IRISH MEDICINES BOARD

Setting Limits in Shared Facilities

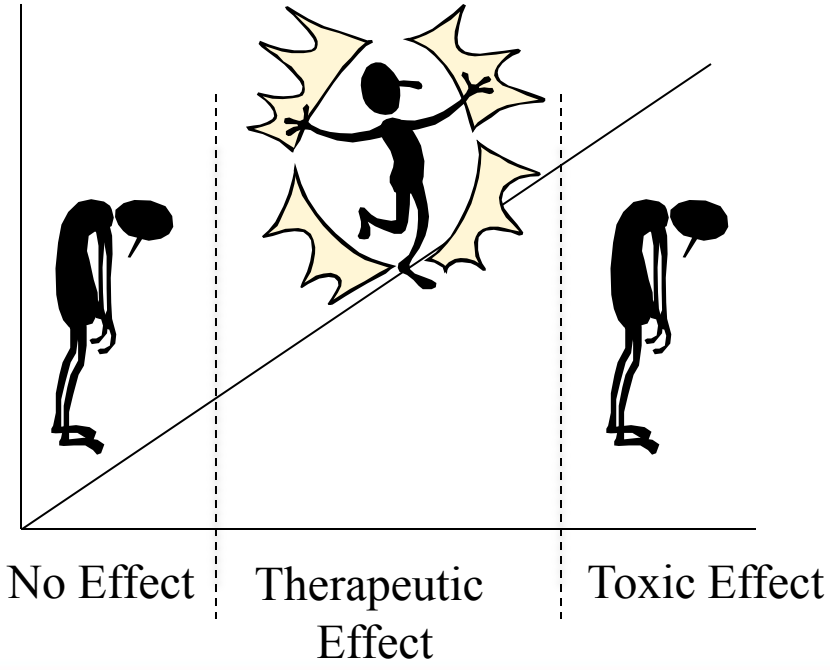
The New Scientific Approach

27h September 2012

Sarah O'Meara, Ph.D.
Non-clinical Assessor & SWP Delegate,
Irish Medicines Board

Principles of Pharmacology and Toxicology

"Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy" Paracelsus 1493-1541



IRISH MEDICINES BOARD

Schematic of Cleaning Validation Process:

Determine the most appropriate cleaning procedure for the equipment:

1. Generate acceptance criteria data for the contaminant.
2. The cleaning method will be determined by the process, the equipment, the cleaning agents and the cleaning techniques available.
3. All aspects of the cleaning procedure should be clearly defined in SOP's be they manual / CIP or COP

↓

Develop and validate the sampling and chosen analytical methods for the compound(s) being cleaned.

1. Swab
2. 2. Rinse

(determine % recovery, limit of detection, limit of quantitation, accuracy of method, reproducibility, stability over time … etc.

↓

Evaluate equipment surfaces and determine

1. Worst case locations to sample (swab sampling)
2. Volume and type of rinse solvennt to be employed (rinse sampling)
3. Equipment surface area (necessary to calculate carryover into subsequent batches)

IRISH MEDICINES BOARD

Current Situation:

Prevention of cross-contamination in production

5.18 Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapours, sprays or organisms from materials and products in process, from residues on equipment, and from operators' clothing. The significance of this risk varies with the type of contaminant and of product being contaminated. **Amongst the most hazardous contaminants are highly sensitising materials, biological preparations containing living organisms, certain hormones, cytotoxics, and other highly active materials.** Products in which contamination is likely to be most significant are those administered by injection, those given in large doses and/or over a long time.

(EU-GMP; Medicinal Products of human and vetinary use; Ch 5)

IRISH MEDICINES BOARD

Revision of Chapters 3 and 5 of the GMP Guide: "Dedicated facilities"

No Change

"GMP/GDP Inspectors Working Group has agreed that the use of dedicated facilities should normally be required when beta-lactam antibiotics are produced. In addition dedicated facilities should be used when live pathogenic organisms are handled." (EMA/INS/GMP/809387/2009)

Going Forward?

"for other products, manufacturers introducing a product into shared facilities should carry out an assessment of all relevant product and process characteristics to evaluate whether it is suitable for production in shared facilities. This assessment should include input from a ***toxicologist.*** ***Where the product has known sensitizing potential, or is highly potent or toxic, the Supervisory Authority should be consulted to discuss the manufacturer's risk management measures."*** **(EMA/INS/GMP/809387/2009)**

IRISH MEDICINES BOARD

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 October 2011
EMA/CHMP/SWP/598303/2011
Committee for Medicinal Products for Human Use (CHMP)

Concept Paper on the development of toxicological guidance for use in risk identification in the manufacture of different medicinal products in shared facilities

IRISH MEDICINES BOARD

Problem Statement

- No defined approach in deriving an acceptable limit
- Plethora of toxicological tools being used
- Lack of harmonised approach/interpretation
- Different production requirements
  - Significant financial impact on manufacture
  - Impaired quality of medicinal products
  - Adverse effect on patient health

IRISH MEDICINES BOARD

Current Approach

- "the philosophy has been to reduce the levels of residual product in each piece of equipment, such that no greater than **1/1000th of the normal therapeutic dose** or **10ppm** will be present per typical dose of the next product to be run in the equipment."

  - Available Pharmacological/Toxicological data?
  - Possible exposure data?
  - Too restrictive, not restrictive enough?

IRISH MEDICINES BOARD

Scientific Approach

"Pharmacological and toxicological descriptions (dose-response, no-observed-adverse-effect level (NOAEL) and ADI) should be used to assess compounds instead of hazard labels. Terms such as potent, cytotoxic, cytostatic, and other product class definitions tend to induce an emotional response that might imply that these compounds are always difficult to handle and require the highest level of control"

ISPE baseline guide Risk-MaPP

IRISH MEDICINES BOARD

Draft Guideline

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

2 February 2012
EMA/CHMP/SWP/85025/2012
<Name of committee (Committee abbreviation)>

Guideline on setting limits for use in risk identification in the manufacture of different drug products in shared facilities

Draft[1]

ARD

Scientific Approach

- **Hazard identification**
  - qualitative appraisal of the inherent property of a substance to produce adverse effects
  - formal review of all available animal and human data should be performed for each compound
  - animal repeat-dose toxicity studies, carcinogenicity studies, studies of genotoxicity *in vitro* and *in vivo*, reproductive and developmental toxicity studies as well as clinical data on therapeutic and adverse effects
  - identified gaps need to be critically assessed

IRISH MEDICINES BOARD

Scientific Approach

- **Critical effect identification**
  - most sensitive indicator of an adverse effect seen in general toxicity studies
  - positive finding in studies of carcinogenicity, genotoxicity and reproductive and developmental toxicity relevant to humans
  - clinical pharmacodynamic/safety effect

IRISH MEDICINES BOARD

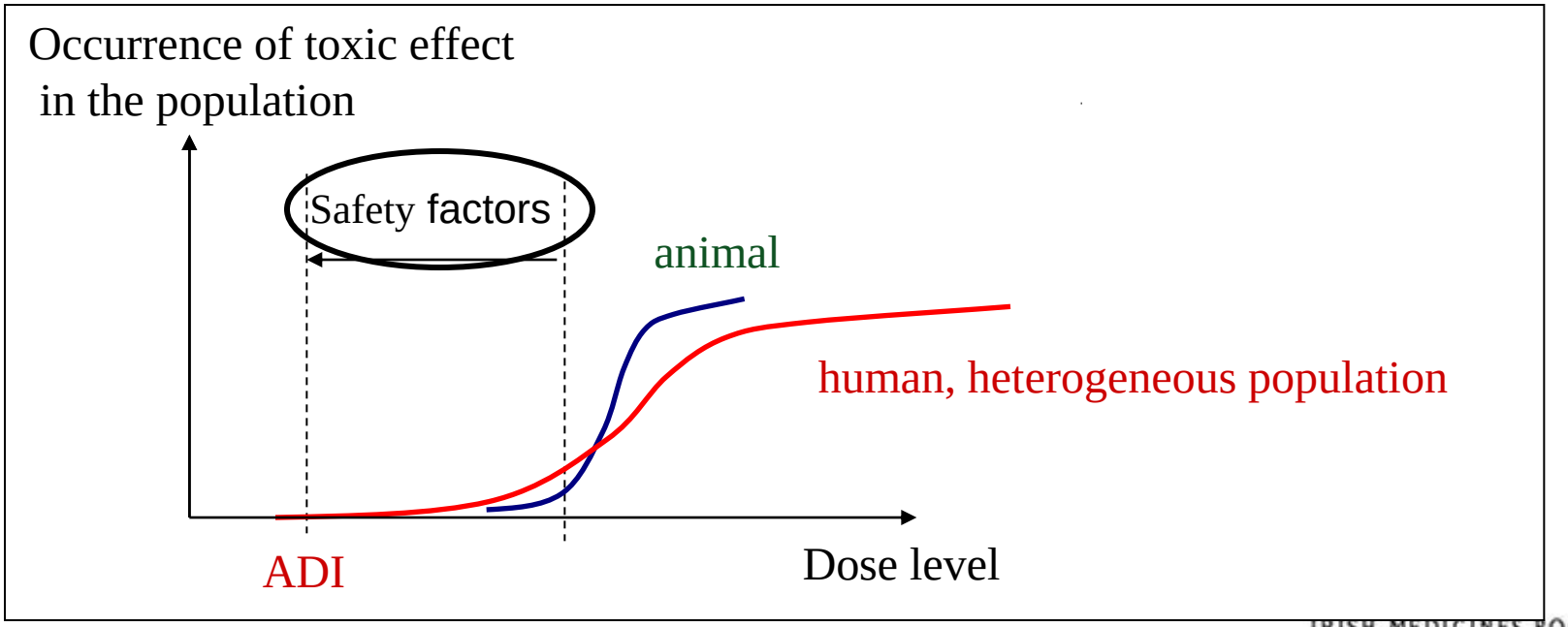
Scientific Approach

- **Establishing NOEL(s)**
  - highest tested dose at which no adverse (“critical”) effect is observed
  - Lowest NOEL should be employed for PDE/ADI calculation
  - If no NOEL established - lower-observed-effect level (LOEL) may be used

IRISH MEDICINES BOARD

Defining and Acceptable Daily Intake

Acceptable Daily Intake (ADI) : Daily dose of a substance below which no adverse effects are anticipated in the human. Used when there is a threshold in the dose response curve: Derived based on animal or human data.



IRISH MEDICINES BOARD

Format of Toxicological Tool to Define an ADI

Example: PDE calculation (ICH Q3C)

PDE = NOAEL x weight adjustement / F1 x F2 x F3 x F4 x F5

- F1: Interspecies extrapolation, takes into account surface area. From 1 to 12.
- F2: Interindividual variability. Equal to 10.
- F3: Relevance of the duration of the animal study. From 1 to 10.
- F4: Severity of the effect. From 1 to 10.
- F5: Quality of the data. From 1 to 10.
- Additional modifying factor for additional uncertainties (e.g. enzyme immaturity in children). Equal to 10.

➔ The choice of the safety factors depends on the professional judgment of the toxicologist: ***there is a need for consensus***

IRISH MEDICINES BOARD

Specific considerations

- **Hormones & Biologics :**
  - Safety threshold could be derived from pharmacological data

- **Cytotoxic compounds:** with a threshold-related mechanism of toxicity:
  - Safety threshold could be derived from NOAELs

- **Genotoxic Compounds:** no threshold related mechanism
  - Application of the Threshold of Toxicological Concern (TTC) as outlined in the Guideline on the Limits of Genotoxic Impurities (EMEA/CHMP/QWP/251344/2006)

IRISH MEDICINES BOARD

Exemptions to Scientific Approach

- The toxicological approach is not envisioned to be applied to:
  - Highly sensitizing materials (e.g. penicillins)
  - Biological preparations (e.g. from live micro-organisms)
  - Non-medicinal products, including pesticides, herbicides
- Require dedicated facilities for manufacture

IRISH MEDICINES BOARD

Risk Assessment Report

- **Risk Assessment Report**
  - Comprehensive literature search
  - In house study data
  - Rationale for choice of critical endpoints used to derive PDE
  - Pivotal animal/human studies should be sourced and reviewed in terms of
    - Study design
    - Description of findings
    - Accuracy of report etc
  - One page summary should be provided

IRISH MEDICINES BOARD

Thank you for your attention

IRISH MEDICINES BOARD