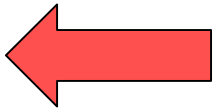
# Overview: 4 Sessions over a Day

## Workshop Goal: Collaborative efforts on future guidance

- **Session 1 Set the Scene from EMEA 'Pts to Consider':**

  3 speakers (Experts from Regulatory Authority, Industry, Medical Practice)

- **Session 2 Set the Science** (PK & PGx):
  - ADME Panel
  - Core Case: Building blocks for Session 3 

- **Session 3 Parallel Small Groups on Cases to Design:**

  Design the next drug development phase on the pipeline:
  - Case 1: Phase 1
  - Case 2: Phase 2a
  - Case 3: Seek Scientific Advice
  - Case 4: Phase 2b

- **Session 4**

  **Agree areas for consensus & next actions to work together**

# *PK & PGx*
# Building Blocks for the Cases in Session 3

**Linda Surh, MD PhD**
GlaxoSmithKline, UK
CEDD Global Regulatory Affairs

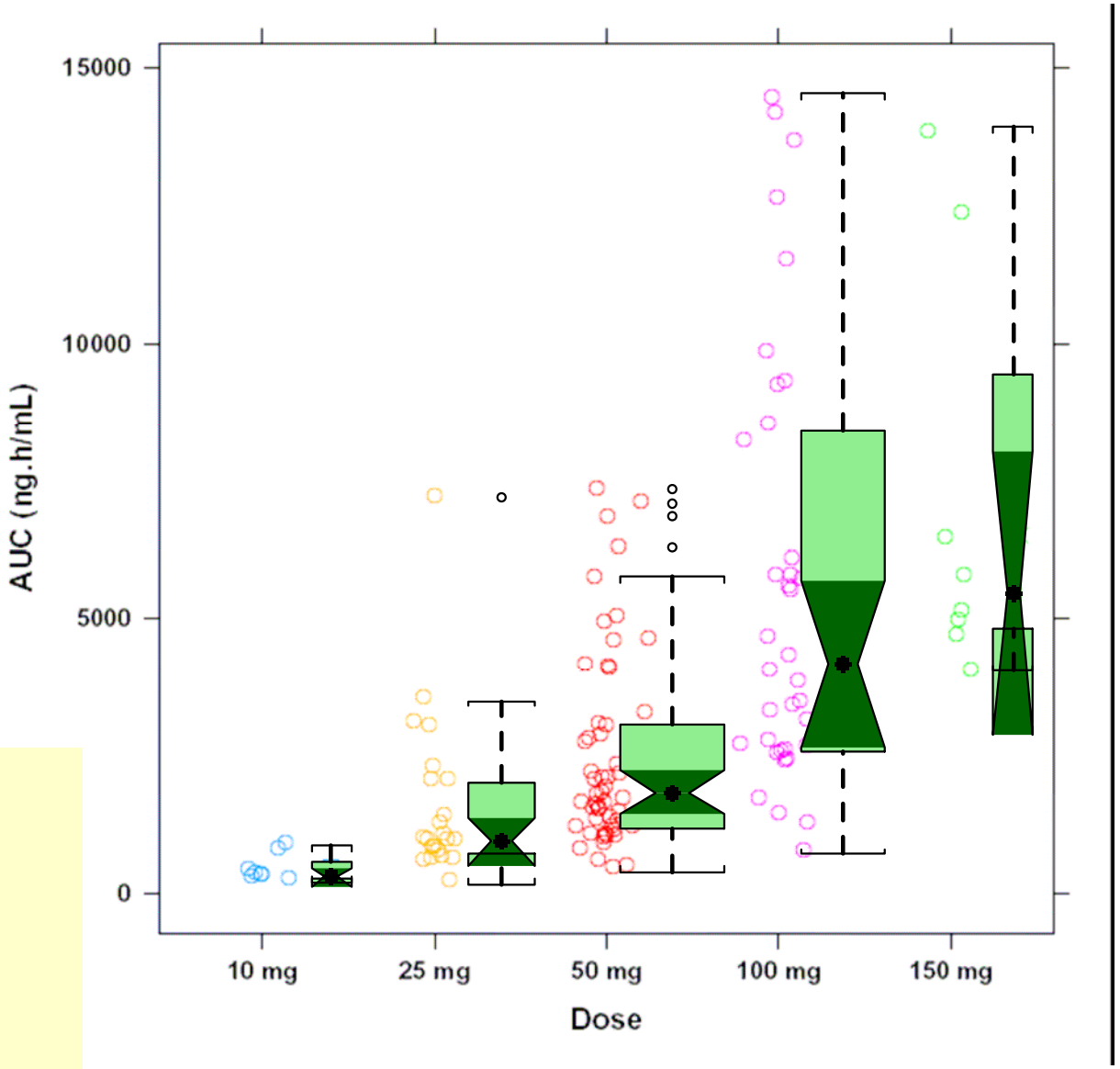
# Why PK for Today's Workshop?

PK Endpoint of Oral Drugs can be described by 3 primary Parameters:

**Absorption rate** | **Clearance** | **Volume of Distribution**

- **Knowledge of the physiological function**
- **Well-established drug development process**
- **Correlation between genetic variation & function**
- **Gap? = correlation between genetic variation & drug response**

# Human Responses are Variable
# Which Variability needs Investigation?




**PK in All Phase 1 Studies** (n=104)

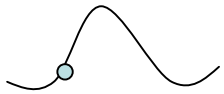
Many Factors contribute to PK Variability

Is it possible **&** useful to determine PGx factor(s)?

# PK Variability

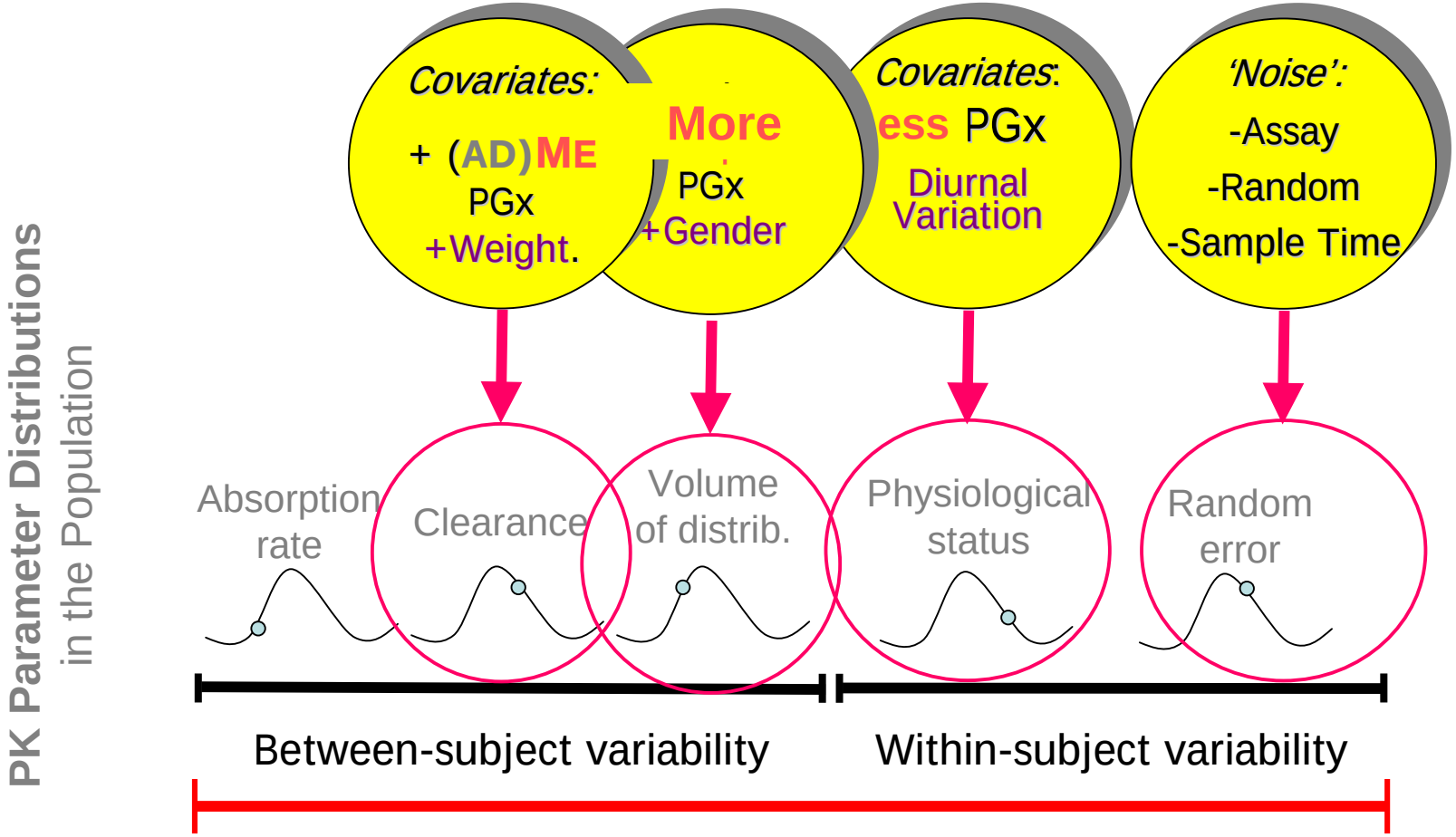
The overall variability is a consequence of multiple factors
Which parameter has the largest PGx effect?

**PK Parameter Distributions**
in the Population



# PK Variability

The overall variability is a consequence of multiple factors
Which parameter has the largest PGx effect?

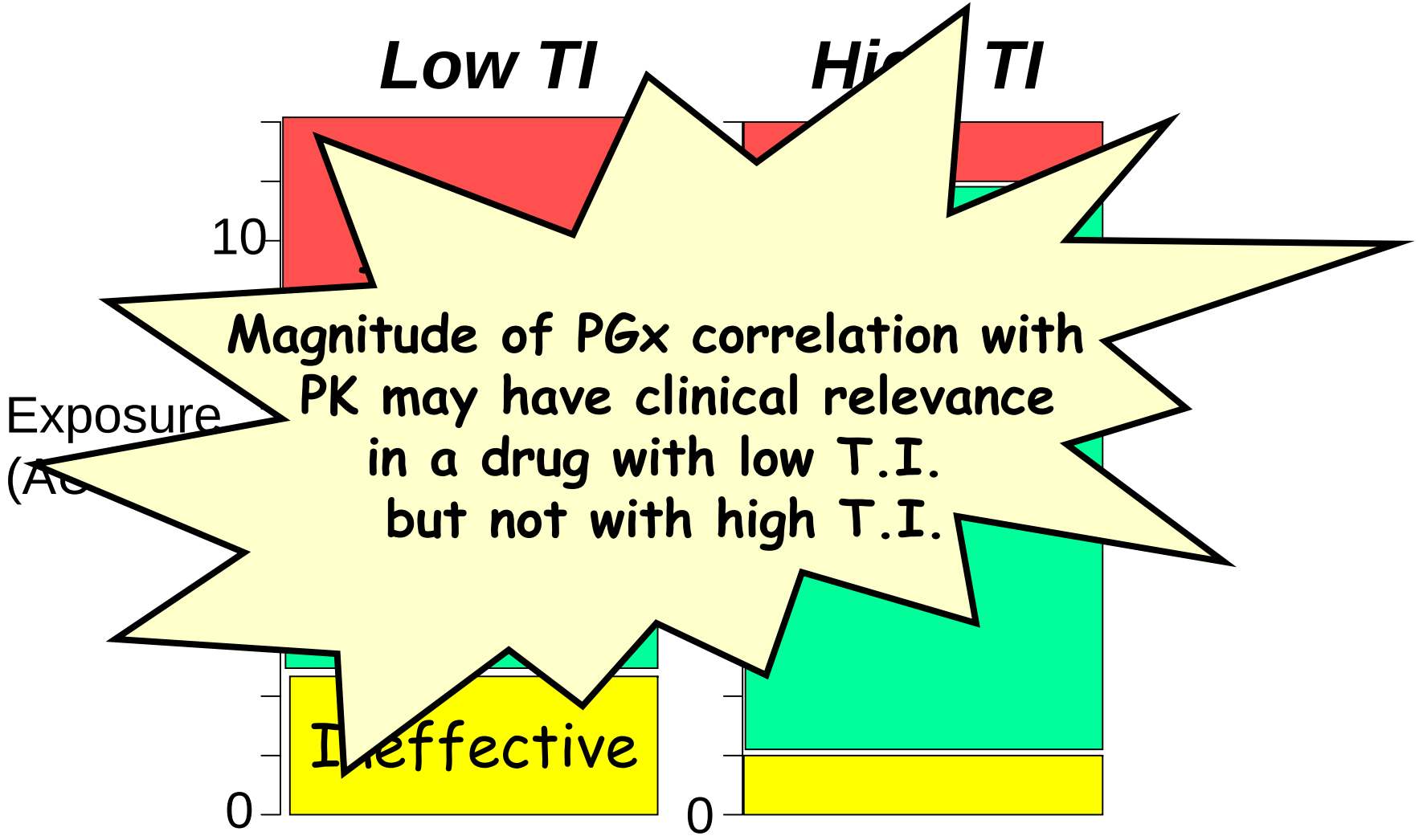


Even if there is a statistically significant PGx Correlation with PK

Is there clinical relevance?

# What type of Clinical Relevance in Drug Dev't?

## *eg* Therapeutic Index: ratio between effective & toxic doses



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# Core Case

You are part of a Project Team
in Company ABC

# For Each Case *

## Workshop Attendees:

- Choose 1 Case (out of 4)
- Become the **Project Team** during the case:
  - Identify who you are and your ***Expertise***
  - Volunteer for ***Project Team Leader*** *(to a team decision)*
  - Volunteer for ***Decision-Table*** to work with Debriefer, in order to generate 1-2 slides for debrief on key messages which arose during the case discussion

## Core Case Panel :

- Are the experts who developed the case and will be on the Team as:
  - Project Team Manager (to time session and facilitate process)
  - Data expert
  - Debriefer after Session 3

# Case Background
# Drug A is in Early Development

*

Company ABC is developing a **second-in-class Drug A** for a serious, chronic disease, **Diabetes Mellitus Type 2**, for which many patients are insufficiently controlled.

- Drug A is an antagonist which shows no major toxicities in animals at exposures expected to provide >80% receptor occupancy.
- Limiting toxicity is elevated body temperature in dogs.
- A narrow therapeutic margin is expected in patients.

# Different Ways to Show PK Variability

*eg* **Variability within a dose:**

- **AUC Fold difference** = highest to lowest value
- **AUC Range** = X to XX times the median value
- **AUC Coefficient of Variation*** = Y%
- **Between Subject Variability Clearance**** =Z%

•Coefficient of Variation (CV) = $\sqrt{\exp((\text{sd on log-scale})^2)-1}$

**Between Subject Variability (BSV) = Population PK Modelling

# Core Case Summary

**Drug A for Diabetes type 2 (***2nd in class***)** has:

| | |
|---|---|
| Predicted Therapeutic Margin | **narrow** |
| Proposed Therapeutic Level *for an antagonist* | **need high receptor occupancy** |
| Exposure:Response Curve | **unknown location on curve** |
| In-vitro ADME Phenotyping | **see data** |
| Observed Clinical Exposures | **see data** |

Your Project Team has until **12:45** to design the next step on the development plan for Drug A using the Decision Table

# Decision Table

## Case nr. 1

Affiliation: ☐ Industry ☐ Non-industry

We'd like to ask all participants to fill in this table during the session, and **hand in at the end of the session to the Case Project Team Leader**.
This information will be very helpful for the debriefing. Thanks !

| **Next Team steps > Scenario: v** | **Do nothing** | **Only collect DNA** | **Genotype Phase I pro-spectively (specify gene)** | **Specific Enriched Phase I study** | **Exclude (eg, PMs)** |
|---|---|---|---|---|---|
| Scenario 1. | | | | | |
| Scenario 2. | | | | | |
| Scenario 3. | | | | | |
| Scenario 4. | | | | | |
| Scenario 5. | | | | | |
| Scenario 6. | | | | | |

# Your Team Task Today

- Breadth rather than depth

  *(ie* Cover each scenario in your case and identify areas for further discussion)

- Identify points of:
  - Consensus
  - Gaps
  - Areas to increase interactions to cover Gaps