

Risk Benefit Assessment and Risk Management

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Outline

- Risk versus perception
- How much risk is acceptable?
- Risk assessment
- PV Planning and risk management: ICH E2E
- Risk minimizing action
- The power of communication

Risk

- a situation involving exposure to danger (Oxford Dictionary)
- A probability or threat of damage, injury, liability, loss, or any other negative occurrence that is caused by external or internal vulnerabilities, and that may be avoided through preemptive action (<http://www.businessdictionary.com/definition/risk.html#ixzz2MxJoKUms>)

Risk Perception

Individual judgement influenced by

- Quality of risk
 - Natural/human made
 - Catastrophic/chronic
 - Familiar/new
 - Imposed/voluntary
- Population affected
 - Vulnerable (children, pregnant)
 - Known victims

- Control
- Uncertainty
- Awareness
- Risk vs benefit

www.nieman.harvard.edu/reportsitem.aspx

How much risk is acceptable?

- Choice made by individuals for themselves
 - Risk- benefit analysis at personal level
 - Choice made by institution/authority for the population
 - Risk –benefit anlyasis at population level
- Different conclusions possible

Risk Assessment

- Severity and seriousness of ADR
- Preventability
- Size of population exposed
 - Vulnerable populations?
- Essential medicine?
- Therapeutic alternatives
- Rapid increase of ADR reports
- Impact on public opinion

ICH Guideline E2E

INTERNATIONAL CONFERENCE ON HARMONISATION OF
TECHNICAL REQUIREMENTS FOR REGISTRATION OF
PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE PHARMACOVIGILANCE PLANNING E2E

ICH E2E

- Recommended for adoption November 2004
- Focus on documents to be submitted when applying for a marketing authorization
 - Safety Specification
 - Pharmacovigilance Plan
- For new chemical entities or products with major changes
 - Populations, indications, dosage, formulation, manufacturing etc

Safety Specification

- Identified risks
 - Preclinical findings not addressed/resolved in clinical phase
- Potential risks
 - General pharmacology
 - Interactions
 - Toxicity
- Important missing information
 - Populations not studied

Pharmacovigilance Plan

- Based on Safety Specification
- Ongoing safety issues
 - From clinical development and/or postauthorization
- Routine PV
 - Spontaneous reporting
 - PBRER
- Action plan for safety issues incl. Milestones
 - Objective/rationale/monitoring
 - Milestones for evaluation and reporting

Benefit/risk balance

- Benefit/risk balance must always be favourable but
 - Benefit at individual level and
 - Benefit at population level

can differ

Benefit/Risk Assessment

- Natural course and epidemiology of disease
- Who is at risk/who benefits?
 - Special populations?
 - Risk factors?
- Magnitude of risk/of benefit?
 - Efficacy = benefit?
 - Surrogate markers
- Preventability/risk mitigation
- Risks/benefits of alternative treatments

Comparative Risk Evaluation

- Medicinal products with different time on the market
- Information mainly from spontaneous reporting systems
- ADRs may differ in clinical significance and not be easily comparable

Transparency

- Publication of PV Plans
 - ANSM (DRA France)
- Publication of Evaluation Reports
 - EMA: EPAR (European Public Assessment Report)
- Approved Risk Evaluation and Mitigation Strategies (REMS)
 - US FDA Website

Risk Minimizing Action

- Watch and wait
- Gather more information
- Inform
- Restrict use
- Restrict availability
- Suspend
- Withdraw

But above all...



Communication

- Product information
- Health Care Professional Communication
- Scientific paper
- DRA website
- PV Newsletter
- Press release
- Stable working relationship with media

The “side effects” of information

Well informed

- HCP will prescribe more rationally
- Patients/consumers will be more alert

More reports on potential safety issues will reach the PV centre/DRA (reporting bias)

Better collaboration within the PV community

Conclusions

- Risk perception is as important as absolute risk
- Acceptability of risk is difficult to quantify
- Risk and benefit go hand in hand
- Comparative assessment is a difficult "must"
- Transparency and communication are our best friends



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