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# A Practical Approach for Implementing Toxicology Based Cross Contamination Control

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# DISCLAIMER

**The opinion expressed in this presentation are solely those of the presenter and not necessarily those of QBiotics Limited or PharmOut.**

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# OVERVIEW

1. Cross Contamination Threshold
2. Requirements
3. Challenges
4. A Practical Approach for Implementing Toxicology Based Cross Contamination Control

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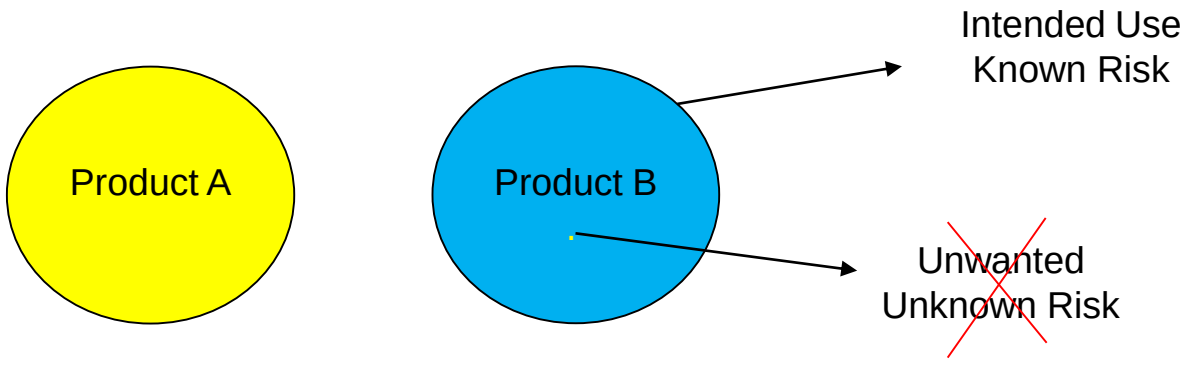
# CROSS CONTAMINATION THRESHOLD

***A level that can be considered safe for all populations***

***An amount that can be taken (daily) for the rest of life without compromising health***



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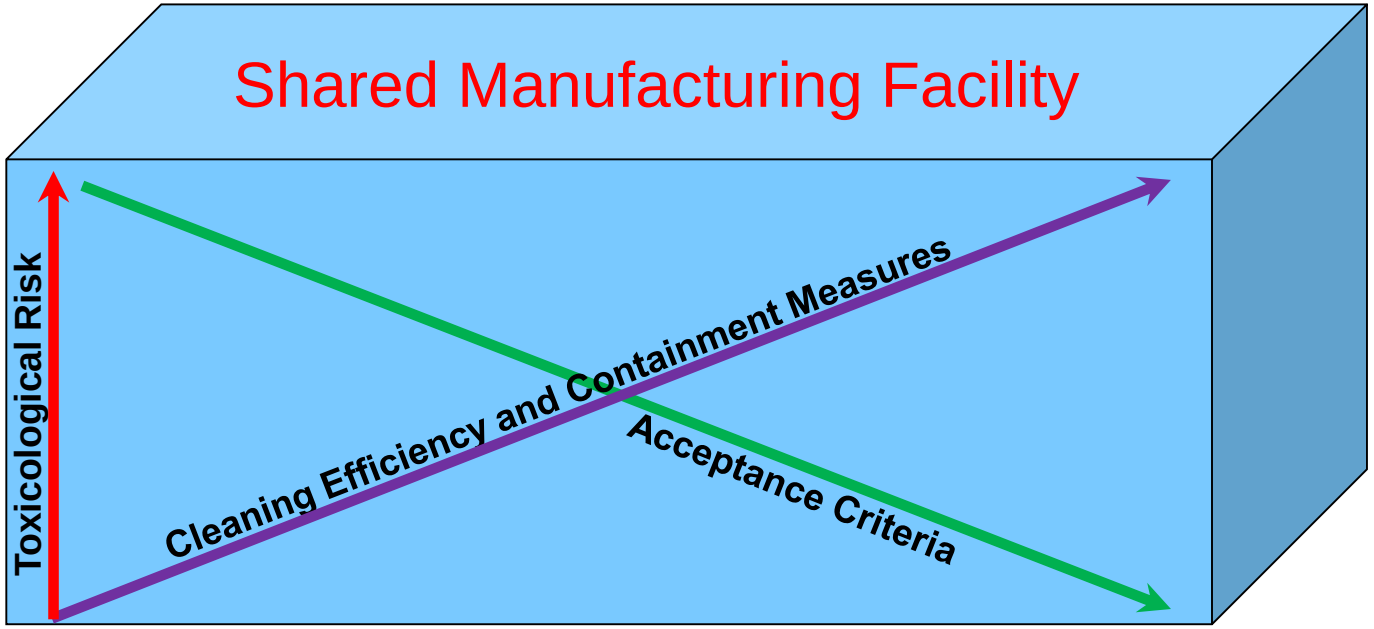
# CROSS CONTAMINATION THRESHOLD



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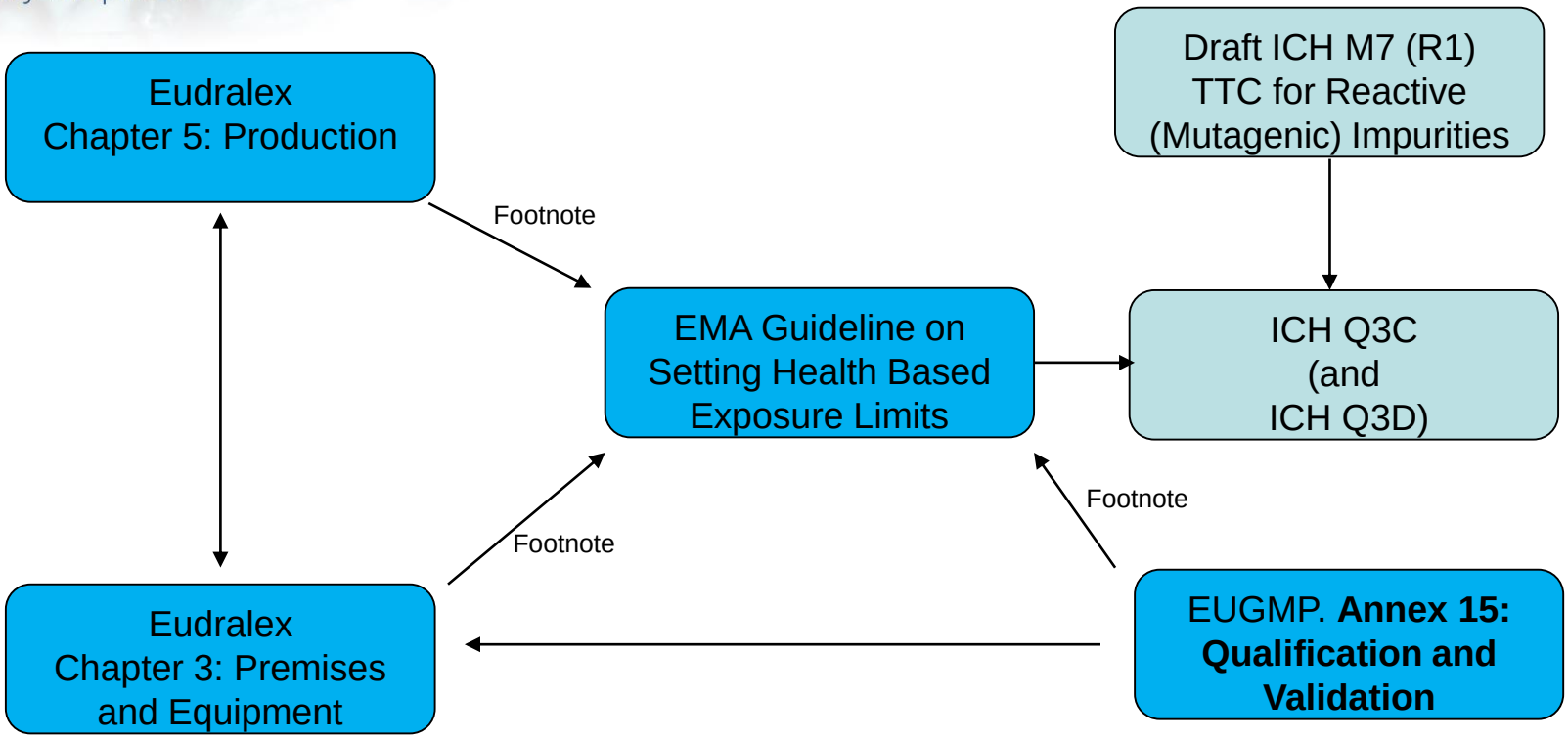
# REQUIREMENTS



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# REQUIREMENTS

**Eudralex**
**Chapter 3: Premises and Equipment**

Maintain cross contamination level within toxicologically evaluated limit, otherwise use dedicated facility.

Utilise QRM principles.

**Eudralex**
**Chapter 5: Production**

Use quality risk management process for the contamination control including potency and toxicological evaluation.

Acceptable technical or organisational measures to confine the manufacturing activities to a segregated or self contained area**.**

**EMA Guideline on Setting Health Based Exposure Limits**

How to derive toxicology based Permitted Daily Exposure (PDE) or Threshold of Toxicological Concern (TTC).

**EUGMP. Annex 15: Qualification and Validation**

Product residues carryover limit should be based on a toxicological Evaluation.

When a toxicological evaluation may not be applicable.

Consider toxicity and potency for cleaning validation worst case selection together with solubility and cleanability.

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# CHALLENGES

- **KNOWLEDGE AND EXPERIENCE**
  - Toxicologist

**An “optometrist” is not expected to answer a “gynecological” question**

- **TIME FRAME**
  - New product **1st June 2015**
  - Existing product
    - Manufacturing facility Human or Human + Vet products **1st Dec 2015**
    - Manufacturing facility Vet product **1st June 2016**

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# CHALLENGES

- **Validated test method**
- **Cost**
  - Toxicological evaluation
  - Risk assessment
  - Cleaning qualification or verification
  - Analytical method development
  - New containment measures
  - Reduced productivity
- **Access to or Lack of Data**
  - Innovator
  - Generic manufacture
  - Contract manufacturer

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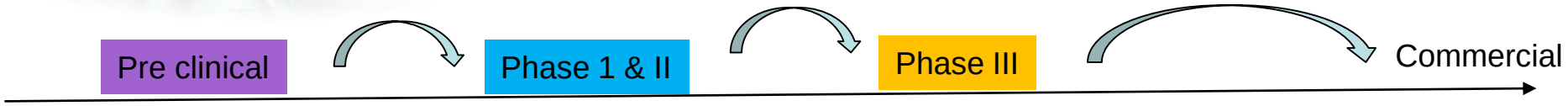
# A PRACTICAL APPROACH DURING DEVELOPEMNT




Classify compound by Characterisation & Stereochemistry

Use Worst case model or Cramer Classification

SafeBridge Category or Disposable or Dedicated equipment

Cleaning verification after every lot. Method?. TOC WFI run Genotox Limit?

Use preclinical data to estimate Worst Case **PDE** limit

Method with LOQ for Cleaning Validation

Perform **Risk Assessment** considering **PDE** of other products

Adjust containment practices

Cleaning verification after every lot

Finalise **PDE** Limit

Final **Risk Assessment**

Finalise Containment

Qualified Containment

Cleaning Validation

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# PDE

$$PDE = \frac{NOEL \times Weight\ Adjustment}{F1 \times F2 \times F3 \times F4 \times F5}$$

ICH Q3C

F1 = A factor to account for extrapolation between species
- F1 = 5 for extrapolation from rats to humans
- F1 = 12 for extrapolation from mice to humans
- F1 = 2 for extrapolation from dogs to humans
- F1 = 2.5 for extrapolation from rabbits to humans
- F1 = 3 for extrapolation from monkeys to humans
- F1 = 10 for extrapolation from other animals to humans

F2 = A factor of 10 to account for variability between individuals

F3 = A variable factor to account for toxicity studies of short-term exposure
- F3 = 1 for studies that last at least one half lifetime (1 year for rodents or rabbits; 7 years for cats, dogs and monkeys).
- F3 = 1 for reproductive studies in which the whole period of organogenesis is covered.
- F3 = 2 for a 6-month study in rodents, or a 3.5-year study in non-rodents.
- F3 = 5 for a 3-month study in rodents, or a 2-year study in non-rodents.
- F3 = 10 for studies of a shorter duration.

F4= Sever toxicity
- F4 = 1 for fetal toxicity associated with maternal toxicity
- F4 = 5 for fetal toxicity without maternal toxicity
- F4 = 5 for a teratogenic effect with maternal toxicity
- F4 = 10 for a teratogenic effect without maternal toxicity

F5 = A variable factor that may be applied if the no-effect level was not established (1-10)

**Final PDE?**

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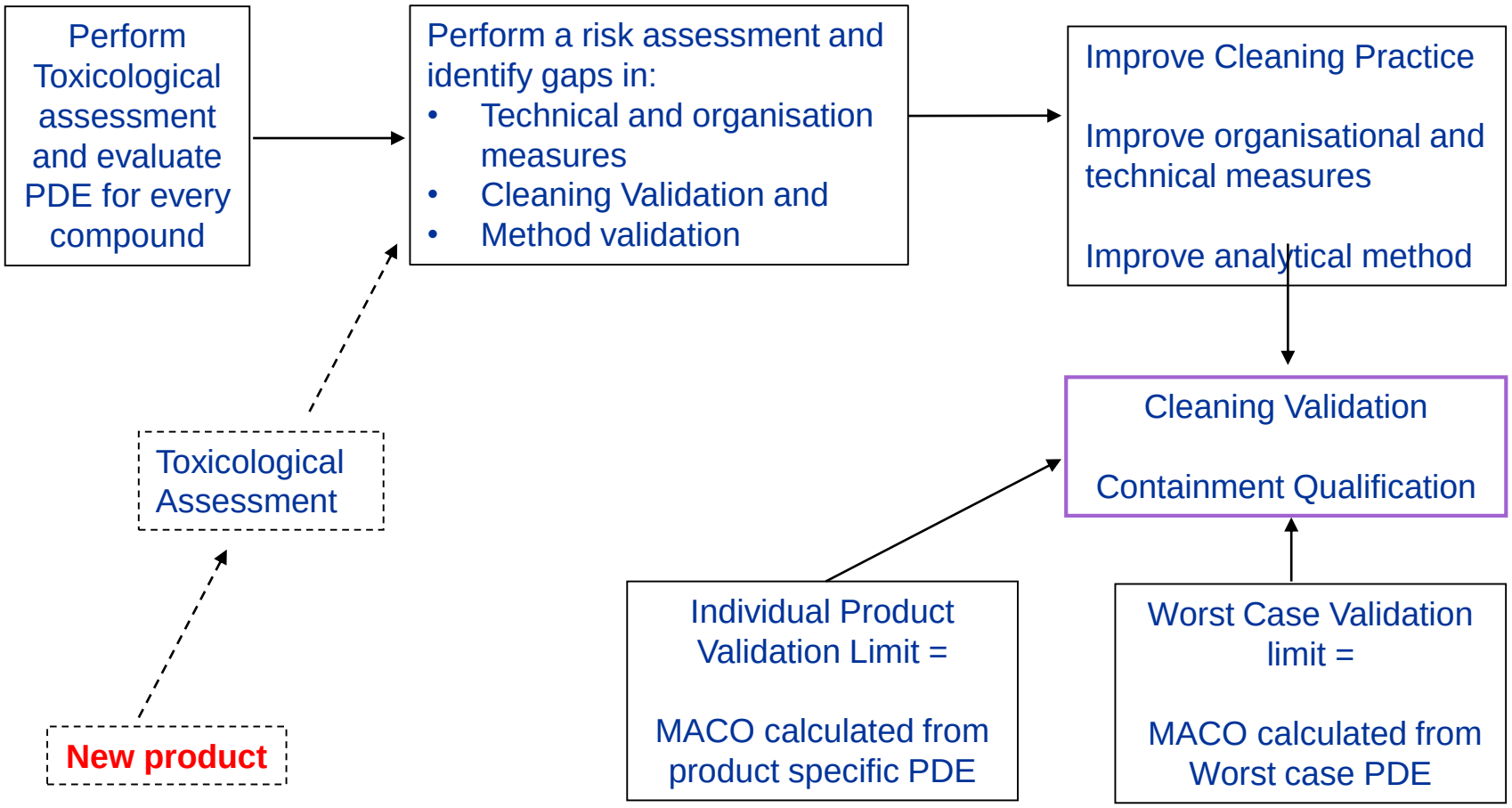
# A PRACTICAL APPROACH
# EXISTING PRODUCTS

## Ahsan's Model **A**



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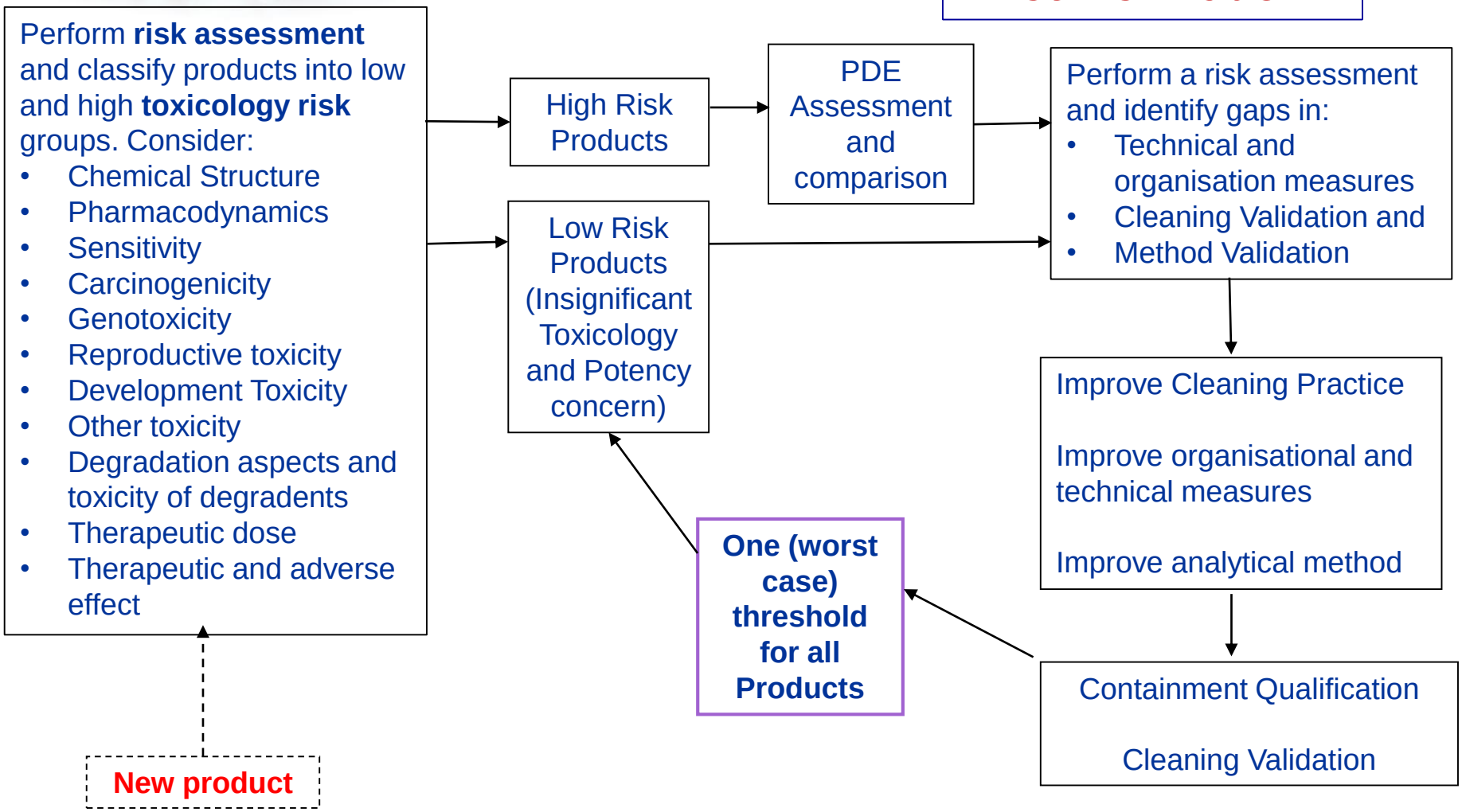
# A PRACTICAL APPROACH
# EXISTING PRODUCTS

Ahsan's Model **B**



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# A PRACTICAL APPROACH
# EXISTING PRODUCTS

## SPECIAL CONSIDERATIONS

- Involvement of Toxicologists in the categorisation of High and Low risk products.
- If high level information is not available or not conclusive then a detailed toxicological valuation and PDE calculation will be required.
- Scientific evidence that PDE of low risk product will be higher than toxicological worst case product.
- Ready to have one standard for all products. You will be using a very low threshold value for products that may have insignificant toxicological concerns.
- How many low risk product do you have. If not many then it may not worth performing a high level risk assessment.

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# A PRACTICAL APPROACH
# EXISTING PRODUCTS

Therapeutic macromolecules and peptides are known to degrade and denature when exposed to pH extremes and/or heat, and may become pharmacologically inactive. A toxicological evaluation may therefore not be applicable in these circumstances. (Annex 15)

**(However, PDE may be required for containment qualification purpose)**

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# A PRACTICAL APPROACH
# EXISTING PRODUCTS

## Cleaning Validation Worst Case Selection

- ❑Solubility
- ❑Cleanability
- ❑Toxicity
- ❑Potency

## Solubility/Cleanability Worst Case Product Using Toxicity/Potency Worst Case Limit

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# A PRACTICAL APPROACH
# EXISTING PRODUCTS

- Quality is conformance to requirements.
- Quality *may be* free. But it is *certainly* NOT a gift.

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# A PRACTICAL APPROACH
# EXISTING PRODUCTS

## Questions ?

- Are API and Drug product manufacturers performing separate toxicological assessment for the same active?
- Are various generic manufactures performing separate toxicological assessment same product?
- Is PDE a confidential information?
- Is PDI/PDE limit listed on the MSDS of the API?
- Can we trust  PDI/PDE information of the MSDSs?
- Is your contract manufacturing agreement indicating who is responsible for toxicological evaluation?

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# THANK YOU

# QUESTIONS ?