors at the planning stage
- Non-exhaustive and of varying importance depending on the specific situation
- Evident «usual suspects», but an adaptive approach to devising CtQ factors is the core message

'Living' Annexes 1-3

- Annex 1:
  - Plots research objectives and respective study examples along drug development process
- Annex 2:
  - ICH E-Guideline family
- Annex 3:
  - Cross-referencing CtQ factors to other ICH documents as applicable

An integrative look on E8 (R1)

General Principles

Quality by Design &
Critical to Quality Factors

Drug development planning

Study design, conduct & reporting

List of CtQ factor examples

Annex 1 – Study Types & Designs

Annex 2 & 3 – Cross-link to ICH GLs

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E8 (R1) offers…

- A principal guidance document:
  - promoting internationally agreed principles and practices of clinical research
  - focussed on identifying and safeguarding critical elements in study planning, conduct and reporting
  - applicable to a broad range of development programmes and study types
- An integrative platform for other ICH guidelines (‘ICH E0’)

Consultation

- Public consultation recently closed in all regions
- ICH had made a commitment to consult on E8 with those involved in clinical trials outside the pharmaceutical industry:
  - a public meeting was held in Washington DC on October 31, 2019
  - some Asian countries also held public workshops

Next steps

Discussion of consultation comments

The E8 WG will:

- review and exchange information on the comments they have received from the public consultation and meetings in the various regions
- consider what further revisions to the draft Guideline might be needed

Anticipating *Step 4* document: June 2020

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E19: Optimisation of Safety Data Collection

Dr. Nashwa Irfan, Marketed Pharmaceuticals and Medical Devices Bureau, Marketed Health Products Directorate, Health Canada

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Objective of Harmonisation Action

- This Guideline is intended to provide internationally harmonised guidance on an optimised approach to safety data collection in some late-stage pre-approval or post-approval studies when the safety profile of a drug is sufficiently characterised.

Perceived Problem

- Some of the safety data routinely collected in clinical studies may provide only limited additional knowledge.
- Ex. Cardiovascular, Diabetes, Renal Drug trials often enroll > 10,000 patients. Can involve class of drugs that have been extensively studied (i.e. angiotensin receptor blockers) and the risk profile is well characterized.
- Ex. Study for Adverse Events data in Cancer Clinical trials Supporting Supplemental Indications. They have looked at 8 studies and found a total of >136,000 concomitant medication records.
- Conclusion: none of concomitant medication records contributed to labeling changes.

Ref. Kaiser et al . 2010 J of Clinical Oncology

Goals

- Stop or reduce the collection of non-serious AEs or other safety data when the safety profile of a drug is well-characterised
- More efficient and cost effective drug clinical development by decreasing excessive and unnecessary data collection
- Decrease patient and investigator burden when participating in clinical trial (better patient retention)
- Facilitate global participation in clinical studies and ultimately stimulate research

General Principles

- Ensuring Patient Safety within Trials
  - This Guideline does not obviate the need for monitoring to protect individual patient welfare.

- Changes in Approach to Safety Data Collection
  - When an unexpected safety issue arises during the course of a trial, a change in the selective safety data collection approach may be warranted, e.g., denoting a new adverse event of special interest; reverting to full safety data collection.

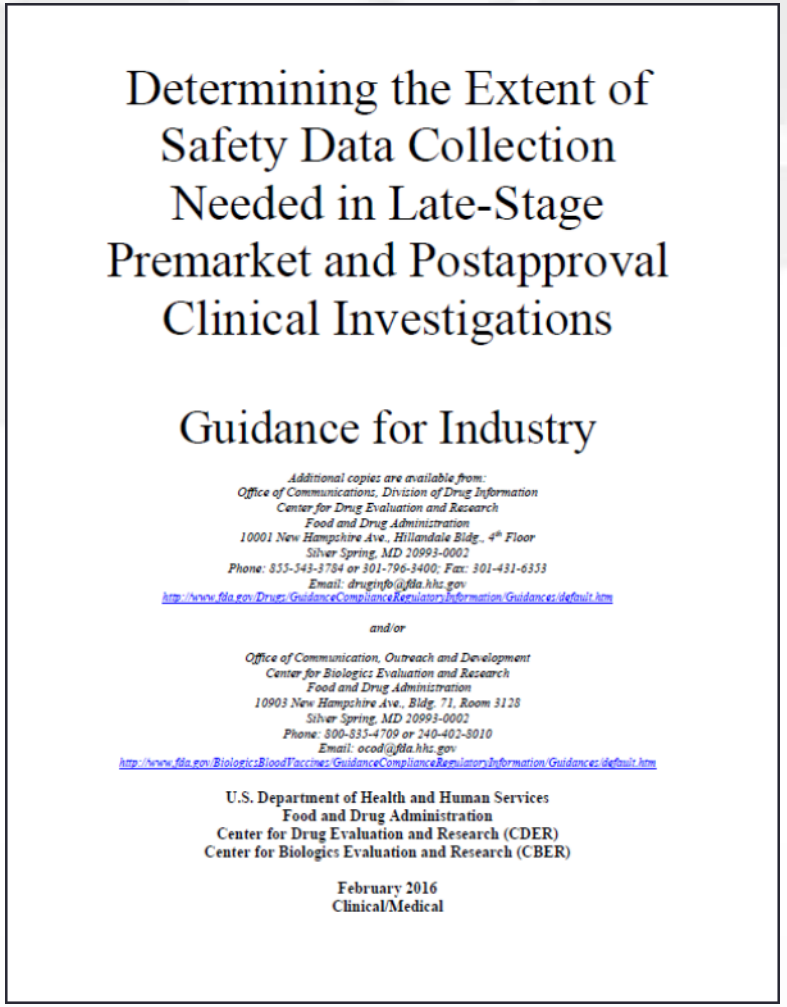
- Early Consultation with Regulatory Authorities
  - Studies must be conducted according to local and regional laws and regulatory requirements.
  - Early consultation with regulatory authorities is strongly recommended to determine if selective safety data collection acceptable.

International Situation

- The FDA currently provides guidance for situations where selected data collection may be sufficient

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm291158.pdf

- Need for International Harmonisation



Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

and/or

Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2016
Clinical/Medical

Types of safety data for which it may be appropriate to limit or stop collection

- Non-serious adverse events
- Routine laboratory tests
- Information on concomitant medications
- Physical examinations (including vital signs)
- Electrocardiograms

Types of Safety Data That Should be Collected

- Deaths
- Serious adverse events
- Significant adverse events that led to an intervention (i.e. withdrawal or dose reduction, addition of concomitant therapy)
- Marked laboratory abnormalities (other than the serious ones)
- Overdose
- Pregnancies
- Adverse events of special interest
- Laboratory data, vital signs, electrocardiograms of special interest (if defined)
- Baseline data

When May Selective Safety Data Collection Be Considered

Contributing factors that contribute to a determination that selective safety data collection would be appropriate include:

1. The medicinal product has received marketing authorisation from a regulatory authority for the indication under investigation
2. Availability of post-approval safety data and findings
3. The dose used in the previously conducted studies are comparable to the proposed study
4. The patient population from previously conducted studies is representative of subjects in the planned study

5. Exposure in previously conducted (or ongoing, if applicable) studies that contribute to the overall safety database, i.e., number exposure to drug, treatment duration

6. Consistency of the safety profile across previous studies

7. Characteristics of previous studies, e.g., study design; study conduct; adequacy of safety monitoring/safety data collection; availability of protocols; statistical analysis plan; and/or access to data

8. Knowledge of the mechanism of action of the medicinal product under study

9. Knowledge of the safety profile of approved drugs in the same pharmacologic class

Types of Studies Where Selective Safety Data Collection May be Considered

- New indications of approved drugs
- To study additional endpoints
- To study comparative effectiveness/efficacy
- Demonstration of superiority when non-inferiority has been demonstrated
- Characterisation of adverse events of special interest
- Late-stage premarketing outcome trial in a relatively large population

EXAMPLES OF METHODS OF IMPLEMENTATION

- Selective Safety Data Collection for All Patients in the Study
  - In the post-approval setting, this approach may be useful to address a specific safety concern.
  - In the pre-approval setting, a development programme may include several Phase 2 and 3 studies. In an additional study with MACE as the primary endpoint, selective safety data collection approach could be justified.

- Full Safety Data Collection for a Specific Subset(s) of the Population, Based on Patient Characteristics
  - If the patient population in previous studies included few patients over the age of 65, it could be of value to collect full data on this population.
  - Other specific subsets could include : geographic location, ethnicity, sex, baseline disease status (renal/hepatic impairment), CYP status, or genetics.

EXAMPLES OF METHODS OF IMPLEMENTATION

- Full Safety Data Collection in a Representative Subset of the Population, with Selective Safety Data Collection for Other Patients

- In some cases, efficacy studies must be quite large in order to be adequately powered, the number of patients planned for enrollment may greatly exceed the number needed to assess the non-serious AEs adequately. In this setting, comprehensive safety data could be collected for only a representative subset of patients.

- Full Safety Data Collection for the Initial Portion of the Study, with Selected Data Collection Thereafter
  - Full safety data are collected from baseline through some pre-determined interval of the study, with selective safety data collection thereafter. These approaches can be useful for studies designed to assess important long-term drug effects, where safety would be adequately characterised in the early part of the trial.

Timelines

- June 2017: Endorsement of Concept Paper
- November 2017 :1st Face-to Face meeting: First draft of the Guidance Document
- January 2019: Finalise technical document and step 1 ; adoption of the draft Guidance step 2a/b
- November 2019: Finalise Step 3 Regulatory Consultation and Discussion
- June 2020: Adoption of Step 4 Adoption of the ICH harmonised Guidance by the ICH Assembly

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Topics Soon to Reach Step 4 of the ICH Process

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E9(R1): Estimands and Sensitivity Analysis in Clinical Trials

Dr. Catherine Njue, Office of Biostatistics, Centre for Regulatory Excellence, Statistics and Trials, Biologics and Genetic Therapies Directorate, Health Canada

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Presentation outline

- Purpose and scope of the addendum to ICH E9
- A new structured framework
  - Aligning clinical trial planning, design, conduct, analysis and interpretation
- Estimands
  - Intercurrent events
  - Strategies to address intercurrent events
  - Estimand attributes
  - Construction of estimands
- Annexes to the guidance
  - clarifications on guideline recommendations

Presentation outline

- Impact on trial design and conduct
- Impact on trial analysis
  - Main estimation
  - Sensitivity analysis
  - Supplementary analysis
- Documenting estimands and sensitivity analysis

Purpose and scope of the addendum to ICH E9

- The benefits and risks of a treatment (medicine) for a given medical condition should be made available to all stakeholders in order to properly inform decision making
- Without such clarity, there is a concern that the reported “treatment effect” will be misunderstood
- Addendum presents a structured framework to strengthen the dialogue between:
  - disciplines involved in the formulation of clinical trial objectives, design, conduct, analysis and interpretation
  - sponsor and regulator regarding the treatment effect(s) of interest that a clinical trial should address

Purpose and scope of the addendum to ICH E9

- Precision in describing a treatment effect of interest is facilitated by constructing the “estimand”
- Estimand: A precise description of the treatment effect reflecting the clinical question posed by the trial objective
- Summarises at a population-level what the outcomes would be in the same patients under different treatment conditions being compared

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Purpose and scope of the addendum to ICH E9

- Clarity requires a thoughtful envisioning of “intercurrent events” such as discontinuation of assigned treatment, use of an additional or alternative treatment and terminal events such as death
- Intercurrent Events: Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest
- It is necessary to address intercurrent events when describing the clinical question of interest in order to precisely define the treatment effect that is to be estimated

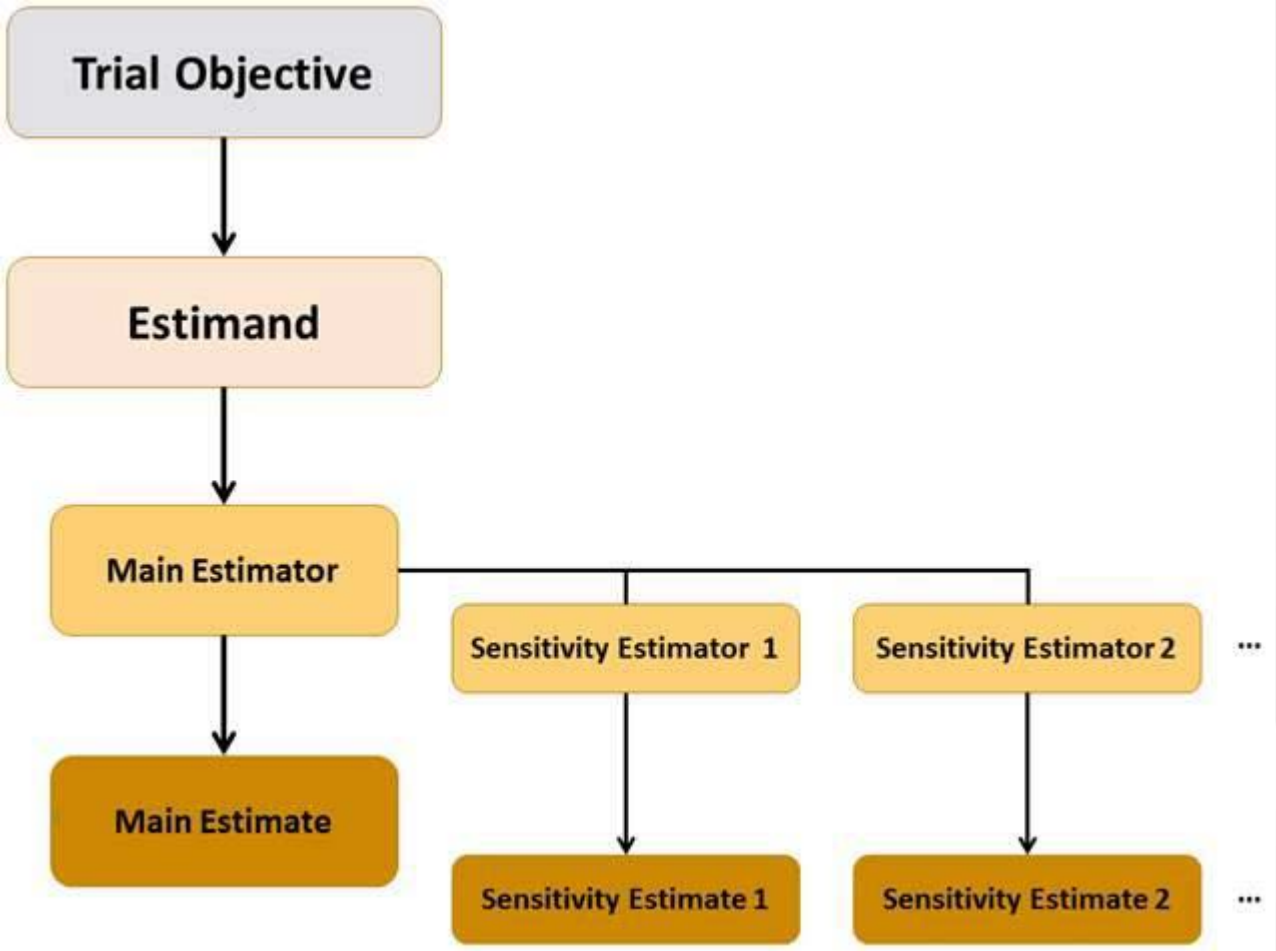
Purpose and scope of the addendum to ICH E9

- Addendum introduces strategies to reflect different questions of interest that might be posed
- Addendum clarifies the definition and the role of sensitivity analysis
- Sensitivity Analysis: A series of analyses conducted with the intent to explore the robustness of inferences from the main estimator to deviations from its underlying modelling assumptions and limitations in the data

Purpose and scope of the addendum to ICH E9

- Addendum also clarifies and extends ICH E9 in respect of several topics including the Intention-To-Treat (ITT) principle, missing data, and issues related to the concept of analysis sets
- Principles introduced in the addendum are applicable not only to randomised controlled clinical trials, but also to single arm studies and observational studies
- Framework also applies to any data type, including longitudinal, time-to-first event, and recurrent event data

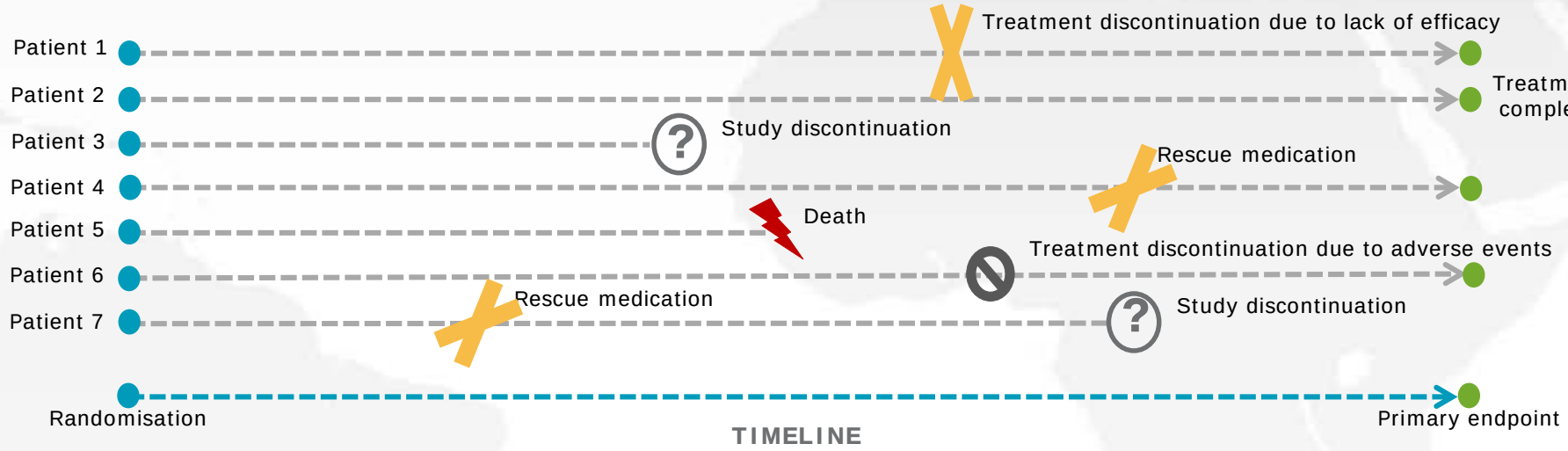
A new framework: Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective



A new framework

- Enables proper trial planning that clearly distinguishes between
  - the target of estimation (trial objective, estimand)
  - the method of estimation (estimator)
  - the numerical result (“estimate”)
  - sensitivity analysis
- Specification of appropriate estimands will usually be the main determinant for aspects of trial design, conduct and analysis

Estimands: Intercurrent events



- Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest
- Such events may include: discontinuation of assigned treatment; use of an additional or alternative therapy; terminal events such as death and leg amputation (when assessing symptoms of diabetic foot ulcers), when these events are not part of the variable itself

Estimands: Intercurrent events

- Might be identified solely by the event itself, such as discontinuation of treatment, or might be more granular including details such as reason, magnitude or timing
- Important: Neither study withdrawal nor other reasons for missing data (e.g. administrative censoring in trials with survival outcomes) are in themselves intercurrent events
- However, it is possible that subjects who withdraw from the trial may have experienced an intercurrent event before withdrawal

Strategies for addressing intercurrent events

- each reflecting a different clinical question of interest in respect of a particular intercurrent event
- the relevance of each strategy will depend on the therapeutic and experimental context

1. Treatment policy strategy

Labels are just an indication

- The occurrence of the intercurrent event is considered **irrelevant**:
  - the value for the variable of interest is used **regardless of whether or not the intercurrent event occurs**
- For example, when specifying how to address use of additional medication as an intercurrent event, the values of the variable of interest are used whether or not the patient takes additional medication
- In general, this strategy cannot be implemented for intercurrent events that are terminal events since values for the variable after the intercurrent event do not exist
  - For example, an estimand based on this strategy cannot be constructed with respect to a variable that cannot be measured due to death

2. Hypothetical strategies

- A scenario is envisaged in which the intercurrent event would not occur
- The value of the variable to reflect the clinical question of interest is the value which the variable would have taken in the hypothetical scenario defined
- Although a wide variety of hypothetical scenarios can be envisaged, some scenarios are likely to be of more clinical or regulatory interest than others
    - For example, when additional medication must be made available for ethical reasons, a treatment effect of interest might concern the outcomes if the additional medication was not available

2. Hypothetical strategies

- A very different hypothetical scenario might postulate that intercurrent events would not occur, or that different intercurrent events would occur
  - For example, for a subject that will suffer an adverse event and discontinue treatment, it might be considered whether the same subject would not have the adverse event or could continue treatment in spite of the adverse event
- However, the clinical and regulatory interest of such hypotheticals is limited
- It is important to have clarity on the hypothetical scenario envisaged if a hypothetical strategy is proposed

Labels are just an indication

3. Composite strategies

- This strategy relates directly to the variable of interest
- An intercurrent event is considered in itself to be informative about the patient's outcome and is therefore incorporated into the definition of the variable
  - For example, a patient who discontinues treatment because of toxicity may be considered not to have been successfully treated
  - If the outcome variable was already success or failure, discontinuation of treatment for toxicity would simply be considered another mode of failure
- Composite variable strategies do not need to be limited to dichotomous outcomes
- Terminal events, such as death, are perhaps the most salient examples of the need for the composite strategy

Labels are just an indication

4. While on treatment strategies

- Response to treatment prior to the occurrence of the intercurrent event is of interest
- If a variable is measured repeatedly, its values up to the time of the intercurrent event may be considered relevant for the clinical question, rather than the value at the same fixed time point for all subjects
  - For example, subjects with a terminal illness may discontinue a purely symptomatic treatment because they die, yet the success of the treatment can be measured based on the effect on symptoms before death
  - Alternatively, subjects might discontinue treatment, and in some circumstances it will be of interest to assess the risk of an adverse drug reaction while the patient is exposed to treatment

5. Principal stratum strategies

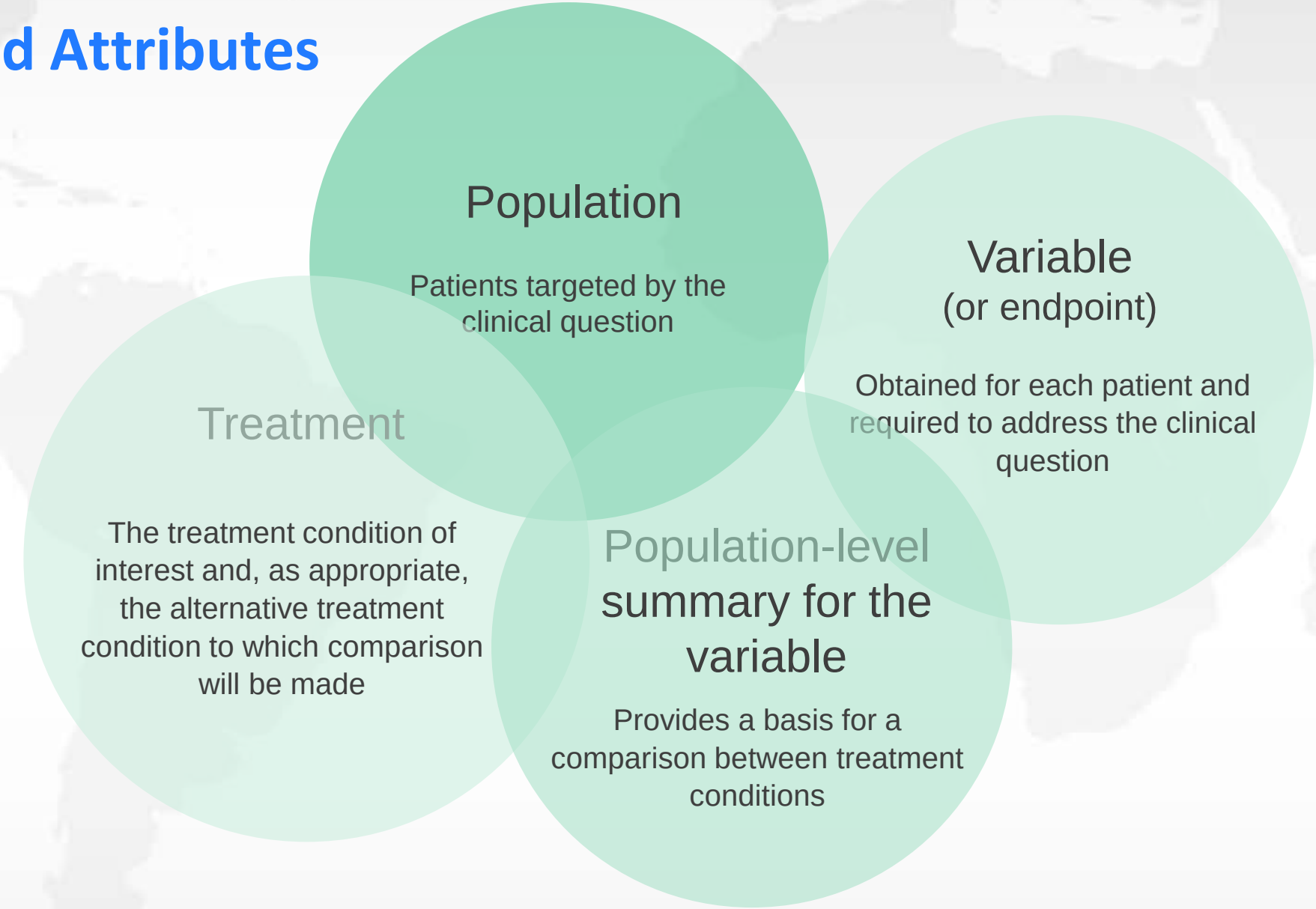
Labels are just an indication

- This strategy relates directly to the population of interest
- The target population might be taken to be the “principal stratum” in which an intercurrent event would occur
- Alternatively, the target population might be taken to be the principal stratum in which an intercurrent event would not occur
- The clinical question of interest relates to the treatment effect only within the principal stratum

5. Principal stratum strategies

- For example
  - toxicity might prevent some patients from continuing the test treatment and
  - it would be of interest to know the treatment effect among patients who are able to tolerate the test treatment
- It is important to distinguish
  - “principal stratification”, which is based on potential intercurrent events (for example, subjects who would discontinue therapy if assigned to the test product)
  - from subsetting based on actual intercurrent events (subjects who discontinue therapy on their assigned treatment)

Estimand Attributes



Estimand Attributes

- Treatment: might consist of
  - individual interventions
  - combinations of interventions administered concurrently, e.g. as add-on to standard of care, or
  - an overall regimen involving a complex sequence of interventions
- Population: might be represented by
  - the entire trial population
  - a subgroup defined by a particular characteristic measured at baseline, or
  - a principal stratum defined by the occurrence (or non-occurrence, depending on context) of a specific intercurrent event

Construction of an Estimand

Should consider:

- What is of clinical relevance for the particular treatment in the particular therapeutic setting including
  - the disease under study
  - the clinical context (e.g. the availability of alternative treatments)
  - the administration of treatment (e.g. one-off dosing, short-term treatment or chronic dosing) and
  - the goal of treatment (e.g. prevention, disease modification, symptom control)
- What is the treatment to which the clinical question of interest pertains

Construction of an Estimand

- Whether specifications for the population and variable attributes should be used to reflect the clinical question of interest in respect of any intercurrent events
- Strategies can then be considered for any other intercurrent events
- Whether an estimate of the treatment effect can be derived that is reliable for decision making
- An iterative process will be necessary to reach an estimand that is of clinical relevance for decision making, and for which a reliable estimate can be made

Construction of an Estimand

- Where significant issues exist to develop an appropriate trial design or to derive an adequately reliable estimate for a particular estimand, an alternative estimand, trial design and method of analysis would need to be considered
- Avoiding or over-simplifying the process of discussing and constructing an estimand risks misalignment between trial objectives, trial design, data collection and method of analysis
- It is critically important to proceed sequentially from the trial objective and an understanding of the clinical question of interest, and not for the choice of data collection and method of analysis to determine the estimand

Construction of an Estimand

- Important considerations related to the construction of hypothetical strategies, the treatment policy strategy, while on treatment strategies and principal stratum strategies are discussed in some detail in the addendum
- Considerations informing the construction of an estimand to support regulatory decision making based on a non-inferiority or equivalence objective are also discussed in the addendum

ICH E9(R1): Section A.4

Impact on trial design and conduct

- The design of a trial needs to be aligned to the estimands that reflect the trial objectives
- Clear definitions for the estimands should inform the choices that are made in relation to trial design including
  - determining the inclusion and exclusion criteria that identify the target population
  - the treatments, including the medications that are allowed and those that are prohibited in the protocol, and
  - other aspects of patient management and data collection

ICH E9(R1): Section A.4

Impact on trial design and conduct

- Efforts should be made to collect all data that are relevant to support estimation, including data that inform the characterisation, occurrence and timing of intercurrent events
- Not collecting any data needed to assess an estimand results in a missing data problem for subsequent statistical inference, and measures should be prospectively in place to minimise the extent of missing data.
- The validity of statistical analyses may rest upon untestable assumptions and, depending on the proportion of missing data, this may undermine the robustness of the results

ICH E9(R1): Section A.4

Impact on trial design and conduct

- Certain estimands may necessitate, or may benefit from, use of trial designs such as
  - run-in or enrichment designs
  - randomised withdrawal designs, or
  - titration designs
- For example, it might be interest to identify the principal stratum of subjects who can tolerate a treatment using a run-in period, in advance of randomising those subjects between test treatment and control.
- A precise description of the treatment effects of interest should also inform sample size calculations

ICH E9(R1): Section A.4

Impact on trial design and conduct

- In situations when synthesising evidence from across a clinical trial programme is envisaged at the planning stage
  - a suitable estimand should be constructed
  - included in the trial protocols, and
  - reflected in the choices made for the design of the contributing trials
- Similar considerations apply to the design of a meta-analysis
  - using estimated effect sizes from completed trials to determine non-inferiority margins, or
  - the use of external control groups for the interpretation of single-arm trials.
- Multiplicity issues should also be addressed for clinical trials with multiple objectives translated into multiple estimands, each associated with statistical testing and estimation

Impact on trial analysis: Main estimation

- For a given estimand, an aligned method of analysis, or estimator, should be implemented
  - that is able to provide an estimate on which reliable interpretation can be based.
  - will also support calculation of confidence intervals and tests for statistical significance
- An important consideration for whether an interpretable estimate will be available is the extent of assumptions that need to be made in the analysis

Impact on trial analysis: Main estimation

- Key assumptions should be stated explicitly together with the estimand and accompanying main and sensitivity estimators
- Assumptions should be justifiable and implausible assumptions should be avoided
- The robustness of the results to potential departures from the underlying assumptions should be assessed through an estimand-aligned sensitivity analysis
- Estimation that relies on many or strong assumptions requires more extensive sensitivity analysis.

Impact on trial analysis: Main estimation

- Some kinds of assumption are inherent in all methods of analysis aligned to estimands that use each of the different strategies discussed previously
- The addendum
  - describes some examples related to the different strategies
  - highlights issues which will be key components of discussions between the sponsor and regulator in advance of an estimand, main analysis and sensitivity analysis being agreed upon
- Even after defining estimands that address intercurrent events in an appropriate manner and making efforts to collect the data required for estimation, some data may still be missing

Impact on trial analysis: Main estimation

- Failure to collect relevant data should not be confused with
  - the choice not to collect, or
  - to collect and not to use data made irrelevant by an intercurrent event
- The handling of missing data makes it necessary to make assumptions regarding the missing data in the statistical analysis
- Handling of missing data should be based on clinically plausible assumptions and, where possible, guided by the strategies employed in the description of the estimand

Impact on trial analysis: Role of Sensitivity analysis

- Inferences based on a particular estimand should be robust to limitations in the data and deviations from the assumptions used in the statistical model for the main estimator
- Sensitivity analysis is used to evaluate this robustness, and should be planned for the main estimators of all estimands that will be important for regulatory decision making and labelling in the product information
- The statistical assumptions that underpin the main estimator should be documented

Impact on trial analysis: Role of Sensitivity analysis

- One or more analyses, focused on the same estimand, should then be pre-specified to investigate these assumptions
- The objective of the sensitivity analyses is to verify whether or not the estimate derived from the main estimator is robust to departures from its assumptions
  - For example, this can be done by assessing the extent of departures from assumptions that change the interpretation of the results in terms of their statistical or clinical significance (e.g., tipping point analysis)

Impact on trial analysis: Choice of Sensitivity analysis

- A structured approach is recommended altering one aspect of the main analysis at a time
  - Accomplished by specifying the changes in assumptions that underlie the alternative analyses, rather than simply comparing the results of different analyses based on different sets of assumptions
  - The need for analyses varying multiple assumptions simultaneously should then be considered on a case by case basis
- Sensitivity analysis with regard to missing data remain important

Impact on trial analysis: Supplementary analysis

- Sensitivity analysis should be clearly distinguished from any other analysis that is planned, presented or requested in order to more fully investigate and understand the trial data
- Such an analysis is referred to as a supplementary analysis, and in general, should be given a lower priority relative to a sensitivity analysis
- If the estimate corresponding to a given estimator is shown to be robust through sensitivity analysis, then the interpretation of trial results should focus on the main estimator for each selected estimand

Impact on trial analysis: Supplementary analysis

- The role of the PPS (Per Protocol Set) in which subjects with major protocol violations and deviations are excluded is revisited in the addendum
- In respect of the framework presented in the addendum, it may not be possible to construct a relevant estimand to which analysis of the PPS is aligned
- Overall, analysis based the PPS might not add additional insights if estimands can be constructed, with aligned method of analysis, that better address the objective usually associated with the analysis of the PPS

Documenting Estimands and sensitivity analysis

- A trial protocol should define and specify explicitly a primary estimand that corresponds to the primary trial objective.
- The protocol and the analysis plan should pre-specify
  - the main estimator that is aligned with the primary estimand and leads to the primary analysis
  - a suitable sensitivity analysis to explore the robustness under deviations from its assumptions
- Estimands for secondary trial objectives (e.g. related to secondary variables) that are likely to support regulatory decisions should also be defined and specified explicitly, each with a corresponding main estimator and a suitable sensitivity analysis

Documenting Estimands and sensitivity analysis

- The choice of the primary estimand will usually be the main determinant for aspects of trial design, conduct and analysis
  - Following usual practices, these aspects should be well documented in the trial protocol
  - Once the above aspects have been taken into account, the conventional considerations for trial design, conduct and analysis remain the same
- Additional exploratory trial objectives may be considered for exploratory purposes, leading to additional estimands
- However, it is not a regulatory requirement to document an estimand for each exploratory objective

Documenting Estimands and sensitivity analysis

- Results from the main, sensitivity and supplementary analyses should be reported systematically in the clinical trial report, specifying whether each analysis was
  - pre-specified
  - introduced while the trial was still blinded, or
  - performed post hoc
- Summaries of the number and timings of each intercurrent event in each treatment group should be reported

Documenting Estimands and sensitivity analysis

- Changes to the estimand during the trial can be problematic and can reduce the credibility of the trial
- A change to the estimand should usually be reflected through amendment to the protocol
- For intercurrent events that were not foreseen at the design stage and that are identified during the conduct of the trial, the following should be provided
  - an explanation of the choices made for the analysis
  - a discussion of effect on the estimand (the treatment effect being estimated), and
  - the interpretation of the trial results

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M9: Biopharmaceutics Classification System-Based Biowaivers

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Health Canada Santé Canada

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

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M9 Guideline Timelines

- New Multidisciplinary Guideline for Biopharmaceutics Classification System (BCS)-based biowaivers.
- Concept Paper and Business Plan, approved by the Management Committee, October 2016
- *Step 1* technical document endorsed by Expert Working Group members, June 2018
- *Step 2* draft guideline endorsed by the Assembly, June 2018
- *Step 3* draft guideline issued by Regulatory Members for public consultation, June 2018
- *Step 4* finalisation of guideline, planned for November 2019

Outline of presentation

- Objectives and scope of the guideline
- Biopharmaceutics classification of the drug substance
  - based on solubility and permeability
- Eligibility of a drug product for a BCS-based biowaiver
  - criteria for drug product composition and *in vitro* dissolution performance
- Annexes to the guidance
  - clarifications on guideline recommendations

M9 Guideline Objectives

- The BCS-based biowaiver approach is intended to reduce the need for *in vivo* bioequivalence studies.
- The guideline:
  - provides recommendations on the biopharmaceutics classification of drug substances, and to support BCS-based biowaivers for drug products.
  - aims to harmonise current regional guidance, and support streamlined global drug development.

Current Regional Guidance

- US FDA
  - Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, December 2017

- Health Canada
  - Biopharmaceutics Classification System Based Biowaiver, 2014

Draft M9 Guideline: Scope

- BCS-based biowaivers are limited to immediate release, solid orally administered dosage forms or suspensions designed to deliver drug to the systemic circulation.
- Fixed-dose combination products are considered eligible in cases where all drug substances fulfill the criteria.
- Narrow therapeutic index drugs are excluded from consideration for a biowaiver.
- Prodrugs may be eligible when absorbed as the prodrug.

BCS: Classification Criteria

- The BCS is a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the drug substance, resulting in four classes:
  - Class I: high solubility, high permeability
  - Class II: low solubility, high permeability
  - Class III: high solubility, low permeability
  - Class IV: low solubility, low permeability

Solubility (1)

- A drug substance is considered highly soluble if the highest single therapeutic dose is completely soluble in 250 ml or less of aqueous media over the pH range of 1.2 – 6.8 at 37°C.

- If the highest strength is soluble over the pH range, a biowaiver may be supported by dose-proportional PK over a range that includes the highest single therapeutic dose.

- The lowest measured solubility over this pH range (1.2 – 6.8) is used to classify the drug substance solubility.

Solubility (2)

- Experimental conditions:
  - shake-flask technique, or an alternate method, if justified;
  - buffers at pH 1.2, 4.5, 6.8 and lowest solubility of the drug;
  - test pH at beginning and at end of the experiment, pH should be adjusted if necessary;
  - at least 3 replicate determinations at each pH level, using a validated assay method;
  - the drug substance should be stable in all media.

Permeability

- A drug substance is considered highly permeable if ≥ 85% of the administered dose is absorbed.
- A conclusion of high permeability may be supported by:
  - an absolute bioavailability ≥ 85%;
  - ≥ 85% of the administered dose recovered in urine and/or feces as absorbed drug material;
  - results of validated *in vitro* Caco-2 permeability assays.
- Of note
  - Human *in vivo* data from published literature may be acceptable.
  - Data to support drug substance stability in the gastrointestinal tract should be provided if mass balance or Caco-2 studies are used,.

Eligibility for a BCS-based Biowaiver

- A drug product is eligible for a BCS-based biowaiver provided that:
  - the drug substance is a Class I or Class III drug;
  - the drug product is an immediate-release oral dosage form with systemic action;
  - the drug product is the same dosage form and strength as the reference product;
  - criteria with respect to composition (excipients) and *in vitro* dissolution performance of the drug product are fulfilled.

Composition of the Drug Product

- Excipient differences between the proposed test and the reference product should be assessed for their potential to affect *in vivo* absorption.
- For BCS Class I drugs, qualitative and quantitative differences in excipients are permitted, except for excipients that may affect absorption, which should be qualitatively the same and quantitatively similar, *i.e.*, within ± 10.0% of the amount of that excipient in the reference product.
- For BCS Class III drugs, all of the excipients should be qualitatively the same and quantitatively similar.

M9 guideline, Table 1: excipient criteria expected to demonstrate similarity

In Vitro Dissolution: Assessment

- Comparative *in vitro* dissolution experiments should use compendial apparatuses and validated analytical methods.
- Experimental conditions:
  - paddle (50 rpm) or basket (100 rpm);
  - pharmacopoeial buffers, at least pH 1.2, 4.5 and 6.8;
  - 900 ml or less media (37 ^{o}C);
  - at least 12 units of test and reference product for each profile;
  - organic solvents or surfactants are not allowed;
  - enzymes may be acceptable (gelatin cross-linking).

In Vitro Dissolution: Acceptance Criteria

- BCS Class I:
  both test and reference products should display either very rapid (≥ 85 % dissolved in ≤ 15 mins), or rapid and similar *in vitro* dissolution (≥ 85% dissolved in ≤ 30 mins, f2 ≥ 50) in all media.

- BCS Class III:
  both test and reference products should display very rapid (≥ 85% dissolved in ≤ 15 mins) *in vitro* dissolution in all media.

Annexes

- Caco-2 cell permeability assay method considerations
  - Validation: rank-order between permeability values and extent of drug absorption in humans, monolayer integrity
  - Assay considerations, including passive transport of test drug
- Further information on the assessment of excipient differences
  - Flow charts to guide BCS-based biowaivers
  - Examples of acceptable differences in excipients
- Clarification annex in question and answer format
  - Addresses questions received during the public consultation

Conclusions

- This harmonised guidance on the basic requirements for accepting and applying BCS-based biowaivers, reduces the need for carrying out additional clinical (bioequivalence) studies in humans. In turn, this may accelerate drug development and approval and may lower costs significantly.

M9 Expert Working Group

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Swissmedic, Switzerland
ANVISA, Brazil
MFDS, Republic of Korea
HSA, Singapore
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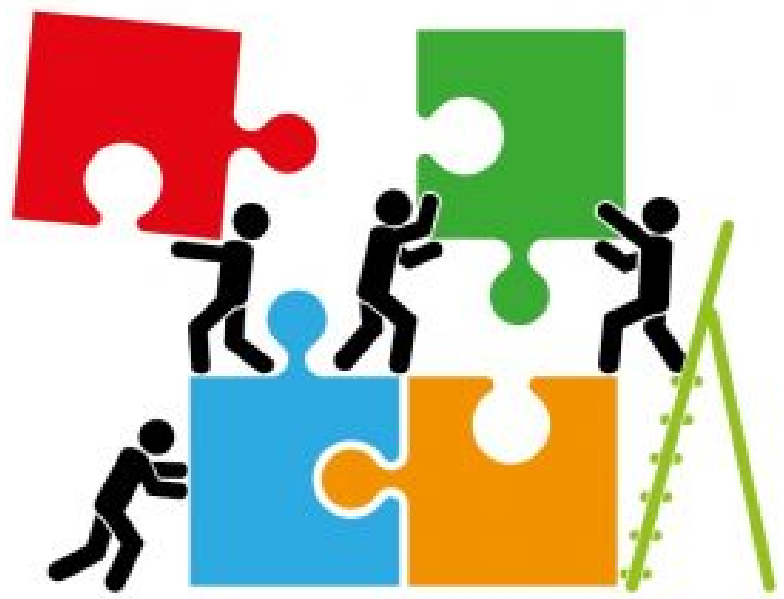

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Update on ICH Q12

"Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management"

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Disclaimer

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

Outline of presentation

- Brief overview of ICH Q12
- Key sections of step 2 document (a reminder)
- Status before Amsterdam
- Progress made in Amsterdam
- Objectives for Singapore
- Acknowledgements

Brief overview of ICH Q12

- **Intended to harmonize lifecycle management to facilitate and encourage continuous improvement in pharmaceutical manufacturing through risk-based oversight**
- **Such improvements and resulting benefits can help to:**
  - Ensure that patients reliably receive quality medicines over the lifecycle of the product
  - Mitigate drug shortages due to quality issues
  - Facilitate innovations in manufacturing
  - Reduce burden to regulators and industry
- **Scope – pharmaceutical drug substances and drug products (chemical and biotech/biological), including authorised products; drug-device combination products that meet the definition of pharmaceutical or biotech/biological product**
- **Challenges – broad scope of the guideline (Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management)**

Key Sections of Step 2 Document

- Categorisation of Post-approval CMC Changes
- Established Conditions
- Post-approval Change Management Protocol
- Product Lifecycle Management Document
- Pharmaceutical Quality System and Change management
- Relationship Between Regulatory Assessment and Inspection

- (Post-Approval Changes for Marketed Products)
  - Structured Approaches to Support the Evaluation of CMC Changes
  - Stability Data Approaches to Support the Evaluation of CMC Changes

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. Regional legal frameworks / regulations / guidance may define ECs with their reporting category and/or may allow the scientific risk-based approaches described in this chapter to be considered
  - 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 shares with regulators the development and manufacturing information at an appropriate level of detail, and helps to justify the initial selection of ECs and their reporting category

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

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.

Product Lifecycle Management (PLCM)

Key Sections of Q12 Step 2 document – Chapter 5

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)

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

Status before meeting in Amsterdam

- Step 1 document, June 2017
- Step 2a/b document reached in November 2017
- Public consultation period ended December 2018
  - Over 900 consolidated comments received
- Significant comments were discussed and revisions to the document made during interim F2F meeting in Tokyo, February 2019
- Further discussion through work of multiple sub-teams and two EWG teleconferences in March and May 2019 to review and align on proposals from the sub-teams

Progress made in Amsterdam

- Objective at the meeting was to reach as close to a final document (core guideline and annexes) as possible
- Remaining significant issues were discussed
- Considered feedback from interim EC legal review; made revisions to the guideline that the EWG believed (at that time) would address the concerns raised
- Identifying Established Conditions (ECs) for manufacturing process
  - Aligned on revised language and flowchart

Progress made in Amsterdam

- Identifying ECs for analytical procedures
  - Face-to-face discussion held between sub-teams of Q12 and Q2(R2)/Q14
    - Confirmed scope of guidances for concepts related to analytical methods
    - Q2/Q14 experts available to assist Q12 re relevant text and examples
  - EWG aligned on approach to revision of text and examples but further review needed before text and examples can be finalised
- Identifying Established Conditions for drug-device combination products
  - Aligned on inclusion of minimal language with possibility to include further details in training materials

Progress made in Amsterdam

- Line by line edits “completed” for most of the document (but still subject to possible changes induced by new changes made elsewhere in the document)
- Workplan developed for Singapore meeting

Conclusions from Amsterdam

- Significant progress made toward finalizing text of the core guideline and parts of the Annex (examples)
- Remaining challenges….
  - Concern about implementation of certain concepts in some regions
  - Remaining examples in the Annex still under discussion; need to be progressed/finalised between Amsterdam and Singapore
  - Line by line edits to Chapter 3 (Established Conditions) and Appendix 1 (CTD Sections that Contain ECs) pending
- EWG proposed to meet at the November 2019 meeting in Singapore

Objectives for meeting in Singapore

- Resolve any remaining minor/clarification comments on core document text
- Reach alignment on content of the Annex and conduct line-by-line edits (as needed)
- Sign Step 3 document
- Progress development of training materials; develop workplan for finalizing training materials post-Singapore

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Moheb Nasr, Rapporteur through Step 2b

Ashley Boam, Rapporteur through Step 4

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)

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

Dr. Ronald Wange, Associate Director, FDA, CDER, Office of New Drugs, Pharmacology/Toxicology Staff

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Outline

- Purpose of the Guidance
- Objectives of Guidance Revision
- Timeline
- Public Comment Overview
- Progress Since April 2018

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 human AUC
- Emphasize the use of relevant 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
- 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.

Timeline (*from previous public update*)

- 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 Internal discussion and proposed responses (ongoing)

Public Comments Received by FDA

- More than 400 comments
- Encompassed nearly all aspects of the document

Overview of Comments (1)

- General support 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 frequently unclear as to whether approaches being discussed are appropriate for small molecule drugs, biologics or both
- Discordant comments received 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 C_{max} overly simplistic
- 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

Summary (*from April 2018 public meeting*)

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

Milestones Since Last Public Update

(from 5 August 2019 EWG Work Plan)

June 2018	*EWG met in Kobe Japan. EWG came to consensus on how to resolve major issues identified during the public comment period and developed work packages for revision of the step 2a/b document.*
November 2018	*EWG met in Charlotte USA. There was an intial review of the revised document and agreement on reorganization. EWG completed line by line editing of the revised step 2a/b document.*
June 2019	*EWG met in Amsterdam Netherlands. The EWG did line by line editing to incorporate comments from internal stakeholder review. The EWG has continued agreement on the need for the maintenance procedure. EWG also made sure to align with S11. The document is in near final version.*

Anticipated Future Milestones

- Step 3 Signoff/Step 4 adoption of final guidance (Nov 2019)
  - EWG did not request to meet in Singapore
  - Outstanding issues from Amsterdam could by handled by TCON
- Prepare training materials

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Overview of Ongoing ICH Topics

Dr. Léo Bouthillier, Director: Bureau of Cardiology, Allergy and Neurological Sciences, Therapeutic Products Directorate, Health Canada

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E11A: Pediatric Extrapolation

Identified Problem:

- It has been estimated that up to 75% of pediatric drug treatment is done off-label, without supporting information for that population.
- In many cases, there is a long gap between the initial adult approval and the inclusion of pediatric-specific information in product labeling.
- There is variability in the interpretation and application of pediatric extrapolation across regulatory authorities.
- The current E11(R1) guideline includes a high level description of pediatric extrapolation that encourages sponsors to initiate regulatory interactions.

Objective:

- To address and align terminology related to pediatric extrapolation.
- To discuss disease similarity, pharmacology, and statistical tools in pediatric extrapolation.
- To provide information on extrapolation concept, plan and evidence synthesis with examples/scenarios that can be utilized to support pediatric extrapolation.
- Overall, to improve the speed of access to new drugs for pediatric patients while limiting the number of children required for clinical trials.

Timeline:

- The topic was adopted in October 2017.
- Initial first draft of guideline for discussion is anticipated at the FTF meeting November 2019.
- Draft Step 2 guideline is anticipated November 2020.

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S7B/E14 Questions and Answers: Clinical and Non-Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential

Identified Problem:

- ICH S7B & E14 describe non-clinical and clinical risk assessment strategies to inform the potential risk of proarrhythmia for a test substance
- The way E14 & S7B have been used in practice has been to sometimes drop compounds or drugs that prolong the QT interval from development, which may not always be appropriate.
- Science has evolved and new technologies are available that can provide improved insight into which QT prolonging drugs are proarrhythmic

Objective:

- Streamline clinical development for drugs that prolong the QT interval but are found to have low proarrhythmic risk and result in fewer products being dropped from development
- Provide a more accurate and comprehensive mechanistic-based assessment of proarrhythmic potential
- Define drug effects on multiple human cardiac ionic currents, characterize integrated electrical responses using in silico reconstructions of human ventricular electrophysiology, and verify effects on human stem-cell derived ventricular myocytes.
- Provide clarity on how new technologies can be applied and a harmonized approach to implementation

Timeline for Development:

- Q&A initiated in 2018
- Q&As have been drafted on the following topics for discussion at the November 2019 meeting:
  - Best practices for hERG voltage clamp assays, in vitro human cardiomyocyte studies, and in vivo QT assays
  - Principles for proarrhythmia models
  - Integrated S7B risk assessment
- First stage Q&As are anticipated to be finalized in May 2020

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E17: Multi Regional Clinical Trials Training Materials

- Regulatory agencies are currently facing some challenges in evaluating data from MRCTs for drug approval and it was deemed necessary to developed a Harmonised international Guideline to promote conducting MRCT appropriately, especially focusing on scientific issues in planning/designing MRCTs.
- The E17 guideline provides guidance on general principles on planning/designing Multi-Regional Clinical Trial (MRCT). Drug development has been globalised and MRCT for regulatory submission has widely been conducted in ICH regions and beyond.
- The E17 guideline was finalised in November 2017.
- An extensive set of training materials including 7 modules has been developed to promote the efficient and consistent implementation of the E17 Guideline in the context of an evolving drug development environment. The training materials can be found on the Efficacy guidelines pages of the ICH website.

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M7(R2): Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

ICH M7 Addendum: Calculation of Compound-Specific Acceptable Intakes

- ICH M7 provides a framework to limit mutagenic impurities and potential carcinogenic risk in drug products and substances.
- An Addendum was finalized in 2017 which contains exposure limits and supporting monographs for 14 mutagenic impurities commonly found or used in drug synthesis.
- The M7(R2) EWG is currently undertaking a maintenance of the Guideline to expand the Addendum.
- Draft version of the monographs anticipated in 2020

Development of M7 Question and Answer Document

- Address quality and safety topics that require clarification as identified since implementation of ICH M7 in 2014.

Topics include:

  - Additional clarification on the justification of control strategy for mutagenic impurities in the marketing authorization dossier
  - Organization and depth of information regarding reporting of individual mutagenic impurities
  - Quantitative structure-activity relationship (QSAR) systems
  - In vivo follow-up assays following identification of an Ames positive impurity
  - Other safety-related information

- Draft version of the Q&A anticipated by the end 2019

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M10: Bioanalytical Method Validation

During pharmaceutical development, bioanalytical methods are used in nonclinical and clinical studies to describe the exposure of animals and humans to drugs and their metabolites.

Purpose:

- To ensure the reliability of data under review by providing recommendations on the requirements for bioanalyses conducted throughout the lifecycle of drugs of both chemical and biological origin
- Harmonise regional requirements for method validation and study sample analysis, supporting streamlined global drug development

Scope:

- Validation of bioanalytical methods for biological and chemical drugs and their metabolite(s) in biological samples
  - Nonclinical toxicokinetic/pharmacokinetic studies
  - All phases of clinical trials

  Any study submitted to make decisions about and/or support Approval, Safety, Efficacy and Labelling

Timeline for Development:

- Guideline initiation in 2016
- Draft guideline posted February 2019
- Final guideline anticipated November 2020

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M11: Clinical electronic Structured Harmonised Protocol (CeSHarP)

Identified Problem:

- Currently there is no internationally harmonized standard template for the format and content of the clinical protocol document to support consistency across sponsors and exchange of protocol information.
- Contributes to inefficiencies and difficulties in reviewing and assessing clinical protocols by regulators, sponsors, ethical oversight bodies, investigators, and other stakeholders.

Objective:

- Create a template to include identification of headers, common text and a set of data fields and terminologies which will be the basis for efficiencies in data exchange
- Establish a technical specification that uses an open, nonproprietary standard to enable electronic exchange of clinical protocol information

Timeline for Development:

- Topic approved by the ICH Assembly in November 2018
- Draft Guideline is anticipated in June 2020

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S1(R1): Revision of 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 - initiated in August 2013
- CADs address carcinogenic potential of investigational pharmaceutical using a weight-of-evidence (WOE) approach. Based on level of certainty of carcinogenic risk and its potential human relevance, a company is expected to indicate the need for and additional value of conducting a 2yr rat study
- Regional drug regulatory authorities independently 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
- CADs were accepted until Dec 2017

Objective:

- This may result in a revision 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

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Q3C(R8): Maintenance of 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 compounds:
  - 2-methyltetrahydrofuran
  - cyclo pentyl methyl ether
  - tert-butanol

Timeline for Development:

- Work on the three solvents began in early 2017
- Draft guideline anticipated by end of 2019

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Q3D(R1)/(R2) Maintenance of Guideline for Elemental Impurities

Objective:

- Q3D provides recommendations for the control of elemental impurities in new drug products.
- Q3D contains monographs and associated Permitted Daily Exposures (PDEs) for 24 elemental impurities for drug products administered by the oral, parenteral and inhalation routes of administration.

Maintenance process:

- The Q3D(R2) Maintenance EWG is developing an Appendix to provide guidance and establish PDEs for the 24 elemental impurities included in the Q3D(R1) Guideline for products administered by the cutaneous and transdermal routes of administration.

Timeline for development:

- Work on the Appendix began in 2017.
- Draft Appendix anticipated toward the end of 2019.

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Q11 Q&A: Selection & Justification of Starting Materials – Training Materials

- Since being finalized in 2012, worldwide experience with implementation of the ICH Q11 Guideline and its recommendations on the development and manufacture of drug substances has given rise to requests for clarification relating to the selection and justification of starting materials.
- The Q11 Implementation Working Group (IWG), established by ICH in 2014, developed a Questions and Answers (Q&A) document which reached *Step 4* of the ICH Process in August 2017.
- These Q&As are intended to provide additional clarification, and to promote convergence and improve harmonisation of the considerations for the selection and justification of starting materials and on the information that should be provided in marketing authorisation applications and/or Master Files.
- The focus of the Q&A document is on chemical entity drug substances.
- Most recently, extensive training materials and a training video on Q11 Q&As were published on the ICH website.

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Q13: Continuous Manufacturing (CM) of Drug Substances and Drug Products

Objective & Benefits:

- Reduce barriers to the adoption of CM technology, such as the lack of harmonization of regulatory expectations internationally
- Capture key technical and regulatory aspects unique to CM of drug substances and drug products for small and large molecules for harmonisation
- Allow drug manufacturers flexibility to develop, implement, or integrate CM for small molecules and therapeutic proteins for new and existing products
- Provide guidance to industry and regulatory agencies regarding regulatory expectations on the development, implementation, and assessment of CM technologies for products intended for commercialization internationally

Timeline for Development :

- Topic initiated in June 2018
- Concept paper and Business plan endorsed November 2018
- Drafting ongoing - Draft Guideline for Step 1 and Step 2a/b anticipated in June 2020

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Q2(R2)/Q14: Analytical Procedure Development and Revision of Q2(R1) Analytical Validation

Q14 Analytical Procedure Development

Identified Problem:

- Lack of existing guidance results in submissions with performance evaluations that are missing analytical development outcomes, applicants typically only report analytical validation results, this makes regulatory communication ineffective especially when non-conventional analytical procedures (for example, real time release testing) are employed.
- Can preclude the applicant from an opportunity to present scientific basis for flexible regulatory approaches to post-approval Analytical Procedure changes.

Objective:

- The new guideline will harmonize the scientific approaches of Analytical Procedure Development and provide principles relating to the description of Analytical Procedure Development process.
- Intended to improve regulatory communication between industry and regulators and facilitate more efficient, sound scientific and risk-based approval as well as post-approval change management of analytical procedures.

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Q2(R2)/Q14: Analytical Procedure Development and Revision of Q2(R1) Analytical Validation

Q2(R2) Revision of Analytical Validation

Identified Problem:

- Current version (Q2(R1)) does not cover more recent application of analytical procedures (e.g. Near Infrared (NIR), Raman, Nuclear Magnetic Resonance, and Mass Spectroscopy)
- Lack of guidance for these analytical procedures can lead to submissions with inadequate validation data, resulting in repeated information requests and responses, which can delay application approval. It can also impede implementation of CM that may require these procedures.

Objective:

- Define common validation characteristics for procedures like NIR and NMR and hyphenated techniques; address procedures reliant on multivariate methods used to compare measurements between test and reference samples
- Continue to provide a general framework for the principles of analytical procedure validation

Q2(R2)/Q14 Timeline for Development:

- Topic initiated in June 2018
- Draft Guideline is anticipated June 2020

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M2: Electronic Standards for the Transfer of Regulatory Information (ESTRI)

Due to the information technology (IT) nature of the electronic transfer of regulatory information, the M2 EWG was developed to make recommendations for ICH electronic standards development.

ICH Topic Assessment & Consultative Support

- Perform technical evaluation of EWG guidelines for technical risk and opportunities; make recommendations on electronic exchange, format and security of information.
- Provide technical/consultative support to EWGs (e.g., terminology list maintenance).

Project Opportunities

- Identify, evaluate and propose technically oriented new topic opportunities with good potential to the ICH MC.

Technology and Regulatory Trends

- Monitor technology and regulatory trends for impact on ICH areas of interest.
- Manage relationships with Standards Development Organizations (e.g., HL7, ISO/TC215, EDQM)

Technical Recommendations

- Publish technical recommendations and implementation status for regulatory submissions (ESTRI)

Current Activity

- White paper on HL7's Fast Healthcare Interoperability Resources (FHIR) standard and considerations for ICH under development; joint discussions with M8 and E2B
- Review technical opportunities/risks for current ICH topics

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M8: Electronic Common Technical Document (eCTD)

- ICH created the electronic messaging standard (eCTD) for the Common Technical Document (CTD), the common format that assembles drug quality, safety and efficacy information.
- Current version eCTD v4.0

Recent Activity:

- Current ICH eCTD v4.0 Implementation Package (v1.3)
  - ICH signoff June 2018
  - General update with additional functionality (e.g. Study Group Order)
- Support Documentation
  - Overview of the eCTD v4.0 Implementation Package
  - Target audience is business and technical personnel
  - Updated in accordance with Implementation Package updates
- Orientation Material
  - Provides an outline of eCTD v4.0 concepts from business perspective
  - Target audience is business personnel and management
  - Updated in accordance with Implementation Package updates
- ICH eCTD v4.0 website (http://estri.ich.org/new-eCTD/index.htm)
  - Implementation Package
  - Links to regional eCTD v4.0 webpages
  - Change Control – Submit questions and change requests

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E2B(R3): Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (ICSRs)

- E2B defines what data elements need to be transmitted in individual case safety reports (ICSRs), regardless of the source or destination.
- With R3, ICH made a key decision that technical specifications should no longer be developed solely within ICH, but should be created in collaboration with Standards Development Organisations (SDOs) to enable wider inter-operability across the regulatory and healthcare communities.
- Supporting documents such as an implementation guide and Q&As have been developed to help support the implementation of R3.

Recent Activity:

- Revised Q&A document signed-off in June 2019
- Training materials
  - Module I: finalized
  - Module II: nearing finalization
  - Module III: under development
- EDQM user guide to be updated
- Future of E2B(R3) EWG/IWG
  - EWG/IWG will continue to support Q&A
  - Regular teleconference with face to face meeting under exceptional circumstances

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Overview of New ICH Topics & ICH Strategic Discussion Groups

Dr. Celia Lourenco, Director General: Biologics and Genetic Therapies Directorate, Health Canada

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E6(R3): Good Clinical Practice

Identified Problem:

- The ICH Reflection Paper on Good Clinical Practice (GCP) "Renovation" outlined the ICH plan for further modernisation of the ICH Guidelines related to clinical trial design, planning, management, and conduct
- The scope of the renovation includes the revision of the current E8 General Considerations for Clinical Trials which is currently under development, and the further revision of the E6 Guideline for Good Clinical Practice, which had last been revised in November 2016 as E6(R2)

Objective is to:

- Provide updated guidance that is both appropriate and flexible enough to address the increasing diversity of study types and data sources that are being employed to support regulatory and other health policy decisions, as appropriate
- The underlying principles of human subject protection and data quality would remain

Timelines:

- The E6(R3) topic was endorsed by the ICH Assembly in June 2019, and an informal Working Group was established in September 2019 to develop a Concept Paper and Business Plan
- The informal Working Group will meet in Singapore to finalize the Concept Paper and Business Plan

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E2D(R1): Post-Approval Safety Data Management

Identified Problem:

- The E2D guideline provides a standardised procedure for post-approval safety data management and the guidance for gathering and reporting information
- New and anticipated technological advances, increased scope of pharmacovigilance, and emerging sources of information beyond the traditional adverse event reports

Objective is to:

- Revise E2D to harmonize definitions, classifications, and methodological approaches to the various types of safety information currently available
- Provide pragmatic future-facing solutions that can be adopted globally to ensure consistent collection, review, analysis and reporting of important safety information from all sources to ensure global data can be leveraged to optimise patient safety and better serve public health

Timelines:

- Topic was endorsed in June 2019, and an informal Working Group was established in September 2019 to develop a Concept Paper and Business Plan
- The informal Working Group will meet in Singapore to finalize the Concept Paper and Business Plan

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E20: Adaptive Clinical Trials

Identified Problem:

- European and US regulatory agencies have issued a reflection paper and draft guidance for adaptive clinical trials
- Differences were noted in these advisory documents and the relevant published literature
- Lack of harmonization hinders the use of these innovative designs in global drug development
- Critical to eliminate some of the limiting factors and ensure appropriate use at global drug development level of potentially efficient designs for the development of effective treatments, limiting patient exposure to unsafe or ineffective treatments

Objective is to address:

- Common terminology for adaptive clinical trials
- Potential benefits of adaptive clinical trials and areas of meaningful applications (e.g., study settings and design features)
- Principles for the design, conduct, analysis, and proper interpretation of adaptive clinical trials, including considerations of the risk of erroneous conclusions (e.g., control of false positive and false negative conclusions, and reliability of effect estimates), maintenance of trial integrity, and handling of operational challenges
- The documentation that is important for the planning and implementation of adaptive clinical trials and the interactions between sponsors and regulatory agencies
- The primary focus of the guideline will be on confirmatory clinical trials, but also the adaptive clinical trials throughout all stages of development are in scope

Timelines:

- Informal Work Group launched in June 2019 to develop Concept Paper and Business Plan
- November 2019: face-to-face meeting in Singapore to finalize the Concept Paper and Business Plan

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M12: Drug Interaction Studies

Identified Problem:

- Drug-drug interaction (DDI) studies are an integral component of many drug development programs, however the need for systematic, risk-based approaches to these studies presents an opportunity for global harmonization

Objective is to:

- Harmonize approaches to designing, conducting, and interpreting DDI studies that are conducted during the development of a therapeutic product to evaluate the potential for DDI
- Harmonize regulatory expectations with respect to evaluation of *in vitro*, *in vivo*, and *in silico* DDI studies

Timelines:

- This topic was endorsed by the ICH Assembly in June 2018, and an informal Working Group was established in June 2019 to develop a Concept Paper and Business Plan
- The informal Working Group will meet in Singapore to finalize the Concept Paper and Business Plan

Q5A(R2): Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin

Identified Problem:

- Q5A(R1) published in 1999 and has not been updated since, while several technological advances have taken place since

Objective is to:

- Introduce possible updates including:
  - Emerging products (e.g., virus-like particles, subunit proteins, viral vectored products)
  - Flexibility in virus testing and virus clearance validation approaches (novel virus detection methods, use of platform data)
  - Novel analytical methodology (e.g., Next Generation Sequencing)
  - Expectations to support advanced manufacturing (e.g., continuous manufacturing)
  - Updates to reflect modern virus clearance practices

Timelines:

- First face-to-face meeting Nov. 16-20 in Singapore to finalize the Concept Paper and Business Plan

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S12: Nonclinical Biodistribution Studies for Gene Therapy Products

Identified Problem:

- The field of gene therapy (GT) is progressing at an exponential pace, with many products in various phases of development
- Nonclinical biodistribution (BD) data form an important element of the nonclinical program of a GT product
- However, existing regulatory guidance documents differ in their scope and expectations for nonclinical BD studies/assessment
- There is, therefore, a need for a harmonised guideline to prevent unnecessary use of animals, increase in the cost of development programs for GT products, and delay in the conduct of animal safety studies and initiation of clinical trials

Objective is to:

- Harmonise the following areas:
  - Identification of what constitutes a GT product and definition of “BD”
  - The need for and timing of the conduct of BD studies
  - Recommendations on BD study design and considerations in analytical tools and assay methodologies
  - Discussion on the interpretation of the BD data and translation of the data to clinical trial design

Timelines:

- The informal working group will meet face-to-face in Singapore and the Concept Paper and Business plan are expected to be submitted for adoption by the Assembly

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Informal Quality Discussion Group (IQDG)

- Established in February 2019 following endorsement of the ICH Reflection Paper on ***Advancing Biopharmaceutical Quality Standards to Support Continual Improvement and Innovation in Manufacturing Technologies and Approaches***
- Outlines a strategic approach to enhance the portfolio of ICH Quality-related guidelines to support continual improvement and innovation in biopharmaceutical manufacturing technologies and approaches
- Continue to advance the ICH Quality Vision to “develop a harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasising an integrated approach to quality risk management and science”
- Activities of the IQDG include reviewing the need for new ICH Quality-related harmonization work, reviewing and recommending training needs related to the content and/or implementation of ICH Quality Guidelines, reviewing and recommending any necessary updates to the ICH Quality Reflection Paper and ICH Quality Vision statement as needed
- For more information:
  - https://admin.ich.org/sites/default/files/2019-04/ICH_AdvancingPharmaceuticalQualityStandards_2018_1122%281%29.pdf

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Informal Generic Drugs Discussion Group (IGDG)

- Established in April 2019 following endorsement of the ICH Reflection Paper on ***Further Opportunities for Harmonization of Standards for Generic Drugs***
- This paper outlines recommendations to develop a series of ICH Guidelines on standards for demonstrating equivalence (e.g., bioequivalence) for (1) non-complex dosage forms and (2) more complex dosage forms and products.
- The IGDG serves as a technical discussion group for issues relevant to harmonisation of scientific and technical standards for generic drugs:
  - The IGDG recommends areas for harmonisation under ICH and assesses feasibility of harmonisation of various topic areas within existing regional regulatory frameworks.
- For more information:
  - https://admin.ich.org/sites/default/files/2019-04/ICH_ReflectionPaper_GenericDrugs_Final_2019_0130.pdf

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Pharmacoepidemiology Discussion Group (PEpiDG)

- The Pharmacoepidemiology Discussion Group (PEpiDG) was established in September 2019 following endorsement of the ICH Reflection Paper on ***Strategic Approach to International Harmonization of Technical Scientific Requirements for Pharmacoepidemiological Studies Submitted to Regulatory Agencies to Advance More Effective Utilization of Real-World Data***
- In recent years, the sophistication of pharmacoepidemiological studies conducted in various countries worldwide has advanced dramatically alongside more active use of Real-World Data
- Many regulatory agencies and industries are now conducting epidemiological safety assessments based on data gathered during the post-marketing stage
- The goal is to harmonise the technical scientific requirements related to pharmacoepidemiological studies submitted to regulatory agencies:
  - Facilitate utilization of Real-World Data and promote a globally-harmonised approach in post-marketing safety-related regulatory actions based on the most current scientific evidence
- The PEpidDG will serve for a two-year period.
- For more information:
  - https://admin.ich.org/sites/default/files/2019-08/ICH_ReflectionPaper_Pharmacoepidemiology_2019_0605.pdf

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Public Comment Period

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