ICH M4E(R2): Revised Guideline on Common Technical Document -- Efficacy

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

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