Background

- Regulatory authorities approve drugs that are demonstrated to be safe and effective for human use
- Definition of “safe” has historically been interpreted as “benefits outweighing risks of the drug”
- Benefit-risk assessment is the fundamental basis of regulatory decision-making
- In the last several years, providing greater structure for benefit-risk assessment has been an important topic in drug regulation
Background, cont.

- There is general guidance in M4E(R1) regarding the expected content of CTD Section 2.5.6 “Benefits and Risks Conclusions”
- There is limited additional guidance to aid industry in structuring their benefit-risk assessment
- Regulators observe variable approaches taken by applicants in presenting benefit-risk information

Charge for M4E(R2) EWG

- The M4E EWG was tasked with revising Section 2.5.6 “Benefits and Risks Conclusions” of the ICH M4E guideline to standardize the content and presentation of benefit-risk information in regulatory submissions
- The M4E Concept Paper and Business Plan were endorsed by the ICH Steering Committee (SC) on June 5, 2014
- In March 2015, the SC endorsed M4E’s plan to revise “other parts of the Clinical Overview to ensure that the revised guidance is both harmonized and appropriate in its entirety.”
- In June 2016, the EWG completed revising Section 2.5.6
**Expert Working Group (EWG) Membership Parties**

- European Commission (EC)
- Pharmaceutical Research and Manufacturers of America (PhRMA)
- U.S. Food and Drug Administration (FDA)
- Ministry of Health, Labour and Welfare (MHLW)
- Japan Pharmaceutical Manufacturers Association (JPMA)
- European Federation Pharmaceutical Industries and Associations (EFPIA)
- SwissMedic
- DOH of Chinese Taipei
- DRA of Korea
- DRA of Brazil
- DRA of Australia
- World Self-Medication Industry (WSMI)

**EWG consensus on general principles for a revised guideline**

- A revised Section 2.5.6 guideline should be concise and not prescriptive; it should suggest elements for consideration by an applicant in the benefit-risk assessment
- The new guideline should not specify methods for the benefit-risk assessment, nor should it specify the review approach used by a regulator
- Section 2.5.6 should be consistent with other benefit-risk relevant ICH guidelines (e.g., ICH E2C(R2) (PBRER))
EWG consensus on general principles for a submitted Section 2.5.6

- Section 2.5.6 should represent the thought process behind the applicant’s weighing of benefits and risks
- It should communicate this thought process to the regulator
- It should communicate a critical and succinct presentation of the benefit-risk assessment
- It should not present new efficacy or safety data

Revised 2.5.6 Structure

2.5.6 Benefits and Risks Conclusions
   2.5.6.1 Therapeutic Context
      2.5.6.1.1 Disease or Condition
      2.5.6.1.2 Current Therapies
   2.5.6.2 Benefits
   2.5.6.3 Risks
   2.5.6.4 Benefit-Risk Assessment
   2.5.6.5 Appendix
Notable aspects of M4E revision: 2.5.6.1 Therapeutic Context

- Discussion includes:
  - **Disease or Condition**—aspects of the disease that are most relevant to the intended population across the spectrum of disease severity
  - **Current Therapies**—major therapies in the intended population and the medical need for a new therapy
- Limitations or uncertainties in understanding the condition or therapies should be discussed
- Information about disease severity in subpopulations should be considered

Notable aspects of M4E revision: 2.5.6.2 Benefits and 2.5.6.3 Risks

- Use of terms ‘Key Benefits’ and ‘Key Risks’ aligns with ICH E2C(R2) (PBRER)
- Suggestions for the types of benefits and risks to consider when identifying key benefits and key risks
- Suggestions for characteristics of benefits and risks to consider when identifying and describing the key benefits and key risks
- Strengths, limitations, and uncertainties of the benefit and risk information should be considered and discussed
Notable aspects of M4E revision: 2.5.6.4 Benefit-Risk Assessment

- No prescribed approach for the assessment
- A descriptive approach will generally be adequate
- Applicants may use other methodologies to express the benefit-risk assessment quantitatively
- Detailed presentations of the methodology may be submitted in an appendix to 2.5.6, although a summary and explanation of the conclusions should be included in 2.5.6

Notable aspects of M4E revision: 2.5.6.4 Benefit-Risk Assessment, cont.

- Summary tables and graphical displays may be considered to communicate the benefit-risk assessment
- Information about patient perspectives may be considered, to include:
  - Descriptive information on patient attitudes and preferences with respect to therapeutic context, benefits, and risks
  - Information obtained directly from patients or indirectly from other stakeholders using qualitative, quantitative, or descriptive methods
Other revisions to Section 2.5: Section 2.5.1 Product Development Rationale

- Submissions of section 2.5.1 often contain information about the therapeutic context.
- 2.5.1 offers guidance on describing the disease, but is silent on discussing other available treatments; the revised 2.5.6 now calls for explicit consideration of current therapies.
- Therefore, an additional bullet in 2.5.1 acknowledges and offers linkage with 2.5.6 on current treatments:
  - “include a brief overview of the major therapies currently used in the intended population.”

Outlook

- Public comments were carefully considered and influenced the finalization of the M4E revision.
- Benefit-risk assessment is a rapidly evolving field with variations in experience and expertise.
- New 2.5.6 captures pan-regional thinking on content, format, and the flexibility to apply different approaches to benefit-risk assessment.