IQ-DILI Initiative:
Pharmacovigilance & Risk Mitigation
Working Group

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Working Group Objectives

• Identify academic/industry/regulatory consensus for “real-world best practices” for medicines with an identified DILI risk

• Illustrate (with examples) the principles for determining when routine labelling (contraindications/warnings/precautions) is inadequate to communicate DILI risk and for which:
  • a US Risk Evaluation and Mitigation Strategy (REMS) is required and additional Elements To Assure Safe Use (ETASU) are needed
  • the EU Risk Management Plan (RMP) may require Additional Risk Minimization Measures (ARMM)

• Examine current approaches and tools used to assess, mitigate and monitor (PV) DILI risk with respect to effectiveness and burden
Literature Survey, Data Sources for Proposed White Paper

- Search PubMed literature for DILI risk evaluation, mitigation & PV outcomes
- Review Regulatory Guidance for risk mitigation (DILI or general) & PV practice
- Review academic/collaborative databases of DILI associated therapies
- Review recent drug applications and approvals describing liver injury or DILI
  - Medical Review/Advisory Committee minutes
  - Labels, Medication Guides & SmPC
  - REMS with or without ETASU
  - RMP with or without AARM
- Survey experience on effectiveness and burden of established practices for DILI risk evaluation, mitigation and PV monitoring among:
  - IQ-Consortium Industry members
  - Academic members
  - Regulatory members
  - Patient advocacy groups
- Outline best practice for risk assessment, mitigation, and monitoring of DILI from late development to real-world use
White Paper Objectives – Review:

1. Current best practices in characterizing DILI risk including:
   1. its potential mechanisms
   2. its characteristic presentation (seriousness and temporal nature)
   3. its incidence in the intended treatment population

2. Approaches for assessing the unmet need (the treated disease’s seriousness and incremental benefit of new drug)

3. Evaluation of controllable and uncontrollable risks:
   1. extent of exposure (treatment duration and population size)
   2. risks for unintended use/misuse of new drug

4. Likelihood of effective mitigation relative to expected burden
Key Elements of Risk Management

• Collect & analyze data to identify & characterize risk
  • Predictable, dose-dependent mechanisms vs. idiosyncratic risk
  • Subpopulations with greater/lesser risk
• Determine relative benefit of intervention
  • Subpopulations with greater/lesser benefit
  • Potential scope of intervention’s use/misuse
• Formulate benefit-risk (B-R) balance
• Evaluate potential for risk mitigation (modifying B-R balance)
• Select optimal risk minimization tools (considering burden)
• Implement evaluation plan to assess effectiveness & compliance
• Iterate to adjust risk minimization tools to improve effectiveness
Risk Management & PV Monitoring Tools

- **Routine**
  - Labeling Risk Management
    - Dosage & Administration, Contraindications, Special Populations
  - Labeling Risk Communication
    - Adverse Drug Reaction Tables, Warnings & Precautions, Boxed Warnings (USPI)
  - PV Monitoring
    - Spontaneous reports, mining external databases, signal detection and PSUR

- **Enhanced**
  - Risk Management
    - Special Communications (Dear HCP letters, patient alert cards, press releases, etc.)
    - Special Training (Registered users, HCP certification)
    - Special Testing (Lab & Treatment Protocols)
    - Controlled Access (Specialty Pharmacy, HCP certification, patient registry)
    - Frequent Assessment/Reporting of risk mitigation effectiveness
  - PV Monitoring
    - Post-approval safety studies/registries
IQ-DILI PV-RM Working Group Members

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