Safety Risk Assessment in Drug Development

• Introduction
All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy.

Philippus Aureolus Theophrastus Bombastus von Hohenheim-Paracelsus (1493-1541)
HAZARD
Inherent potential for harm

RISK
Probability of harm under specific conditions
Safety Risk Assessment in Drug Development

Hazard + No exposure = No risk

Hazard + exposure = Risk
Requires a multifactorial, multidisciplinary approach:
  – Nature of the hazard (i.e. “seriousness” of the toxicity)
  – Dose-response and exposure-response relationship
  – Therapeutic Index (“safety margin”)
  – Mechanism
    • species specificity / relative sensitivity
    • Metabolism / drug distribution
  – Reversibility
  – Availability of early markers
  – Target population
  – Risk/benefit ratio (depends on target disease)
  – Comparison with existing therapy
    • concept of acceptability of “class effects”
• Preclinical Safety Assessment conducts a set of studies with the active ingredient, based on:
  – Regulatory guidelines
  – Internal harmonisation
  – Acceptability to internal and external ethics boards
  – Scientific rationale

• General expectation is to induce toxicity
• Purpose must be:
  – identify and characterise hazards
  – establish dose-response & exposure-response relationships
  – allow informed assessment of risks

Modified from “Risk Assessment in Drug Development” by Colin Fish
Focus is on the drug itself, and safety in volunteers and patients

But also it is important to consider:
- impurities, extractables, solvents, degradation products, intermediates, metabolites etc
- safety of manufacturing staff, dosing technicians, etc
- Overdose implications / special scenarios (misuse, incorrect administration, etc.)

Modified from “Risk Assessment in Drug Development” by Colin Fish
Is not as simple as just “following a recipe”
3. Eliminate it -

4. Find a substitute -

Modified from "Risk Assessment in Drug Development" by Colin Fish
Safety Risk Assessment in Drug Development

Modified from “Risk Assessment in Drug Development” by Colin Fish
Safety Risk Assessment in Drug Development

7... OR RUN!

Presence of mind is good - absence of body is better!

Philip Quested

Modified from "Risk Assessment in Drug Development" by Colin Fish
BEFORE
- Safety divided into pre and post-marketing
- Reactive management through passive observation
- Reliance on SR databases
- Burden on HAs to detect risks
- Risk management plans rare, drug specific
- Routine pharmacovigilance was the standard
- Risk activities generally not disclosed to public

TODAY
- HAs view safety as a lifecycle discipline
- Prevention is focus of earlier and better risk management
- New databases and technologies
- HA and sponsor share risk detection responsibilities
- Starts since drug development and continues in postmarketing phase
- Risk management plans are now required for most new dossiers
- Drug-specific PV often requested
- Risk activities made public by HA
Different Players involved in Safety Risk Assessment / Management

**PATIENTS:**
Effectiveness at no risk | Freedom to choose

**HEALTH CARE PROFESSIONALS:**
Good effectiveness at low risk | Litigation fear

**REGULATORS, PAYERS, POLITICIANS:**
Good effectiveness, acceptable risk | Fear of litigation and fear of the media
Resource constraints

**PHARMACEUTICAL COMPANIES:**
Enough effectiveness, acceptable risk | Fear of litigation and fear of the media | Resource constraints | Return maximization: shareholders | Sources
**GOAL** is to maximize the benefit of medications while minimizing risk.

Systems should be based on risk identification and assessment, risk confrontation, identification of options to manage risk, communication, and finally assessment of results (Involving the different players).

Pharmaceutical companies must design an effective and robust risk management planning processes since drug development.

Authority have directed a significant shift in risk assessment from traditional routine PV activities to earlier and more intensive study of safety during clinical development.
Optimize the safe use of drugs and optimize the benefit/risk balance throughout a product's life cycle.

Pharmacoepidemiology studies to characterize patient populations and study risk, both during the development phase and after launch.

Earlier identification and study of safety issues during the development phase and earlier planning of risk management and PV activities after launch and during product's life cycle.

Early identification, assessment, communication, and management of risk in order to maximize benefit and minimize risk to patients.
Safety Risk Assessment in drug development

Starts early in drug development with collection of data designed to build safety risk awareness.

Include any known safety information about compound/compounds; about the natural history of the disease; characteristics of the target population, and exposure assessment.

Summary of the identified risks of a drug, potential for important unidentified risks, and populations that could potentially be at risk (not studied in development phase).

Guidance intended to aid industry and regulators in planning PV activities in preparation for the early postmarketing period of a new drug.

Drug Information Association

www.diahome.org

Dr. Cecilia Calderon | October 2013
Ways to better identify and assess Risk during drug development:
* Larger safety database
* Use of a diverse patient population,
* Study of multiple drug doses
* Long-term safety studies
* Available scientific information
* Many Others

Ways to ensure that drugs are prescribed / used correctly, through Risk Minimization Action Plans:
- Education programs to HP and Patients
- Reminder systems
- Performance-linked access system tools

The challenge is to develop a process that would collect and update relevant risk information and put it in one place for review and decision-making.
All products will have a risk management plan by the end of development considering all known and potential risks and will recommend strategies to manage these risks.

The rationale for this plan will be based on scientific data and should reassure all stakeholders that all aspects of risk have been studied and considered.

For the majority of drugs, this plan will be based on good PV practices and communication of risks via the approved product label.

Risk management strategies & activities, in the development and postmarketing should be tailored to the specific drug, target population, and known and potential risks.
Safety Risk Assessment and/or Management in Drug Development and Post Marketing Drugs is a must, and will keep maintain a continuous moving from Theory to Practice.
• Increased expectations on the public as well as emerging regulatory trends that emphasize a scientific, strategic approach to management of safety/risk information present new challenge for all the players

• It is Necessary to establish and execute best PV practices for Risk Assessment and Management.
• Evident improvements are now evident, however this is not yet a cultural practice in all countries.

• Still is mooving from theory to practice. But in the real life where we are today?...
• Thank you for your attention!

Dr. Cecilia Calderon
Mexican Association of Pharmacovigilance
The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to Drug Information Association, Inc. (“DIA”), its directors, officers, employees, volunteers, members, chapters, councils, Special Interest Area Communities or affiliates, or any organization with which the presenter is employed or affiliated.

These PowerPoint slides are the intellectual property of the individual presenter and are protected under the copyright laws of the United States of America and other countries. Used by permission. All rights reserved. Drug Information Association, DIA and DIA logo are registered trademarks or trademarks of Drug Information Association Inc. All other trademarks are the property of their respective owners.